World Family Medicine Journal
incorporating the Middle East Journal of Family Medicine

ISSN 1839-0188

September 2023 - Volume 21, Issue 8

Nad alhamar Health and Training Center, Dubai Academic and Health Corporation

The clinical significance of thyroid antibodies in non-thyroid diseases

... page 33

Editorial

4 Dr. Abdulrazak Abyad

Original Contribution

6 Knowledge and Awareness of the Public toward Pediatric Eye Health and Diseases in Aseer region, Saudi Arabia: A Cross-Sectional Population Study
Abdulrahamn Alamri, Faisal Saud I. Alhudaithi, Bandar Mohammed Mushabbab Asiri, Abdulaziz saad mohammed Al-shahrani, Rozan Abdulaziz Ali AlGhamdi, Turki bjad share alotaibi, Abdulrahim Ali Hassan Hassan, Faisal Nabil Fouad Abughazalah, Abdullah Jallwi Mohammed Korkoman, Bader Abdulmohsen Abdulhadi Alghamdi, Sultana Jalwi Korkoman, Hassan Adel Hassan Alasiri
DOI: 10.5742/MEWFM.2023.95256176

19 Autosplenectomy may be a good prognostic sign in sickle cell diseases
Mehmet Rami Helvaci, Ummuhan Kodal Tuncsezen, Aysenur Varol, Kuddusi Onay, Ramazan Davran, Mustafa Yaprak, Abdulrazak Abyad, Lesley Pocock
DOI: 10.5742/MEWFM.2023.95256177

Review Article

33 The clinical significance of thyroid antibodies in non-thyroid diseases
Almoutaz Alkhier Ahmed Abdulrahman
DOI: 10.5742/MEWFM.2023.95256178

44 Vitamin B-12 deficiency in type 2 diabetes patients on metformin therapy – A narrative review
Amir Tauqir Chaudhary, Shiraz Ali A
DOI: 10.5742/MEWFM.2023.95256179

55 Robot-Assisted Versus Laparoscopic Radical Nephrectomy: A Systematic Review and Meta-Analysis
Hazim Mohammed alsufyani, Mohammed Adel Mohammed Shami, Ahmed abdelazim abdelaziz haty, Mohammed Mutlaq Hamdan Althobaiti, Ayman Khalid Kurdi, Ahmed Faisal Siraj, Abdulaziz M Althaqafi, Hussain A Albarqi
DOI: 10.5742/MEWFM.2023.95256180

Case Report

70 Rare Presentation of Aortic Aneurysm: A Diagnostic Challenge
Shiraz Ali, Amir Tauqir Chaudhary H
DOI: 10.5742/MEWFM.2023.95256181

Population and Community Studies

74 **Physical and Emotional Domestic Violence Knowledge among Jazan University Female Students**
Mona H El Mahdy, Sarah El-Reffaey, Samy S. Mahmoud, Amani Osman Abdelmola, Azhar Mohammed Alfaifi, Fatimah H. Dallak, Anwar jafar Alnass, Roaa Shaikhain, Maryam Othman Gharawi, Asayel Ahmad Hozaimi, Hoida Hadi Hadi Sahl, Nada Mohammed Makein
DOI: 10.5742/MEWFM.2023.952561826

87 **Non-Urgent Pediatric Presentations to the Emergency Department, Khamis Mushayt Maternity and Children Hospital, Saudi Arabia**
Waleed Al Jabir; Badr Ayed Al-alfard; Abdullatef Ali Muhaya; Abdullah Al Farhan
DOI: 10.5742/MEWFM.2023.95256183

Case Report

98 **A Patient with Crohn's Disease Presenting with a Picture Mimicking a Strangulated Incisional Hernia: A Case Report**
Saad Dhafer Hussain Alshahrani
DOI: 10.5742/MEWFM.2023.95256184

Review Article

105 **Hypertonic Saline Solution Compared to Mannitol for the Management of Elevated Intracranial Pressure in Children: A Systematic Review**
Abdullah Saleh A. Alfarhan, Khalid Mohammed S. Alsleem, Sultan Abdulwahab M. Asiri, Ahmed Mohammed Hadi Hadadi, Talal Mohammed Saeed Alshahrani
DOI: 10.5742/MEWFM.2023.95256187

Editorial

Chief Editor:
A. Abyad
MD, MPH, AGSF, AFCHSE
Email::
aabyad@cyberia.net.lb
Mobile: 961-3-201901

Ethics Editor and Publisher
Lesley Pocock
medi+WORLD International
AUSTRALIA
Email:
lesleypocock@mediworld.com.au
publishermwi@gmail.com

Publisher: Lesley Pocock
medi+WORLD International
Lesley Pocock

In this issue we have a number of paper of high relevance to the practicing physician and a number of challenging case report.

Alhudaithi et al., did a Cross-Sectional Population Study Knowledge and Awareness of the Public toward Pediatric Eye Health and Diseases in Aseer region, Saudi Arabia. Pediatric ophthalmic conditions are a common and a serious public health problem, as they can not only impact the child's ability to learn, have a normal social life, and get a better quality of life, but they can also lead to complete blindness or visual impairment. Early intervention is necessary for childhood eye diseases since they can result in ongoing issues. The underlying causes of blindness in children differ significantly from region to region, depending on some factors, including socioeconomic development and access to primary healthcare services and facilities. However, it is estimated that there are over 19 million people globally with visual impairments and that there are roughly 1.4 million cases of blindness. As a result, the purpose of this study is to assess the parents' and caregivers' awareness in Aseer, Saudi Arabia, about various common pediatric ophthalmic diseases, including strabismus, amblyopia, refractive errors, and congenital glaucoma. By identifying the gap in knowledge and awareness, this could help create targeted educational and awareness programs geared toward the parents and the public of Aseer, Saudi Arabia, which could help prevent or reduce the prevalence of pediatric ophthalmic conditions, and boost the children's eye health.

Al Jabir1 et al., followed a quantitative cross-sectional design at Khamis Mushayt Maternity and Children's Hospital (KMMCH) to explore parents' perspectives regarding why parents (caregivers) prefer to escort their less urgent, or non-urgent sick children to the emergency departments (EDs) instead of using other more appropriate healthcare services. The age of 18.3% of parents was <30 years, while 28.5% were 30-39 years old. More than half of the parents' visits were non-urgent, while 43.25% were less-urgent, 55.3% of patients visited the ED before due to similar complaints, while 46% visited a primary health care center before their ED visits. The main reasons for visiting the ED instead of the primary healthcare centers (PHCCs) were to save time (49.3%) and to get an earlier appointment (48%). Patients' triage levels differed significantly according to parents' age groups ($p<0.001$), nationality ($p=0.022$), educational level ($p=0.022$), ED visits for similar complaints ($p<0.001$), and previously visiting the PHCC for the current health problem ($p=0.002$). Triage levels also differed significantly according to some reasons for choosing to go to the ED instead of the PHCC, especially to get an earlier appointment ($p=0.044$), preferring the healthcare services provided by the ED ($p=0.005$), having a nearby ED ($p=0.001$), or being at the hospital at that time ($p=0.002$). The authors concluded that there is a clear relationship between inappropriate ED visits and certain associated factors, indicating that prevention would be best targeted to certain categories, such as Saudi, younger, and educated parents. The main reasons for inappropriate ED visits are to save time and to avoid getting a late appointment.

Alsufyani et al., did a systematic review and meta-analysis to compare the perioperative results of RARN and LRN in the treatment of RCC. The meta-analysis revealed no statistically significant demographic differences between the two surgical techniques. There were no significant differences between RARN and LRN in terms of predicted blood loss, length of hospital stay, conversion rate, or transfusion rate. The meta-analysis of complications revealed no significant differences between the two surgical methods for intraoperative or postoperative problems. The authors concluded that this comprehensive review and meta-analysis suggests that RARN and LRN had comparable perioperative results when used to treat RCC. Although RARN may give prospective benefits in the form of enhanced visibility and dexterity, the clinical significance of these benefits remains unknown. Further high-quality studies with long-term follow-up are required to further comprehend the possible advantages and disadvantages of RARN against LRN in the treatment of RCC.

El Mahdy, et al., tried to estimate the prevalence of violence against female students at Jazan University, Saudi Arabia, and identify their knowledge and response towards emotional and physical domestic violence. Domestic violence against females is one of the most important social problems negatively affecting health psychologically and physically. It is a descriptive cross-sectional, observational type of epidemiologic study conducted on 450 female students at 3 Faculties, female sections, Jazan University, for eight weeks. The data is collected using an Arabic questionnaire containing 35 questions and analyzed by SPSS Program. 25.6% of the female students in the studied sample are exposed to domestic violence at some point. The emotional type is the most prevalent (18.3%), followed by the physical type (16.9%). The authors concluded that domestic violence against females is prevalent in the Jazan community, with various socio-demographic and economic determinants influencing its occurrence. The most prevalent type is emotional domestic violence. Art faculties show the highest rating of domestic violence, health faculties, and the least scientific faculties. They recommended effort to Increase community awareness about domestic violence. Religious leaders sustain the greatest responsibility to increase awareness according to the rules of the Islamic religion.

Dr Ali & Chaudhary, presented a rare presentation of Aortic Aneurysm which was a diagnostic challenge. This case report highlights a rare presentation of abdominal aortic aneurysm, which posed a diagnostic challenge due to its atypical clinical manifestations. The patient initially presented with vague symptoms of renal colic and underwent a comprehensive evaluation, including imaging studies to establish the diagnosis. Through a multidisciplinary approach and careful analysis of the diagnostic findings, a rare form of aortic aneurysm was identified. This case emphasizes the importance of considering unusual presentations of aortic aneurysms and the need for thorough investigation to ensure accurate diagnosis and appropriate management.

Dr Chaudhary & Ali did a narrative review elucidates association between metformin therapy in T2DM and cobalamin (Vit. B12) deficiency. According to various studies, diabetic patients receiving metformin medication had a higher risk of Vit. B12 (vitamin B12) deficiency than those T2DM

patients not receiving metformin therapy, ranging from 14% to 22.4% in those taking metformin and from 6% to 10% in those not taking metformin. Odds ratios for Vit. B12 deficiency associated with using metformin ranged from 2.2 to 2.7, indicating a moderate to high risk. The management of Vit. B12 deficiency in T2DM involves a combination of accurate diagnosis, appropriate supplementation strategies, patient education, and interdisciplinary collaboration. Consensus and guidelines recommend routine monitoring of serum vitamin B12 levels, high-dose oral supplementation, intramuscular injections for severe deficiency, and consideration of alternative routes of administration, along with lifestyle modifications.

Dr. Alkhier, reviewed the clinical significance of thyroid antibodies in non- thyroid diseases. Epidemiological studies showed that the population has a high immune disease prevalence, and thyroid immune diseases are among the top autoimmune disorders seen in clinical practice. Investigators noticed an association between Some non-thyroidal conditions with thyroid autoantibodies, and some of the outcomes of these non–thyroid diseases may be affected by the presence of these thyroid antibodies. A systematic literature review was done using selection criteria with the help of search questions. Multiple search engines were searched for eligible articles. Eighteen (18) articles fulfilled the inclusion and exclusion criteria; 44.4% were analytical cross-section studies,5% were prospective studies, 5.5% were meta-analysis studies,5.5% were case-control studies, and 16.7% were retrospective studies. The authors concluded that Thyroid autoantibodies are not exclusively markers of thyroid autoimmune diseases but can also be markers and indicators of non-thyroidal illnesses. Their presence could be either a favourable prognostic indicator, as with breast carcinoma cases or unfavorable prognostic, as with abortion. Further studies are recommended to explore more association.

Helvaci, et al., looked at Autosplenectomy in sickle cell diseases. Patients with red blood cells (RBCs) transfusions of less than 50 units in their lives were put into the first and 50 units or higher were put into the second groups. There were 224 patients in the first and 92 patients in the second groups. Mean ages were similar in them (28.9 vs 30.0 years, respectively, $p>0.05$). The male ratio was higher in the second group (45.5% vs 64.1%, $p<0.001$). In contrast to the lower prevalence of autosplenectomy (56.2% vs 45.6%, $p<0.05$), painful crises per year, digital clubbing, chronic obstructive pulmonary disease (COPD), leg ulcers, stroke, chronic renal disease (CRD), and coronary heart disease (CHD) were all higher in the second group ($p<0.05$ for all). The authors concluded that the sickled or just hardened RBCs-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood. Although RBCs suspensions and corticosteroids in acute, and aspirin with an anti-inflammatory dose plus low-dose warfarin plus hydroxyurea both in acute and chronic phases decrease severity, survivals are still shortened in both genders, dramatically. In contrast to the lower prevalence of autosplenectomy, painful crises per year, digital clubbing, COPD, leg ulcers, stroke, CRD, and CHD were higher in the second group. So there may be an inverse relationship between prevalence of autosplenectomy and severity of SCDs, and spleen may act as a chronic inflammatory focus as a filter of blood for these abnormally hardened RBCs.

Alfarhan et al., did a systemic review to explore the effectiveness of commonly used dosing for mannitol (MN) compared with hypertonic saline solution (HSS) in children with elevated intracranial pressure (ICP) due to diabetic ketoacidosis (DKA), head trauma, or acute central nervous system (CNS) infections. A structured literature review was carried out using the component of the PICO framework. The literature search was conducted in Medline, Ovid, Embase, Google Scholar, and PubMed. A total of 169 articles were identified through the searches, while 8 articles met the inclusion criteria. The characteristics and results of included studies were discussed, regarding the study design, sample size, and outcome. The authors concluded that Osmotic agents, such as HSS and MN are commonly used in the management of high ICP. HSS (3% or 7.5%) has superior therapeutic effects over MN (20%) in lowering increased ICP in children with cerebral edema.

Alshahrani report a case of Crohn's disease that presented with a clinical picture mimicking a strangulated incisional hernia. A 33-year-old Saudi male patient presented to the Emergency Department (ED) with vomiting, pain, and swelling at the right iliac fossa after lifting heavyweight objects two days earlier. The patient had a past history of appendectomy through a transverse incision nine years earlier. Clinically, the patient was vitally stable. He had tenderness at the right iliac fossa, and rebound tenderness. A tender swelling (6 x 8 cm) was observed underneath the previous scar. It was firm, not expansile on cough, and not reducible, with no redness or skin changes. The laboratory report showed normal results for complete blood count, apart from slight leukocytosis. Blood electrolyte levels, renal and liver function tests were normal. Plain CT abdomen showed a defect in the transversus abdominis muscle with the presence of swelling beneath the oblique muscles associated with air, which were connected to the bowel. The preliminary diagnosis was a "strangulated incisional hernia". After laparotomy, the swelling showed pus within the external oblique aponeurosis, with a fistula tract connected to the ileum. After abdominal exploration, the inflammation was observed to be limited to the ileum and cecum with no other abnormality noted. Ileocecoctomy was done with side-to-side anastomosis between the ileum and ascending colon. The resected part was sent for histopathology, which confirmed the characteristics of Crohn's disease. The diagnosis of Crohn's disease remains challenging. Its management is multi-disciplinary. Surgical management is dependent on disease location and severity. It seems that early surgery is gradually going to play a more important role in the multidisciplinary management of Crohn's disease, rather than being a last-resort therapy.

Chief Editor:
A. Abyad
MD, MPH, AGSF, AFCHSE

Knowledge and Awareness of the Public toward Pediatric Eye Health and Diseases in Aseer region, Saudi Arabia: A Cross-Sectional Population Study

Abdulrahamn Alamri [1], Faisal Saud I. Alhudaithi [2], Bandar Mohammed Mushabbab Asiri [2] Abdulaziz saad mohammed Al-shahrani [2], Rozan Abdulaziz Ali AlGhamdi [3], Turki bjad share alotaibi [2], Abdulrahim Ali Hassan Hassan [2], Faisal Nabil Fouad Abughazalah [2], Abdullah Jallwi Mohammed Korkoman [2] Bader Abdulmohsen Abdulhadi Alghamdi [2], Sultana Jalwi Korkoman [4] Hassan Adel Hassan Alasiri [2]

1 Principal investigator, Professor of Ophthalmology, Department of Surgery, College of medicine, King Khalid University, Saudi Arabia
2 College of medicine, King Khalid University
3 King Abdulaziz University, Saudi Arabia
4 College of Medicine, Bisha University

Corresponding author:
Prof. Abdulrahman Al-Amri MD,
Professor of Ophthalmology, Department of Surgery, College of medicine,
King Khalid university, Saudi Arabia
Phone : +966553755973
Email: profalamri@hotmail.com

Received: July 2023. Accepted: August 2023; Published: September 1, 2023.
Citation: Abdulrahamn Alamri et al. Knowledge and Awareness of the Public toward Pediatric Eye Health and Diseases in Aseer region, Saudi Arabia: A Cross-Sectional Population Study. World Family Medicine. August 2023; 21(8): 6-18
DOI: 10.5742/MEWFM.2023.95256176

Abstract

Pediatric ophthalmic conditions are a common and a serious public health problem, as they can not only impact the child's ability to learn, have a normal social life, and get a better quality of life, but they can also lead to complete blindness or visual impairment. Early intervention is necessary for childhood eye diseases since they can result in ongoing issues. The underlying causes of blindness in children differ significantly from region to region, depending on some factors, including socioeconomic development and access to primary healthcare services and facilities. However, it is estimated that there are over 19 million people globally with visual impairments and that there are roughly 1.4 million cases of blindness. As a result, the purpose of this study is to assess the parents' and caregivers' awareness in Aseer, Saudi Arabia, about various common pediatric ophthalmic diseases, including strabismus, amblyopia, refractive errors, and congenital glaucoma. By identifying the gap in knowledge and awareness, this could help create targeted educational and awareness programs geared toward the parents and the public of Aseer, Saudi Arabia, which could help prevent or reduce the prevalence of pediatric ophthalmic conditions, and boost the children's eye health.

Key words: knowledge, awareness, paediatric eye health, eye diseases, Aseer, Saudi Arabia

Introduction

Impact on a child's growth, education, future employment opportunities, and quality of life are only a few of the many reasons why pediatric ophthalmic problems are crucial. Eye disorders in children can occur as a result of prenatal, neonatal, and childhood etiologies. Orbit, eyelid, whole globe, conjunctiva, cornea, sclera, lens, vitreous, retina, uvea, optic nerve, and refractive system are all possible locations for an eye lesion (Sethi, 2008).

Pediatric eye conditions rank high among the reasons for medical consultation, so it's important for every child having an eye disease to seek immediate intervention since eye diseases are common and may represent a serious public health issue among children globally to the extent that about 500,000 children go blind every year around the world; of them, half die within the first two years (Nwosu, 1999). About 1.5 million children are blind worldwide, with more than a million of those living in Asia (Bikebele and Olusanya, 2006). The most frequent ocular abnormalities encountered in American school-aged children are strabismus, amblyopia, and optical problems, which affect their visual acuity (Castenes, 2003).

Africa also showed a high prevalence of eye diseases among children. For example, ocular injuries (13.5%), vernal conjunctivitis (25.3%), corneal inflammation (12.5%), and refractive error (25.7%) were the major causes of ocular morbidity in Nigerian children (Isawummi, 2003). However, strabismus (36.1%), refractive error (26.5%), ocular trauma (7.5%), and conjunctivitis (7.3%) were the most common childhood eye illnesses in Jizan, Saudi Arabia (Darraj et al, 2016). Since the prevalence of pediatric ophthalmic diseases might vary from one region to another, the most common causes of eye morbidity in children in a private hospital in Dammam, KSA, were refractive errors (REs; 44.4%), strabismus (38%) and amblyopia (9.1%) (Al-Tamimi et al., 2015).

The incapacity to express distress and the risk of amblyopia in the event of visual impairment make ocular morbidities in children particularly challenging (Bodunde and Onabolu, 2004). Vision disorders and eye morbidities are preventable and can have a negative impact on a child's learning, personality, and social development at school, so it's important that they get the care they need immediately after they get an eye disease (Pratab and Lai, 1989). Therefore, the three levels of intervention, including primary, secondary, and tertiary prevention, should be utilized to manage pediatric ophthalmic disorders (Salman, 2016).

The Aim of the Study

The study aims to investigate the awareness of pediatric eye diseases and conditions, including strabismus, amblyopia, refractive errors, and congenital glaucoma, among the public in the Aseer region of Saudi Arabia. Since there are not sufficient studies performed in Aseer, Saudi Arabia, the proposal aims to assess the level of knowledge and understanding of these eye conditions among the general population, specifically focusing on parents or caregivers of children. By conducting this research, the aim is to identify gaps in awareness and knowledge, as well as potential misconceptions, regarding these eye conditions. The findings of the study will help inform the development of targeted educational and awareness campaigns to improve early detection, timely intervention, and overall eye health outcomes in children in Aseer, Saudi Arabia.

Objectives

The main objectives of this research proposal are:
a) To determine the level of awareness among parents and caregivers regarding pediatric eye diseases and conditions, including strabismus, amblyopia, refractory errors, and congenital glaucoma, in Aseer, Saudi Arabia.
b) To identify the sources of information that parents and caregivers in Aseer, Saudi Arabia, rely on for their knowledge of pediatric eye diseases and conditions, including strabismus, amblyopia, refractory errors, and congenital glaucoma.
c) To assess the understanding of the signs, symptoms, risk factors, and severe complications associated with strabismus, amblyopia, refractive errors, and congenital glaucoma among the public, parents, and caregivers in Aseer, Saudi Arabia.
d) To explore the perception of the importance of early detection and treatment of pediatric eye diseases and conditions among parents and caregivers.
e) To investigate any associations between demographic factors (e.g., age, education, socioeconomic status) and the level of awareness among the public in Aseer, Saudi Arabia.

Research Questions

• To what extent are pediatric ophthalmic conditions, including strabismus, amblyopia, refractory errors, and congenital glaucoma, prevalent in Aseer, Saudi Arabia?

• What is the level of knowledge of parents and caregivers about pediatric ophthalmic conditions, including strabismus, amblyopia, refractory errors, and glaucoma in Aseer, Saudi Arabia?

• What are the risk factors for pediatric ophthalmic conditions, including strabismus, amblyopia, refractory errors, and congenital glaucoma, in Aseer, Saudi Arabia?
• What are the sources of information that parents and caregivers in Aseer, Saudi Arabia, rely on to learn about eye diseases and conditions in children?

• What are the attitudes and beliefs of parents and caregivers in Aseer, Saudi Arabia, towards seeking professional help and treatment for eye diseases and conditions in children?

Literature Review

The prevalence of eye diseases and conditions among children is a significant public health concern globally; early detection and intervention are crucial in preventing long-term visual impairment and promoting optimal eye health in children. However, to effectively address these issues, it is essential to understand the level of awareness among parents and caregivers regarding pediatric eye diseases and conditions, including strabismus, amblyopia, refractive errors, and congenital glaucoma. This literature review aims to examine the existing body of knowledge on the awareness of these eye diseases and conditions, the prevalence of these eye conditions, their impact on children's visual health, and the importance of early detection and treatment among the general public in Aseer region, Saudi Arabia.

The review will provide a comprehensive overview of the current literature available on the awareness of eye diseases and conditions among parents and caregivers. By synthesizing the existing evidence, this review identifies gaps, patterns, and trends in awareness levels, as well as the factors influencing knowledge and understanding of these eye conditions in the target population.

Dale et al. (2018) defined strabismus as a manifest deviation of the eyes that exceeds the control of the fusional mechanism so that the eyes are misaligned under binocular conditions.

Williams et al. (2008) stated that the frequency of strabismus in children is estimated to be between 0.8% and 5.65%. Bez et al. (2009) also investigated the challenges associated with the diseases, including diminished binocularity and amblyopia, as well as the long-term psychological and social consequences, including low self-esteem, depression, troubled relationships, and difficulty holding down a job.
Cotter et al. (2011) reported that strabismic amblyopia is one of the most common and frequent eye disorders in childhood. Patients with strabismus often complain of difficulties with binocular vision and depth perception, as well as with their appearance, their ability to learn, their relationships with others, their solitude, and their fear of surgery.

Although the main etiology of strabismus remains poorly established, Zhu et al. (2015) noted that there are some factors that could increase the chances of getting the disease, including ocular factors like hyperopia, myopia, astigmatism, anisometropia, and amblyopia; family history of strabismus and amblyopia; maternal factors like smoking or alcohol use during pregnancy; and perinatal factors like intrauterine growth retardation, prematurity, and low birth weight. They also addressed the fact that hyperopia and esotropia are highly associated with ocular risk factors. Donnelly (2012) also reported some risk factors, including family history, race or ethnicity, genetics, smoking, premature birth, low birth weight, refractive error, and neurological impairment.

According to Sharimawat (2015), if strabismus is diagnosed and treated early on, it can have positive effects on patients' visual and socioeconomic well-being. Refractive correction and vision therapy, when performed on children at a younger age, are the most effective non-invasive management alternatives that restore vision and eye deviation. Amblyopia, the leading cause of visual impairment or blindness due to laziness of the eye, can be prevented or at least mitigated by early detection and treatment of strabismus in children.

Barrett et al. (2004) defined amblyopia as a reduced visual acuity or visual impairment that occurs at a young age due to conditions like strabismus and anisometropia, even in the absence of obvious injury to the eye or visual system or ocular pathology. Al-Yahya et al. (2012) addressed the fact that amblyopia is one of the most widespread health issues, affecting an estimated 5% of the population. Robaei et al. (2006) stated that amblyopia is the leading cause of blindness in both children and adults with unilateral visual impairment. Webber and Wood (2005) revealed that although amblyopia most often affects just one eye, it can affect both eyes. Tailor et al. (2016) identified deprivation, anisometropia, and strabismus as the most common causes of amblyopia in one eye.

Several studies were conducted to assess amblyopia's prevalence in Saudi Arabia. Fatani (1994) reported that it's about 2.6% in the capital city of Riyadh, while Aldebasi (2015) found that it's 3.9% in the province of Qassim. Another study by Bardisi and Binsadiq (2002) reported that it's 1.3% in the city of Jeddah, and Abolfotouh et al. (1994) assumed that it's 1.9% in the city of Abha. So, the characteristics of the analyzed patients, the criteria and cutoff points of visual measures used to characterize amblyopia may account for these discrepancies in prevalence.

De Zarate and Tejedore (2007) reported that the treatment for amblyopia is most effective before the age of 8, so it can occur at any time between 4 months and 8 years. They also stated that high, untreated refractive errors are one of the leading causes of binocular amblyopia. In addition to a decrease in visual acuity, other visual impairments such as poor accommodation, binocular dysfunction, abnormal contour interactions, positional uncertainty, reduced contrast sensitivity, spatial distortions, abnormal eye movements, suppression, and fixation instability can contribute to amblyopia.

Alzahranti et al. (2018) supported the role of patching in the treatment of amblyopia, addressing the fact that patching, from 1 hour to complete occlusion, is used to treat amblyopia. A Pediatric Eye Disease Investigator Group (2002) performed a randomized controlled study to compare the effectiveness of atropine and patching in the treatment of amblyopia, and they reported that when it comes to the initial therapy of moderate amblyopia in children aged 3 to less than 7 years old, both atropine and patching are appropriate modalities because they elicit improvement of similar magnitude.

According to Bourne et al. (2013), myopia, hyperopia, and astigmatism are examples of refractive errors (RE), which are abnormalities in the optical structure of the eye. They continue to be one of the leading contributors to vision impairment in school-aged children and one of the most prevalent ocular diseases worldwide.

Rose et al. (2002) suggested that over the past few decades, there has been a sharp rise in the prevalence of RE worldwide, especially myopia, which indicates that RE in people is sensitive to environmental influences in a variety of physical environments, groups, and lifestyles. In addition, Saw (2003) reported that higher levels of education were linked to a higher prevalence of myopia. According to Ma (2010), the prevalence of RE in Saudi Arabia ranged from 4.5% to 34.9%, depending on the age of the children.

Guo et al. (2015) stated that the primary cause of RE may be influenced by a number of variables. Some potential risk factors are usually linked to myopia development, including educational level, lifestyle characteristics related to schools, and near-work activity in general. A recent study by Huang et al. (2015) linked near-work activity to myopia, reporting that children between the ages of 6 and 18 who engaged in more near-work activity had an increased prevalence of myopia. They added that it could hasten the progression of myopia.

Bejjani et al. (1998) stated that in the absence of other specific ocular or systemic diseases that can cause glaucoma, primary congenital glaucoma (PCG) is typically a severe form of glaucoma defined by elevated intraocular pressure from birth. PCG is thought to be up to ten times more common in Saudi Arabia than it is in the West. Kotb et al. (2006) reported that around 20% of childhood blindness in the Kingdom is attributed to PCG, making it a prominent cause of childhood blindness.

Since most pediatric ophthalmic diseases are preventable if they are diagnosed in the early stages, several studies were conducted to assess the level of awareness of parents and caregivers in Saudi Arabia about various pediatric ophthalmic conditions. Alsaqr and Masmali (2019) conducted a cross-sectional population study to assess the level of awareness among the Saudi Arabian community, and they reported that the Saudi population as a whole lacked knowledge of amblyopia. They also demonstrated that the children's eyesight can be damaged or impaired because of this lack of awareness. In addition, they suggested raising awareness among the general public through health care providers, schools, the media, and community groups. Another cross-sectional population study by Rashed et al. (2017) reported that only 51.5% of the population in Riyadh, Saudi Arabia, had appropriate knowledge about pediatric eye illnesses. Al Mazrou et al. (2020) also performed a cross-sectional study, and they reported that both parents have a reduced level of knowledge and awareness about the common pediatric eye conditions. They also supported the role of educational and awareness programs for common pediatric ophthalmic disorders in improving children's eye health, assuming that such programs should target both parents and focus more on mothers.

Methodology

Study Design

Our study utilized a quantitative cross-sectional population study design to gather data on awareness levels of pediatric eye conditions, including strabismus, amblyopia, refractory errors, and congenital glaucoma in the Aseer region.

Sample Selection

A representative sample of 597 parents and caregivers with children aged 0–12 years was selected from various communities in the Aseer region of Saudi Arabia.

Inclusion Criteria:

- Parents or caregivers of children aged between 0 and 14 years.
- Residents of the Aseer region of Saudi Arabia.
- Individuals who can understand and respond to the survey/questionnaire in Arabic or English.
- Willingness to participate voluntarily in the study.

Exclusion Criteria:

- Individuals who are not parents or caregivers of children.
- Parents or caregivers who have children older than 14 years.
- Non-residents of the Aseer region.
- Unwillingness to participate or provide informed consent for the study.

These criteria were designed to ensure that the research focused specifically on the target population of parents or caregivers in the Aseer region, who are directly responsible for the health and well-being of children. By defining these criteria, the study gathered relevant data from individuals who meet the inclusion criteria while excluding those who did not fit the intended target population.

Sampling Technique

Non-probability Sampling Method, i.e., convenience sampling; we chose participants based upon availability and willingness to partake in our research.

Data Collection

A structured questionnaire was developed and administered to gather data according to our criteria, including awareness levels, sources of information, understanding of signs and symptoms, and perceptions regarding pediatric ophthalmic conditions (strabismus, amblyopia, refractory errors, and glaucoma). Participants who agreed to participate were given a full explanation of the purpose of this study, and after that they were asked to sign an informed consent form.

Data Analysis:
Descriptive statistics was used to summarize awareness levels, and knowledge of **eye infections**. Inferential statistics, such as chi-square tests. SPSS Statistical Package was used to analyze the data.

Ethical Considerations:
Ethical approval was sought from the relevant research ethics committee. Informed consent was obtained from the participants, ensuring the confidentiality and anonymity of their responses. The research adhered to the principles of ethical research conduct.

Results

First, we designed a descriptive well-structured online questionnaire, which was given to parents and caregivers in Aseer, Saudi Arabia so that we can assess the level of knowledge and the sources of information of parents and caregivers of the Aseer region of Saudi Arabia regarding some pediatric ophthalmic disorders including strabismus, amblyopia, congenital glaucoma, and refractory errors. Our study also aimed to assess the prevalence of these conditions among the children of Aseer, Saudi Arabia.

After analyzing the data, the results showed that up to 597 participants agreed to take our online questionnaire. Of the 597 responses, 344 participants were males (57.6%), and the other 253 respondents were females (42.4%).

The results also showed that out of 597 participants, 474 (79.4%) had children with no eye problems, while 123 (20.6%) had children with eye problems.

Table 1 shows that about 395 (66.2%) agreed that wearing glasses for children if they need them can help their vision develop normally, while 146 (24.5%) were not sure about this information. In addition, only 56 (9.4%) disagreed with the statement. Moreover, 186 (31.2%) agreed that it's normal for children between one and seven years to roll up their eyes sometimes, while approximately 187 (31.3%) disagreed with that. About 224 (37.5%) were not sure about that.

Table 1: Current General Knowledge of the participants regarding specific statements

Wearing glasses if you need them when you are less than 7 years old will make your eyes and vision develop normally?		
	Frequency	Percent
Agree	395	66.2%
Disagree	56	9.4%
Not sure	146	24.5%
Is it normal for a child between the ages of one and seven years to roll his eyes sometimes?		
	Frequency	Percent
Agree	186	31.2%
Disagree	187	31.3%
Not sure	224	37.5%

Table 2 shows the level of awareness among the participants regarding lazy eye (Amblyopia) and cataracts in children. It shows that about 27% of the participants don't know what lazy eye is, however up to 42.9% of them address that it's defined as a difficulty in seeing in one or both eyes. In addition, 41% of the participants don't know the definition of cataract. The table also shows that 2.3% of the respondents stated that cataracts don't affect children, and 35.5% don't know whether cataracts affect children or not.

Table 2 also addresses that 65.3% of the participants don't know whether cataracts may lead to permanent blindness in children or not.

Table 2: Awareness of the parents and caregivers about lazy eye and cataracts in children

What is the definition of lazy eye?		
	Frequency	**Percent**
Imbalance in both eyes	1	0.2%
Decreased night vision	22	3.7%
Deterioration of the optic nerve	92	15.4%
Difficulty seeing in one or both eyes	256	42.9%
Loss of parallelism between the eyes	65	10.9%
I don't know	161	27%
What is a cataract?		
	Frequency	**Percent**
White spot in the eye	94	15.7%
The lens changes as the lens become opaque	156	26.1%
A white membrane that grows over the eye	100	16.8%
I don't know	247	41.4%
Does cataract affect children?		
	Frequency	**Percent**
Yes	371	62.2%
No	14	2.3%
I don't know	212	35.5%
Can cataracts lead to permanent blindness in children?		
Yes	165	27.7%
No	42	7%
I don't know	390	65.3%

Table 3: Awareness of the parents and caregivers about strabismus and congenital glaucoma in children

What is glaucoma?		
	Frequency	**Percent**
Increased eye pressure	2	0.3%
High eye pressure that leads to damage to eye nerve	218	36.5%
Opacity of the lens of the eye	55	9.2%
An age-related process that leads to a decrease in peripheral vision	42	7%
I don't know	280	46.9%
Can glaucoma affect children?		
	Frequency	**Percent**
Yes	242	40.6%
No	30	5%
I don't know	325	54.4%
Can congenital glaucoma lead to blindness?		
	Frequency	**Percent**
Yes	213	35.7%
No	17	2.8%
I don't know	367	61.5%
What do you know about strabismus?		
	Frequency	**Percent**
Deviation of the eyes	1	0.2%
Deviation and abnormal movements of the eye	1	0.2%
A refractive defect that occurs due to the irregular shape of the eyeball	71	11.9%
Opacity in the lens of the eye	19	3.2%
An optical defect that puts the eyes in an imbalanced state so that each eye turns in a different direction	420	70.4%
I don't know	85	14.2%
Can strabismus be treated?		
	Frequency	**Percent**
Yes	412	69%
No	28	4.7%
I don't know	157	26.3%
According to your knowledge, what are the options for strabismus treatment?		
	Frequency	**Percent**
Glasses	99	16.6%
Glasses or contact lenses	1	0.2%
Eye glasses and surgery	1	0.2%
Cover the eye	21	3.5%
Eye surgery	156	26.1%
All of the above	194	32.5%
I don't know	125	20.9%
What are the risk factors for developing a squint?		
	Frequency	**Percentage**
Eye refractive errors	53	8.9%
Systemic diseases (Down's syndrome, cerebral palsy)	18	3%
Family history	85	14.2%
All of the above	203	34%
I don't know	238	39.9%
What do you know about the complications of untreated squint?		
	Frequency	**Percent**
Poor self-image	42	7%
Poor personal relationships and appearance	29	4.9%
Visual loss	67	11.2%
Cosmetic stigma	26	4.4%
All of the above	211	35.3%
I don't know	222	37.2%

Table 3 shows that almost 46.9% of the participants are not aware of the definition of glaucoma. Moreover, only 5% of the participants believe that glaucoma can affect children. 61% of the respondents don't know whether congenital glaucoma may lead to blindness or not.

Table 3 also reveals that 70.4% of the respondents define strabismus as an optical defect that puts the eyes in an imbalanced state so that each eye turns in a different direction. In addition, 69% of the participants believe that strabismus can be treated. However, only 32.5% of the participants address that strabismus can be treated by using glasses, contact lens, eye coverage, or even eye surgery. In addition, 39.9% of the respondents are not aware of the risk factors for developing strabismus. 35.3% also address that complications of untreated strabismus may include poor self-image, poor personal relationship and appearance, cosmetic stigma, and even visual loss.

Table 4 shows that 76,9% of the participants are not aware of refractory errors, and up to 60% of them don't know the symptoms of refractory errors. Moreover, 61.6% of the respondents don't know the risk factors for developing refractory errors. Only 29% of the participants note that deviation-astigmatism, farsightedness, and nearsightedness are types of refractory errors.

Table 4 also shows that up to 51.4 of the participants don't know whether refractory errors affect academic performance or not. In addition, about 68.2% of the participants have no idea if refractory errors may cause blindness. 60.3% also state that hospital is the appropriate place to request assistance in case they have refractory errors.

Table 4: Awareness of the parents and caregivers about refractory errors in children

Do you know what refractive errors are?		
	Frequency	Percent
No	459	76.9%
Yes	138	23.1%
What are the symptoms of refractive defects?		
	Frequency	Percent
Secretions	20	3.4%
Blurry vision	195	32.7%
Rubbing the eye	24	4%
I don't know	358	60%
What are the risk factors for developing refractive defects?		
	Frequency	Percent
Family history	113	18.9%
Eye infections	80	13.4%
Patient contact	20	3.4%
Malnutrition	16	2.7%
I don't know	368	61.6%
When do refractive defects occur?		
	Frequency	Percent
Eye infections	43	7.2%
When undernourished	26	4.4%
When light rays are not focused on the retina	163	27.3%
I don't know	365	61.1%
What are the types of refractive defects?		
	Frequency	Percent
Deviation-Astigmatism	35	5.9%
Farsightedness	19	3.2%
Nearsightedness	32	5.4%
All of the above	173	29%
I don't know	338	56.6%
What is the distance affected by refractive defects?		
	Frequency	Percent
Vision near and far	89	14.9%
Seeing from a different distance	73	12.2%
Only remote vision	48	8%
Just seeing up close	21	3.5%
I don't know	366	61.3%
What is the effect of refractive defects on academic performance?		
	Frequency	Percent
Decreased academic performance	203	34%
Increased academic performance	29	4.9%
No effect on academic performance	58	9.7%
I don't know	307	51.4%
Can refractive errors cause blindness?		
	Frequency	Percent
Yes	108	18.1%
No	82	13.7%
I don't know	407	68.2%
What is the appropriate place to request assistance due to refractive defects?		
	Frequency	Percent
Optical shop	20	3.4%
Health center	29	4.9%
Hospital	360	60.3%
I don't know	188	31.5%

Table 5 shows that about 50.9% of the participants get their information about eye diseases from medical staff, however, up to 25.6% get the information about eye diseases from friends and neighbors. Up to 43.2% use social media to get their information.

Table 5 also shows that up to 84.3% of the participants don't consider Television as a source of information of eye diseases, and up to 99% don't consider radio as a source of information.

Table 5: The source of information for the parents and caregivers about pediatric ophthalmic conditions

Do you consider medical staff as a source of your information about eye diseases?		
	Frequency	Percent
Yes	304	50.9%
No	293	49.1%
Do you consider friends and neighbors as a source of your information about eye diseases?		
	Frequency	Percent
Yes	153	25.6%
no	444	74.4%
Do you consider social media as a source of your information about eye diseases?		
	Frequency	Percent
Yes	258	43.2%
No	339	56.8%
Do you consider Television as a source of your information about eye diseases?		
	Frequency	Percent
Yes	94	15.7%
No	503	84.3%
Do you consider radio as a source of your information about eye diseases?		
	Frequency	Percent
Yes	6	1%
No	591	99%
Do you consider internet browser as a source of your information about eye diseases?		
	Frequency	Percent
Yes	264	44.2%
No	333	55.8%

Discussion

The goal of our study was to assess the prevalence of pediatric ophthalmic conditions, including strabismus, amblyopia, refractory errors, and congenital glaucoma, among the public in Aseer, Saudi Arabia. We used a well-structured online survey to assess the level of knowledge of parents and caregivers regarding these pediatric eye conditions and to evaluate the sources of information that parents rely on.

Our findings showed that out of 597 participants, 474 (79.4%) had children with no eye problems, while 123 (20.6%) had children with eye problems, which indicated that the prevalence of pediatric ophthalmic conditions is relatively low among the participants from the Aseer region of Saudi Arabia. Our results are in conflict with the findings by Darraj et al. (2016), who found that the frequency of pediatric ophthalmic conditions was high among the population in Jizan, Saudi Arabia. This conflict may be due to the demographic variations of pediatric ophthalmic conditions prevalence from region to region or to the lack of knowledge of the parents or caregivers about such eye conditions, which could let them believe that their children don't have an eye problem.

According to Dale et al. (2018), strabismus is defined as a manifest deviation of the eyes that exceeds the control of the fusional mechanism so that the eyes are misaligned under binocular conditions. Our study also investigated the parents' knowledge of whether it's normal for the child to roll their eyes sometimes. Up to 37.5% of the participants were not sure whether it was normal or not, which indicated their lack of knowledge about pediatric strabismus. Our study also revealed that 69% of the participants believe that strabismus can be treated, which converges with the findings by Sharimawat (2015), addressing the fact that if strabismus is diagnosed and treated early on, it can have positive effects on patients' visual and socioeconomic well-being. Our study stated that only 32.5% of the participants addressed the fact that strabismus can be treated by using glasses, contact lenses, eye coverage, or even eye surgery. In addition, 39.9% of the respondents are not aware of the risk factors for developing strabismus. So, most participants know that strabismus can be treated, but they are not aware of the treatment options or the risk factors for developing such a condition.

According to Barrett et al. (2004), amblyopia, or eye laziness, is a reduced visual acuity or visual impairment that occurs at a young age due to conditions like strabismus and anisometropia, even in the absence of obvious injury to the eye, visual system, or ocular pathology. Our study noted that only 42.9% of the participants were knowledgeable about amblyopia's definition, which converges with the findings of Alsaqr and Masmali (2019), who conducted a cross-sectional population study to assess the level of awareness among the Saudi Arabian community, and they reported that the Saudi population as a whole lacked knowledge of amblyopia.

According to Bejjani et al. (1998), primary congenital glaucoma (PCG) is typically a severe form of glaucoma defined by elevated intraocular pressure from birth. PCG is thought to be up to ten times more common in Saudi Arabia than it is in the West. Although Alsaqr and Masmali (2019) addressed the fact that PCG is the primary cause of childhood blindness in the Kingdom of Saudi Arabia, our findings revealed the parents' lack of knowledge about congenital glaucoma in children, so 46.9% of the participants are not aware of the definition of glaucoma, and up to 61% of the respondents don't know whether congenital glaucoma may lead to blindness or not.

Our study also assessed the general knowledge of parents in Aseer, Saudi Arabia, about refractory errors, and we found that 76.9% of the participants were not aware of refractory errors, and up to 60% of them didn't know the symptoms of refractory errors. Moreover, 61.6% of the respondents didn't know the risk factors for developing refractory errors. Only 29% of the participants noted that deviation-astigmatism, farsightedness, and nearsightedness are types of refractory errors.

In addition, about 68.2% of the participants have no idea if refractory errors may cause blindness. So, our study also indicated that participants' lack of knowledge of refractory errors, could delay the early detection of such conditions in children, thus impacting the child's academic performance and quality of life.

Our findings also revealed that participants mostly consider medical staff and social media as sources of information about eye diseases. About 50.9% of the participants get their information about eye diseases from medical staff, and up to 43.2% use social media to get their information, which indicates the power of social media in improving the general awareness of the public in Aseer, Saudi Arabia, regarding pediatric ophthalmic conditions.

Taken together, our findings are the first to point towards the lack of knowledge of the parents and caregivers in the Aseer region of Saudi Arabia regarding pediatric ophthalmic conditions including strabismus, amblyopia, refractory errors, and congenital glaucoma, their signs and symptoms, risk factors, and treatment options. Our study suggests raising the awareness and general knowledge of the public in Aseer region, Saudi Arabia by creating focused educational programs through health care providers, schools, the media, and community groups geared towards parents and caregivers.

Our study has two main limitations. First, our sampling size is relatively small compared to the total population based in Aseer, Saudi Arabia. The explanation is that we utilized an online questionnaire to get our results, so only 597 participants had the time and opportunity to take the survey. Another limitation is that the data collected in this study relied on self-reported responses from parents. There is a possibility of response bias, as participants may have provided socially desirable answers or overestimated their knowledge level due to social desirability bias. Inaccurate

or incomplete reporting of information may have influenced the results and affected the reliability of the findings. Future research may extend this work by developing more cross-sectional studies regarding more pediatric ophthalmic conditions with a larger sampling size, which would better investigate the general awareness of the public, and trying to create innovative educational programs geared to people in Aseer, Saudi Arabia.

Conclusion

We designed a cross-sectional study geared towards parents and caregivers in Aseer, Saudi Arabia, to assess the prevalence of pediatric eye conditions including strabismus, amblyopia, refractory errors, and congenital glaucoma. Our study also aimed to investigate the general knowledge of parents regarding the signs, symptoms, risk factors, treatment options, and sources they utilize to get information about these conditions. Our findings indicated the low prevalence of pediatric ophthalmic conditions, including strabismus, amblyopia, refractory errors, and congenital glaucoma, among the public in Aseer, Saudi Arabia. In addition, most parents and caregivers lack basic knowledge about such conditions. Moreover, most parents who participated in our study rely on medical staff and social media as sources of information. So, our study suggests raising the general awareness of the public in Aseer, Saudi Arabia, by developing educational campaigns on social media platforms, schools, healthcare providers, and hospitals, which could significantly make the parents and caregivers more knowledgeable about the risk factors, signs, and symptoms of such conditions, which could help them earlier detect, treat, and maintain their children's eye health.

References

Abolfotouh, M. A., Badawi, I., & Faheem, Y. (1994). Prevalence of amblyopia among schoolboys in Abha city, Asir Region, Saudi Arabia. J Egypt Public Health Assoc, 69, 19–30.

Al Mazrou, A., Alsobaie, N. A., Abdulrahman, A. K. B., & AlObaidan, O. (2020). Do Saudi parents have sufficient awareness of pediatric eye diseases in Riyadh? Saudi Journal of Ophthalmology: Official Journal of the Saudi Ophthalmological Society, 34(3), 171–176. https://doi.org/10.4103/1319-4534.310415

Aldebasi, Y. H. (2015). Prevalence of amblyopia in primary school children in Qassim province, Kingdom of Saudi Arabia. Middle East Afr J Ophthalmol, 22, 86–91.

Alsaqr, A. M., & Masmali, A. M. (2019). The awareness of amblyopia among parents in Saudi Arabia. Therapeutic Advances in Ophthalmology, 11, 251584141986810. https://doi.org/10.1177/2515841419868103

Al-Tamimi, E. R., Shakeel, A., Yassin, S. A., Ali, S. I., & Khan, U. A. (2015). A clinic-based study of refractive errors, strabismus, and amblyopia in pediatric age-group. Journal of Family & Community Medicine, 22(3), 158–162. https://doi.org/10.4103/2230-8229.163031

Al-Yahya, A., Al-Odan, K., & Allam, K. (2012). Compliance to patching in the treatment of amblyopia. Saudi J Ophthalmol, 26, 305–307.

Alzahrani, N., Alhibshi, N., & Bukhari, D. (2018). Awareness, perceptions and knowledge of amblyopia among pediatrics and ophthalmology clinics attendees in King AbdulAziz University Hospital, Jeddah. Jeddah. Int J of Adv Res, 6, 1506–1517.

Bardisi, W. M., & Binsadiq, B. M. (2002). Vision screening of preschool children in Jeddah, Saudi Arabia. Saudi Med J, 23, 445–449.

Barrett, B. T., Bradley, A., & Mcgraw, P. V. (2004). Understanding the neural basis of amblyopia. Neuroscientist, 10, 106–117.

Bejjani, B. A., Lewis, R. A., & Tomey, K. F. (1998). Mutations in CYP1B1, the gene for cytochrome P4501B1, are the predominant cause of primary congenital glaucoma in Saudi Arabia. Am J Hum Genet, 62(2), 325–333.

Bekibele, C. O., & Olusanya, B. A. (2006). Chronic Allergic Conjunctivitis: an Evaluation of Environmental Risk Factors. Asian J. of Ophthalmol, 8, 147–150.

Bez, Y., Coskun, E., Erol, K., Cingu, A. K., Eren, Z., & Topcuoglu, V. (2009). Adult strabismus and social phobia: a case-controlled study. J Aapos, 13(3), 249–252.

Bodunde, O. T., & Onabolu, O. O. (2004). Childhood eye diseases in Sagamu. Nigerian J.of Ophthalmol, 12, 6–9.

Bourne, R. R., Stevens, G. A., White, R. A., Smith, J. L., Flaxman, S. R., & Price, H. (2013). Causes of vision loss worldwide, 1990-2010: A systematic analysis. Lancet Glob Health, 1, e339-349.

Castenes, M. S. (2003). Major review: The under utilization of vision screening (for amblyopia, optical anomalies and strabismus) among preschool age children.

Cotter, S. A., Varma, R., Tarczy-Hornoch, K., McKean-Cowdin, R., Lin, J., Wen, G., Wei, J., Borchert, M., Azen, S. P., Torres, M., Tielsch, J. M., Friedman, D. S., Repka, M. X., Katz, J., Ibironke, J., & Giordano, L. (2011). Risk factors associated with childhood strabismus. Ophthalmology, 118(11), 2251–2261. https://doi.org/10.1016/j.ophtha.2011.06.032

Dale, E., Fajardo, B., & Wilson, A. M. (2018). Pediatric Ophthalmology and Strabismus. Pediatric Ophthalmology and Strabismus. American Acadamy of Ophthalmology, 86–123.

Darraj, A., Barakat, W., Kenani, M., Shajry, R., Khawaji, A., Bakri, S., Makin, A., Mohanna, A., & Yassin, A. O. (2016). Common eye diseases in children in Saudi Arabia (Jazan). Ophthalmology and Eye Diseases, 8, OED.S39055. https://doi.org/10.4137/oed.s39055

De Zarate, B. R., & Tejedor, J. (2007). Current concepts in the management of amblyopia. Clin Ophthalmol, 1, 403–414.

Donnelly, U. M. (2012). Horizontal strabismus worldwide – what are the risk factors? Ophthalmic Epidemiology, 19(3), 117–119. https://doi.org/10.3109/09286586.2012.681002

Fatani, A.-A. A. (1994). Vision screening of preschool children in Riyadh. Saudi J Ophthalmol, 8, 9–14.

Guo, K., Yang, D. Y., Wang, Y., Yang, X. R., Jing, X. X., & Guo, Y. Y. (2015). Prevalence of myopia in schoolchildren in Ejina: The Gobi desert children eye study. Invest Ophthalmol Vis Sci, 56, 1769–1774.

Huang, H. M., Chang, D. S., & Wu, P. C. (2015). The association between near work activities and myopia in children - A systematic review and meta-analysis. PLoS One, 10.
Isawunmi, M. A. (2003). Ocular disorders amongst school children in Ilesa east Local Government area.
Kotb, A. A., Hammouda, E. F., & Tabbara, K. F. (2006). Childhood blindness at a school for the blind in Riyadh, Saudi Arabia. Ophthalmic Epidemiol, 13(1), 1–5.
Ma, A.-R. (2010). Prevalence of refractive errors among pre-school children at King Abdulaziz Medical City, Riyadh, Saudi Arabia. Saudi J Ophthalmol, 24, 45–48.
Nwosu, S. (1999). Childhood eye diseases in Anambra State, Nigeria. Nigeria. Nigeria J. of Ophthalmology, 7, 34–38.
Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. (2002). Arch Ophthalmol, 120, 268–278.
Pratab, V. B., & Lai, H. B. (1989). Pattern of pediatric ocular problem in North India. India J Ophthalmol, 37, 171–172.
Rashed, A., Abdulrahman, B., Zarban, A. K., Almasri, A. A., Mirza, M. S., & Khandekar, A. S. (2017). Public awareness regarding common eye diseases among Saudi Adults In Riyadh City: A quantitative study. J Ophthalmol, 2017, 1–5.
Robaei, D., Rose, K. A., & Ojaimi, E. (2006). Causes and associations of amblyopia in a population-based sample of 6-year-old Australian children. Arch Ophthalmol, 124, 878–884.
Rose, K. A., Morgan, I. G., Smith, W., & Mitchell, P. (2002). High heritability of myopia does not preclude rapid changes in prevalence. Clin Exp Ophthalmol, 30, 168–172.
Salman, M. S. (2016). Pediatric eye diseases among children attending outpatient eye. Iasj.net. https://www.iasj.net/iasj/download/a730d326a05026fe
Saw, S. M. (2003). A synopsis of the prevalence rates and environmental risk factors for myopia. Clin Exp Optom, 86, 289–294.
Sethi, S. (2008). Pattern of common eye disease in children attending out patient eye department in Khyber teaching hospital. J Med Sci, 16(2), 99–101.
Sharimawat, S. (2015). Associated Risk Factors Of Strabismus: The Sydney Childhood Eye Study. 2015, 2–291.
Tailor, V., Bossi, M., & Greenwood, J. A. (2016). Childhood amblyopia: current management and new trends. Br Med Bull, 119, 75–86.
Webber, A. L., & Wood, J. (2005). Amblyopia: prevalence, natural history, functional effects and treatment. Clin Exp Optom, 88, 365–375.
Williams, C., Northstone, K., Howard, M., Harvey, I., Harrad, R. A., & Sparrow, J. M. (2008). Prevalence and risk factors for common vision problems in children: data from the ALSPAC study. The British Journal of Ophthalmology, 92(7), 959–964.
Zhu, H., Yu, J. J., Yu, R. B., Ding, H., Bai, J., & Chen, J. (2015). Association between childhood strabismus and refractive error in Chinese preschool children. PloS One, 10(3).

Autosplenectomy may be a good prognostic sign in sickle cell diseases

Mehmet Rami Helvaci [1], Ummuhan Kodal Tuncsezen [2], Aysenur Varol [2], Kuddusi Onay [2], Ramazan Davran [3], Mustafa Yaprak [1], Abdulrazak Abyad [4], Lesley Pocock [5]

(1) Specialist of Internal Medicine, MD, Turkey
(2) Manager of Writing and Statistics, MD, Turkey
(3) Specialist of Radiology, MD, Turkey
(4) Middle-East Academy for Medicine of Aging, MD, Lebanon
(5) medi-WORLD International, Australia

Corresponding author:
Prof Dr Mehmet Rami Helvaci, MD
07400, ALANYA, Turkey
Phone: 00-90-506-4708759
Email: mramihelvaci@hotmail.com

Received: July 2023. Accepted: August 2023; Published: September 1, 2023.
Citation: Helvaci M R et al. Autosplenectomy may be a good prognostic sign in sickle cell diseases. World Family Medicine. August 2023; 21(8): 19-32. DOI: 10.5742/MEWFM.2023.95256177

Abstract

Background: Sickle cell diseases (SCDs) are inborn and destructive processes on vascular endothelium, particularly at the capillaries.

Methods: Patients with red blood cells (RBCs) transfusions of less than 50 units in their lives were put into the first and 50 units or higher were put into the second groups.

Results: There were 224 patients in the first and 92 patients in the second groups. Mean ages were similar in them (28.9 vs 30.0 years, respectively, p>0.05). The male ratio was higher in the second group (45.5% vs 64.1%, p<0.001). In contrast to the lower prevalence of autosplenectomy (56.2% vs 45.6%, p<0.05), painful crises per year, digital clubbing, chronic obstructive pulmonary disease (COPD), leg ulcers, stroke, chronic renal disease (CRD), and coronary heart disease (CHD) were all higher in the second group (p<0.05 for all).

Conclusion: The sickled or just hardened RBCs-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood. Although RBCs suspensions and corticosteroids in acute, and aspirin with an anti-inflammatory dose plus low-dose warfarin plus hydroxyurea both in acute and chronic phases decrease severity, survivals are still shortened in both genders, dramatically. In contrast to the lower prevalence of autosplenectomy, painful crises per year, digital clubbing, COPD, leg ulcers, stroke, CRD, and CHD were higher in the second group. So there may be an inverse relationship between prevalence of autosplenectomy and severity of SCDs, and spleen may act as a chronic inflammatory focus as a filter of blood for these abnormally hardened RBCs.

Key words: Sickle cell diseases, sickled or just hardened red blood cells, capillary endothelial edema, myocardial infarction, stroke, sudden deaths, autosplenectomy

Introduction

Chronic endothelial damage may be the main underlying cause of aging and death by causing end-organ failures (1). Much higher blood pressures (BPs) of the afferent vasculature may be the chief accelerating factor by causing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the destructive process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature which eventually reduces blood flow to the terminal organs, and increases systolic and decreases diastolic BPs further. Some of the well-known accelerating factors of the harmful process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, overweight, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), stroke, peripheric artery disease (PAD), mesenteric ischemia, osteoporosis, dementia, early aging, and premature death (2, 3). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of obesity, HT, DM, cirrhosis, COPD, CRD, CHD, stroke, PAD, mesenteric ischemia, osteoporosis, aging, and dementia-like end-organ insufficiencies, the endothelial changes can not be reversed due to their fibrotic natures, completely. The accelerating factors and terminal consequences of the harmful process are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature (4-6). Similarly, sickle cell diseases (SCDs) are highly destructive processes on vascular endothelium initiated at birth, and terminated with an advanced atherosclerosis-induced end-organ failure in much earlier ages of life (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably loss of elasticity instead of shape is the major problem because sickling is rare in peripheric blood samples of the patients with associated thalassemia minors (TMs), and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present even at birth, but exaggerated with inflammation, infections, and emotional stress of the body. The sickled or just hardened RBCs-induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia all over the body (9). As a difference from other causes of chronic endothelial damage, SCDs keep vascular endothelium particularly at the capillaries which are the actual distributors of the sickled or just hardened RBCs into the tissues (10, 11). The sickled or just hardened RBCs-induced chronic endothelial damage builds up an advanced atherosclerosis in much earlier ages of life. Vascular narrowings and occlusions-induced tissue ischemia and end-organ failures are the terminal results, so the life expectancy is decreased by 25 to 30 years for both genders in the SCDs (8).

Material and Methods

The study was performed in the Hematology Service of the Mustafa Kemal University between March 2007 and February 2014. All patients with the SCDs were studied. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Their medical histories including numbers of painful crises per year, units of transfused RBCs in their lives, smoking habit, regular alcohol consumption, leg ulcers, stroke, and surgical operations were learnt. Cases with a history of one pack-year were accepted as smokers, and cases with a history of one drink a day for one year were accepted as drinkers. A check up procedure including serum iron, total iron binding capacity, serum ferritin, serum creatinine value on three occasions, hepatic function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves, and to measure the systolic BPs of pulmonary artery, an abdominal ultrasonography, a Doppler ultrasonography to evaluate the portal blood flow in required cases, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips was performed. Other bone areas for avascular necrosis were scanned according to the patients' complaints. Cases with acute painful crises or any other inflammatory event were treated at first, and then the spirometric pulmonary function tests to diagnose COPD, the Doppler echocardiography to measure the systolic BPs of pulmonary artery, peripheral blood counts, renal and hepatic function tests, and measurement of serum ferritin were performed on the silent phase. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70% (12). Systolic BPs of the pulmonary artery of 40 mmHg or higher during the silent phase are accepted as pulmonary hypertension (13). Avascular necrosis of bones was detected via MRI (14). Autosplenectomy is diagnosed, ultrasonographically. CRD is diagnosed with a permanently elevated serum creatinine level which is 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females on the silent phase. Cirrhosis is diagnosed with hepatic function tests, ultrasonographic findings, ascites, and histologic procedure in case of requirement. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (15, 16). Associated TMs were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC, because the SCDs with associated TMs show a milder clinical profile than the sickle cell anemia (SCA) (Hb SS) alone (17). A stress electrocardiography is performed in cases with an abnormal electrocardiogram and/or angina pectoris. A coronary angiography is obtained just for the stress electrocardiography positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders of the cardiac walls. Eventually, patients with RBCs transfusions of less than 50 units in their lives were put into the first and 50 units or higher were put into the second groups, and were compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 316 patients with the SCDs (155 females and 161 males). There were 224 cases (70.8%) in the first and 92 cases (29.1%) in the second groups (p<0.001). There was a nonsignificant difference according to the prevalence of associated TMs between the groups (Table 1). Mean ages of the groups were similar, too (28.9 vs 30.0 years, respectively, p>0.05). The mean units of transfused RBCs were 12.9 vs 99.0, respectively (p<0.000). Interestingly, the male ratio was significantly higher in the second group (45.5% vs 64.1%, p<0.001). Although both the white blood cells (WBCs) and platelets (PLTs) counts of the peripheric blood were higher in the second group, the difference was only significant for the PLTs counts (p= 0.005), probably due to the small sample sizes of the study (Table 2). In contrast to the lower prevalence of autosplenectomy, painful crises per year, digital clubbing, COPD, leg ulcers, stroke, CRD, and CHD were all higher in the second group (p<0.05 for all) (Table 3). There was no patient with regular alcohol consumption among the study cases. Mean ages of the mortality were 29.5 ± 9.8 (19-50) vs 34.6 ± 6.7 (26-44) years in the first and second groups, respectively (p>0.05). Mean ages of mortality were 29.7 ± 9.6 (19-50) vs 33.3 ± 8.5 (21-44) years in males and females, respectively (p>0.05).

Table 1: Sickle cell patients with the units of red blood cells transfusions

Variables	Cases with RBC* transfusions of less than 50 units	*p*-value	Cases with RBC transfusions of 50 units or higher
Prevalence	***70.8% (224)***	***<0.001***	***29.1% (92)***
Mean RBCs units	***12.9 ± 11.2 (0-48)***	***<0.000***	***99.0 ± 56.5 (50-362)***
Mean age (year)	28.9 ± 9.9 (5-59)	ns†	30.0 ± 9.2 (9-56)
Male ratio	***45.5% (102)***	***<0.001***	***64.1% (59)***
TMs‡	62.0% (139)	ns	58.6% (54)
Autosplenectomy	***56.2% (126)***	***<0.05***	***45.6% (42)***

*Red blood cells †Nonsignificant (p>0.05) ‡Thalassemia minors

Table 2: Sickle cell patients with peripheric blood values

Variables	Cases with RBCs* transfusions of less than 50 units	*p*-value	Cases with RBCs transfusions of 50 units or higher
Mean WBCs† counts (µL)	14.931 ± 6.791 (2.460-39.200)	ns‡	15.346 ± 5.640 (1.580-36.900)
Mean PLTs§ counts (µL)	***435.670 ± 236.693 (48.000-1.827.000)***	***0.005***	***498.310 ± 224.570 (53.000-1.370.000)***
Mean hematocrit value (%)	23.8 ± 4.8 (11-42)	ns	23.7 ± 4.9 (13-39)

*Red blood cells †White blood cells ‡Nonsignificant (p>0.05) §Platelets

Table 3: Clinical features of the sickle cell patients

Variables	Cases with RBCs* transfusions of less than 50 units	*p*-value	Cases with RBCs transfusions of 50 units or higher
Painful crises per year	***3.8 ± 6.3 (0-52)***	***0.000***	***8.4 ± 10.9 (0-52)***
Smoking	12.0% (27)	ns†	17.3% (16)
Digital clubbing	***7.1% (16)***	***<0.01***	***15.2% (14)***
Pulmonary hypertension	11.6% (26)	ns	10.8% (10)
COPD‡	***6.6% (15)***	***<0.001***	***20.6% (19)***
Leg ulcers	***11.6% (26)***	***<0.01***	***21.7% (20)***
Stroke	***5.8% (13)***	***<0.05***	***11.9% (11)***
CRD§	***4.9% (11)***	***<0.001***	***14.1% (13)***
Avascular necrosis of bones	20.5% (46)	ns	17.3% (16)
Cirrhosis	4.4% (10)	ns	4.3% (4)
CHD¶	***4.0% (9)***	***<0.05***	***8.6% (8)***
Rheumatic heart disease	8.4% (19)	ns	3.2% (3)
Exitus	4.4% (10)	ns	5.4% (5)

*Red blood cells †Nonsignificant (p>0.05) ‡Chronic obstructive pulmonary disease §Chronic renal disease ¶Coronary heart disease

Discussion

Acute painful crises are the most disabling symptoms of the SCDs. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stress are the most common precipitating factors of the crises (18). Although the sickled or just hardened RBCs-induced capillary endothelial damage, inflammation, and edema are present even at birth, the increased basal metabolic rate during such stresses aggravates the sickling and capillary endothelial damage, inflammation, and edema, and may terminate with disseminated tissue hypoxia and multiorgan failures-induced sudden deaths in the SCDs (19). So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with the following crises by leaving some sequelae on the capillary endothelial system all over the body. After a period of time, the sequelae may terminate with sudden end-organ failures and death during a final acute painful crisis that may even be silent, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCDs. Unfortunately, most of the deaths develop just after the hospital admission, and majority of such cases are without hydroxyurea therapy (20). Rapid RBCs supports are usually life-saving for such patients, although preparation of RBCs units for transfusion usually takes time. Beside that RBCs supports in emergencies become much more difficult in such terminal patients due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBCs complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBCs transfusions should be kept just for acute events and emergencies in the SCDs (21). According to our experiences, simple and repeated transfusions are superior to RBCs exchange in the SCDs (22). First of all, preparation of one or two units of RBCs suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk cases. Secondly, transfusions of one or two units of RBCs suspensions in each time decrease the severity of pain and relax anxiety of the patients and their relatives because RBCs transfusions probably have the strongest analgesic effects during such crises. Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation in whole body. Thirdly, transfusions of lesser units of RBCs suspensions in each time by means of the simple transfusions decrease transfusions-related complications including infections, iron overload, and blood group mismatch. Fourthly, transfusions of RBCs suspensions in the secondary health centers prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices. On the other hand, pain is the result of complex and poorly understood interactions between RBCs, WBCs, PLTs, and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis by releasing

cytotoxic enzymes is unknown. The adverse actions of WBCs on the capillary endothelium are of particular interest with regard to the cerebrovascular diseases in the SCDs. For instance, leukocytosis even in the absence of an infection was an independent predictor of the severity of the SCDs, and it was associated with the higher risk of stroke (23). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Because of the severity of pain, narcotic analgesics are usually required to control them (24), but according to our long term experience, simple and repeated RBCs transfusions are much more effective than the narcotics to control the intolerable pain in the SCDs.

Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCDs (25). It is an orally-administered, cheap, safe, and effective drug, and it may be the only life-saving drug in the treatment of the SCDs (26, 27). It interferes with the cell division by blocking the formation of deoxyribonucleotides via inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the prevention of leukocytosis and thrombocytosis by blocking the DNA synthesis (28, 29). In this way, the inborn inflammatory and destructive process of the SCDs is suppressed to some extent. Due to the same action, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As also seen in the viral hepatitis cases, although presence of a continuous damage of sickled or just hardened RBCs on the capillary endothelium, the severity of destructive process may be exaggerated by the patients' own WBCs and PLTs. So suppression of proliferation of the WBCs and PLTs may limit the capillary endothelial damage, inflammation, edema, tissue ischemia, and end-organ failures in the body (30). Similarly, final Hb F levels in the hydroxyurea users did not differ from their pretreatment levels (31). The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with the SCA, and compared the results of patients treated with hydroxyurea or placebo (32). The study particularly researched effects of hydroxyurea on the painful crises, ACS, and requirement of RBCs transfusion. The outcomes were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was started for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations (32). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (32). But this study was performed just in severe SCA cases alone, and the rate of painful crises was decreased from 4.5 to 2.5 per year (32). Whereas we used all subtypes of the SCDs with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7 per year ($p<0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p<0.000$) (27). Parallel to our results, adults using hydroxyurea therapy for frequent painful crises appear to have a reduced mortality rate after a 9-year follow-up period (33). The complications start to be seen even in infancy in the SCDs. For instance, infants with lower hemoglobin values were more likely to have higher incidences of clinical events such as ACS, acute painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidence of them (34). Hydroxyurea therapy in early years of life may improve growth, and prevent end-organ failures. Transfusion programmes can also reduce all of the complications, but transfusions carry many risks including infections, iron overload, and development of allo-antibodies causing subsequent transfusions difficult. On the other hand, elevation of liver enzymes during some acute painful crises cannot be reversed by withdrawing of the hydroxyurea therapy alone, instead withdrawal of all of the medications was highy effective in such cases during the 20-year experience on such patients. After normalization of the liver enzymes, the essential medications must be started one by one, instead of all of them at the same time, again. Thus hydroxyurea must even be used during the acute painful crises. Additionally, we observed mild, moderate, or even severe bone marrow suppressions and pancytopenia in some patients using high-dose hydroxyurea (35 mg/kg/day). Interestingly, such cases were completely silent other than some signs and symptoms of anemia, and all of them were resolved completely just by giving a few-days break for the hydroxyurea therapy and starting with smaller doses again.

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) used to reduce inflammation and acute thromboembolic events. Although aspirin has similar anti-inflammatory effects with the other NSAIDs, it also suppresses the normal functions of PLTs, irreversibly. This property causes aspirin being different from other NSAIDs, which are reversible inhibitors. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin's ability to suppress the production of prostaglandins (PGs) and thromboxanes (TXs) is due to its irreversible inactivation of the COX enzyme required for PGs and TXs synthesis. PGs are the locally produced hormones with some diverse effects, including the transmission of pain into the brain and modulation of the hypothalamic thermostat and inflammation. TXs are responsible for the aggregation of PLTs to form blood clots. In another definition, low-dose aspirin use irreversibly blocks the formation of TXA2 in the PLTs, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLTs (8-9 days). Since PLTs do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin inhibited the enzyme. The antithrombotic property of aspirin is useful to reduce the incidence of myocardial infarction, transient ischemic attack, and stroke (35). Heart attacks are caused primarily by blood clots, and low dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction (36). According to

the medical literature, aspirin may also be effective in prevention of colorectal cancers (37). On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Reye syndrome is a rapidly worsening brain disease (38). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (39). The syndrome mostly affects children, but it can only affect fewer than one in a million children a year (39). It usually starts just after recovery from a viral infection, such as influenza or chicken pox (39). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (38). Although the liver toxicity typically occurs in the syndrome and the liver is enlarged in most cases, jaundice is usually not seen with it (38). Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling (39). Although death occurs in 20-40% of patients, about one third of survivors get a significant degree of brain damage (38). Interestingly, about 90% of cases in children are associated with an aspirin use (40). Due to the risk of Reye syndrome, the US Food and Drug Administration recommends that aspirin or aspirin-containing products should not be prescribed for febrile patients under the age of 16 years (41). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (38). When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% of Reye syndrome was seen (39). Due to the higher side effects of corticosteroids in long term, and due to the very low risk of Reye syndrome but much higher risk of death due to the SCDs even in children, aspirin should be added into the acute and chronic phase treatments of the SCDs with an anti-inflammatory dose even in childhood (42).

ACS is a significant cause of mortality in the SCDs (43). It occurs most often as a single episode, and a past history is associated with a higher mortality rate (43). Similarly, all of 14 patients with ACS had just a single episode, and two of them were fatal in spite of the immediate RBCs and ventilation supports and antibiotic therapy in the other study (44). The remaining 12 patients were still alive without a recurrence at the end of the 10-year follow up period (44). ACS is the most common between two to four years of age, and its incidence decreases with aging (45). As a difference from atherosclerotic consequences, the incidence of ACS did not show an increase with aging in the above study, and the mean ages of the patients with ACS and SCDs were similar (30.3 vs 30.5 years, $p>0.05$, respectively) (44). The decreased incidence with aging may be due to the high mortality rate during the first episode and/or an acquired immunity against various antigens, and/or decreased strength of immune response by aging. Probably, ACS shows an inborn severity of the SCDs, and the incidence of ACS is higher in severe patients such as patients with the SCA and higher WBCs counts (43, 45). According to our long term experiences on the SCDs, the increased metabolic rate during infections accelerates sickling, thrombocytosis, leukocytosis, and capillary endothelial damage and edema, and terminates with end-organ failures-induced sudden deaths. ACS may also be a collapse of the pulmonary vasculature during such infections, and the exaggerated immune response against the sickled or just hardened RBCs-induced diffuse capillary endothelial damage may be important in the high mortality rate. A preliminary result from the Multi-Institutional Study of Hydroxyurea in the SCDs indicating a significant reduction of episodes of ACS with hydroxyurea therapy suggests that a considerable number of episodes are exaggerated with the increased numbers of WBCs and PLTs (46). Similarly, we strongly recommend hydroxyurea for all patients that may also be the cause of low incidence of ACS in our follow up cases (2.7% in males and 3.7% in females) (44). Additionally, ACS did not show an infectious etiology in 66% (43, 45), and 12 of 27 cases with ACS had evidence of fat embolism in the other study (47). Beside that some authors indicated that antibiotics did not shorten the clinical course (48). RBCs support must be given as earliest as possible. RBCs support has the obvious benefits of decreasing sickle cell concentration directly, and suppressing bone marrow for the production of abnormal RBCs and excessive WBCs and PLTs. So they prevent further sickling-induced exaggerated capillary endothelial edema, disseminated tissue hypoxia, and end-organ failures-induced sudden deaths in the SCDs.

PHT is a condition of increased BPs within the arteries of the lungs. Shortness of breath, fatigue, chest pain, palpitation, swelling of legs and ankles, and cyanosis are common symptoms of PHT. Actually, it is not a diagnosis itself, instead solely a hemodynamic state characterized by resting mean pulmonary artery pressure of 25 mmHg or higher. An increase in pulmonary artery systolic pressure, estimated noninvasively by the echocardiography, helps to identify patients with PHT (49). The cause is often unknown. The underlying mechanism typically involves inflammation, fibrosis, and subsequent remodelling of the arteries. According to World Health Organization (WHO), there are five groups of PHT including pulmonary arterial hypertension, PHT secondary to left heart diseases, PHT secondary to lung diseases, chronic thromboembolic PHT, and PHT with unknown mechanisms (50). PHT affects about 1% of the world population, and its prevalence may reach 10% above the age of 65 years (51). Onset is typically seen between 20 and 60 years of age (50). The most common causes are CHD and COPD (50, 52). The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy (53). But the pulmonary vascular remodeling in the COPD may have a much more complex mechanism than just being the medial hypertrophy secondary to the long-lasting hypoxic vasoconstriction alone (53). In fact, all layers of the vessel wall appear to be involved with prominent intimal changes (53). The specific pathological picture could be explained by the combined effects of hypoxia, prolonged stretching of hyperinflated lungs-induced mechanical stress and inflammatory reaction, and the toxic effects of cigarette smoke (53). On the other hand, PHT is also a common consequence, and its prevalence was detected between 20% and 40% in the

SCDs (54, 55). Whereas we detected the ratio as 12.2% in the above study (44). The relatively younger mean ages of the study cases (30.8 years of males and 30.3 years of females) may be the cause of the lower prevalence of PHT in the above study (44). Although the higher prevalences of smoking and alcohol-like atherosclerotic risk factors in male gender, and although the higher prevalences of disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CRD, COPD, and stroke-like atherosclerotic consequences in male gender, and the male gender alone is being a risk factor for the systemic atherosclerosis, the similar prevalences of PHT and ACS in both genders also support nonatherosclerotic backgrounds of them in the SCDs in the above study (44). Similar to our result, women have up to four times of the risk of men for development of idiopathic PHT, and generally develop symptoms 10 years earlier than men in the literature with the unknown reasons, yet (56). Although COPD and CHD are the most common causes of PHT in the society (52, 57), and although COPD (25.2% vs 7.0%, $p<0.001$) and CHD (18.0% vs 13.2%, $p<0.05$) were higher in male gender in the above study (44), PHT was not higher in males, again. In another definition, PHT may have a sickled or just hardened RBCs-induced chronic thromboembolic whereas ACS may have an acute thromboembolic backgrounds in the SCDs (58, 59), because the mean age of ACS was lower than PHT (30.3 and 34.0 years, $p<0.05$) (44), but its mortality was much higher than PHT in the literature (43, 45, 50).

COPD is the third leading cause of death with various underlying etiologies all over the world (60, 61). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, male gender, excess weight, chronic inflammations, prolonged infections, and cancers may be the major underlying causes. Beside smoking, regular alcohol consumption is also an important risk factor for the pulmonary and systemic atherosclerotic processes, since COPD was one of the most common diagnoses in alcohol dependence (62). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (63). Probably an accelerated atherosclerotic process is the main structural background of functional changes seen with the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may just be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD (64, 65). For example, there may be close relationships between COPD, CHD, PAD, and stroke (66), and CHD was the most common cause of deaths in the COPD in a multi-center study of 5.887 smokers (67). When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again (67). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (68). Similarly, COPD may just be the pulmonary consequence of the systemic atherosclerotic process caused by the sickled or just hardened RBCs in the SCDs (60).

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (69). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (70). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (16). But according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, or hepatic diseases or smoking which are characterized by chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect each other's functions in a short period of time. Similarly, digital clubbing is also common in the SCDs, and its prevalence was 10.8% in the above study (44). It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillaries in the SCDs. Beside the effects of SCDs, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, $p<0.001$) may also show some additional risks of male gender in the systemic atherosclerosis (44).

Leg ulcers are seen in 10% to 20% of the SCDs (71), and the ratio was 13.5% in the above study (44). Its prevalence increases with aging, male gender, and SCA (72). Similarly, its ratio was higher in males (19.8% vs 7.0%, $p<0.001$), and mean age of the leg ulcer patients was higher than the remaining ones in the above study (35.3 vs 29.8 years, $p<0.000$) (44). The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (71). As an evidence of their atherosclerotic background, the leg ulcers occur in the distal segments of the body with a lesser collateral blood supply (71). The sickled or just hardened RBCs-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes, again (72). Prolonged exposure to the sickled or just hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCDs. The sickled or just hardened RBCs-induced venous insufficiencies may also accelerate the highly destructive process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood may be the main cause of delayed wound and fracture healings in the lower extremities. Smoking and alcohol may also have some additional atherosclerotic effects on the leg ulcers in males. Although presence of a continuous damage of hardened RBCs on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBCs counts were associated with lower crises rates, and if a

tissue infarct occurs, lower WBCs counts may decrease severity of pain and tissue damage (31). Because the main action of hydroxyurea may be the suppression of hyperproliferative WBCs and PLTs in the SCDs (30), prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBCs and PLTs counts-induced exaggerated capillary endothelial inflammation and edema.

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States (6). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being, and increased prevalence of excess weight all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it became the most common cause of chronic liver disease even at childhood, nowadays (73). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (73). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases (74). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (75). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCDs (76). Probably smoking also has a role in the inflammatory process of the capillary endothelium in liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (77). Increased oxidative stress, inactivation of antiproteases, and release of proinflammatory mediators may terminate with the systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious or inflammatory processes and cancers may also terminate with an accelerated atherosclerosis in whole body (78). For example, chronic hepatitis C virus (HCV) infection raised CIMT, and normalization of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (78, 79). As a result, cirrhosis may also be another atherosclerotic consequence of the SCDs.

The increased frequency of CRD can also be explained by aging of the human being, and increased prevalence of excess weight all over the world (80, 81). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, smoking, alcohol, inflammatory or infectious processes, and cancers may be the main underlying causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts. Excess weight-induced hyperglycemia, dyslipidemia, elevated BPs, and insulin resistance may cause tissue inflammation and immune cell activation (82). For example, age (p= 0.04), high-sensitivity C-reactive protein (p= 0.01), mean arterial BPs (p= 0.003), and DM (p= 0.02) had significant correlations with the CIMT (81). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BPs with excess weight (83). Excess weight also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (83). However, along with the increased BPs, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (84). With prolonged weight excess, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in cases with excess weight, CRD progresses much faster (83). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (85). Although some authors reported that alcohol was not related with the CRD (85), various metabolites of alcohol circulate even in the renal capillaries, and give harm to the renal capillary endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature (78). Although CRD is due to the atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (86), and the most common cause of death was the cardiovascular diseases in the CRD again (87). The sickled or just hardened RBCs-induced capillary endothelial damage may be the main cause of CRD in the SCDs, again (88).

CHD is the most common of the cardiovascular diseases (89). In adults who go to the emergency department with an unclear cause of pain, about 30% have pain due to CHD (90). Although half of cases are linked to genetics, physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, high BP, high blood glucose, dyslipidemia, smoking, alcohol, chronic inflammations, prolonged infections, and cancers may be the most common causes (91). It is the reduction of blood flow to the heart muscle due to build-up of atherosclerotic plaques secondary to the chronic inflammation of the arteries. It can present with stable angina, unstable angina, myocardial infarction, and sudden cardiac death (89). It is usually symptomatic with increased basal metabolic rate and emotional stress (92). It is the cause of deaths in 15.6% of all deaths, globally (92). So it is the most common cause of death in the world, nowadays (92). In the United States in 2010, about 20% of those over the age of 65 years had CHD, while it was present in 7% of those between the ages of 45 to 64 years, and 1.3% of those between 18 and 45 years of age, and the rates were higher among men (93). On average, women experience symptoms 10 years later than men, and women are less likely to recognize symptoms and seek treatment

(91). Women who are free of stress from work life show an increase in the diameter of their blood vessels, leading to decreased progression of atherosclerosis (94). Similarly, CHD was detected as 18.0% vs 13.2% in men and women in the above study , respectively ($p<0.05$) (44).

Stroke is an important cause of death, and usually develops as an acute thromboembolic event on the chronic atherosclerotic background. Aging, male gender, smoking, alcohol, and excess weight may be the major underlying causes. Stroke is a common complication of the SCDs, too (95, 96). We detected prevalences of stroke as 12.1% vs 7.5% in males and females in the above study, respectively ($p<0.05$) (44). Similar to the leg ulcers, stroke is particularly higher with the SCA and higher WBCs counts (97). Sickling-induced capillary endothelial damage, activations of WBCs, PLTs, and coagulation system, and hemolysis may cause inborn and severe capillary endothelial inflammation, edema, and fibrosis in the SCDs (98). Probably, stroke may not have a macrovascular origin in the SCDs, and diffuse capillary endothelial edema may be much more important (44). Infections, inflammations, medical or surgical emergencies, and emotional stress may precipitate stroke by increasing basal metabolic rate, sickling, and capillary endothelial edema. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed secondary to the increased WBCs and PLTs-induced exaggerated capillary endothelial inflammation and edema in the absence of prominent fibrosis, yet (46).

The venous capillary endothelium may also be involved in the SCDs (99). Normally, leg muscles pump veins against the gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and telangiectasias develop. DVT may also cause varicose veins and telangiectasias. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus physical examination must be performed in the upright position. Although the relatively younger mean ages and significantly lower body mass index of the SCDs cases in the literature (10), the prevalences of DVT and/or varices and/or telangiectasias of the lower limbs were relatively higher in the above study (9.0% vs 6.6% in males and females, $p>0.05$, respectively) (44), indicating an additional venous involvement of the SCDs. Similarly, priapism is the painful erection of penis that can not return to its flaccid state within four hours in the absence of any stimulation (100). It is an emergency because repeated damaging of the blood vessels may terminate with fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, and non-erectile penis (100). It is mainly seen with SCDs, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (101, 102). Ischemic (veno-occlusive), stuttering (recurrent ischemic), and nonischemic priapisms (arterial) are the three types (103). Ninety-five percent of clinically presented priapisms are the ischemic (veno-occlusive) disorders in which blood can not return adequately from the penis as in the SCDs, and they are very painful (100, 103). RBCs support is the treatment of choice in acute whereas hydroxyurea should be the treatment of choice in chronic phases (104). According to our experiences, hydroxyurea is highly effective for prevention of attacks and consequences of priapism if iniatiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillaries if initiated later in life.

Warfarin is an anticoagulant, and first came into large-scale commercial use in 1948 as a rat poison. It was formally approved as a medication to treat blood clots in human being by the U.S. Food and Drug Administration in 1954. In 1955, warfarin's reputation as a safe and acceptable treatment was bolstred when President Dwight David Eisenhower was treated with warfarin following a massive and highly publicized heart attack. Eisenhower's treatment kickstarted a transformation in medicine whereby CHD, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. Warfarin is found in the List of Essential Medicines of WHO. In 2020, it was the 58th most commonly prescribed medication in the United States. It does not reduce blood viscosity but inhibits blood coagulation. Warfarin is used to decrease the tendency for thrombosis, and it can prevent formation of future blood clots and reduce the risk of embolism. Warfarin is the best suited for anticoagulation in areas of slowly running blood such as in veins and the pooled blood behind artificial and natural valves, and in blood pooled in dysfunctional cardiac atria. It is commonly used to prevent blood clots in the circulatory system such as DVT and pulmonary embolism, and to protect against stroke in people who have atrial fibrillation (AF), valvular heart disease, or artificial heart valves. Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery. The warfarin initiation regimens are simple, safe, and suitable to be used in ambulatory and in patient settings (105). Warfarin should be initiated with a 5 mg dose, or 2 to 4 mg in the very elderly. In the protocol of low-dose warfarin, the target INR value is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR value is between 2.5 and 3.5 (106). When warfarin is used and international normalised ratio (INR) is in therapeutic range, simple discontinuation of the drug for five days is usually enough to reverse the effect, and causes INR to drop below 1.5 (107). Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Blood products should not be routinely used to reverse warfarin overdose, when vitamin K1 could work alone. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticlotting protein C and protein S are also inhibited, but to a lesser degree. A few days are required for full effect to occur, and these effects can last for up to five days. The consensus agrees that patient self-testing and patient self-management are effective methods of monitoring oral anticoagulation therapy, providing outcomes at least as good as, and possibly

better than, those achieved with an anticoagulation clinic. Currently available self-testing/self-management devices give INR results that are comparable with those obtained in laboratory testing. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is low with a yearly rate of 1-3% (108). All types of bleeding may occur, but the most severe ones are those involving the brain and spinal cord (108). The risk is particularly increased once the INR exceeds 4.5 (108). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (109). But thirteen publications from 11 cohorts including more than 48.500 total patients with more than 11.600 warfarin users were included in the meta-analysis (110). In patients with AF and non-end-stage CRD, warfarin resulted in a lower risk of ischemic stroke ($p= 0.004$) and mortality ($p<0.00001$), but had no effect on major bleeding ($p>0.05$) (110). Similarly, warfarin resumption is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (111). Death occured in 18.7% of patients who resumed warfarin and 32.3% who did not resume warfarin ($p= 0.009$) (111). Ischemic stroke occured in 3.5% of patients who resumed warfarin and 7.0% of patients who did not resume warfarin ($p= 0.002$) (111). Whereas recurrent ICH occured in 6.7% of patients who resumed warfarin and 7.7% of patients who did not resume warfarin without any significant difference in between ($p>0.05$) (111). On the other hand, patients with cerebral venous thrombosis (CVT) those were anticoagulated either with warfarin or dabigatran had low risk of recurrent venous thrombotic events (VTEs), and the risk of bleeding was similar in both regimens, suggesting that both warfarin and dabigatran are safe and effective for preventing recurrent VTEs in patients with CVT (112). Additionally, an INR value of about 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted in no increase in the number of men ever reporting minor bleeding episodes, although rectal bleeding occurs more frequently in those men who report this symptom (113). Non-rheumatic AF increases the risk of stroke, presumably from atrial thromboemboli, and long-term low-dose warfarin therapy is highly effective and safe in preventing stroke in such patients (114). There were just two strokes in the warfarin group (0.41% per year) compared with 13 strokes in the control group (2.98% per year) with a reduction of 86% in the risk of stroke ($p= 0.0022$) (114). Mortality was markedly lower in the warfarin group, too ($p= 0.005$) (114). The warfarin group had a higher rate of minor hemorrhage (38 vs 21 patients) but the frequency of bleedings that required hospitalization or transfusion was the same in both group ($p>0.05$) (114). Additionally, very-low-dose warfarin was a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer (115). The warfarin dose was 1 mg daily for 6 weeks, and was adjusted to maintain the INR value of 1.3 to 1.9 (115). The average daily dose was 2.6 mg, and the mean INR was 1.5 (115). On the other hand, new oral anticoagulants had a favourable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding (116). Interestingly, rivaroxaban and low dose apixaban were associated with increased risks of all cause mortality compared with warfarin (117). The mortality rate was 4.1% per year in the warfarin group, as compared with 3.7% per year with 110 mg of dabigatran and 3.6% per year with 150 mg of dabigatran ($p>0.05$ for both) in patients with AF in another study (118). On the other hand, warfarin induced skin necrosis is a rare complication with a prevalence of 0.01-0.1% (119). It usually occurs in patients with a deficiency of protein C, the innate anticoagulant that requires vitamin K1-dependent carboxylation for its activity. Because warfarin initially decreases protein C levels faster than the other coagulation factors, it can paradoxically increase the blood's tendency to coagulate. Just to prevent the side effect, heparin should be given together with warfarin during the initiation regimens. But warfarin induced skin necrosis often occurs in association with the administration of a large initial loading dose of warfarin (119).

The spleen is found in all vertebrates with a similar structure to the lymph nodes. It acts primarily as a blood filter, and removes old and abnormal RBCs and recycles the iron. Additionally, it synthesizes antibodies and removes antibody-coated bacteria and blood cells from the circulation. Like the thymus, the spleen has only efferent lymphatic vessels, and it is the major lymphatic organ of the body. It has a central role in the reticuloendothelial system, and retains the ability to produce lymphocytes after birth. The spleen acts as a pool of peripheral blood cells which are released in case of a need. For example, it stores half of the body's monocytes in mice (120). In case of an injury, the monocytes migrate to the injured tissues and transform into dendritic cells and macrophages, and assist tissue healing (121). It was detected in the present study that 56.2% of cases of the first and 45.6% of cases of the second groups ($p<0.05$) had autosplenectomy, and these ratios were the highest ones among all other affected tissues of the body. So the spleen is probably the primarily affected organ in the SCDs, and it may act as a chronic inflammatory focus, particularly due to the high WBCs content. Although, a 28-year follow-up study of 740 veterans of World War II with surgical removal of spleen on the battlefield found that they showed significant excesses of mortality from pneumonia and CHD (122), the prevalence of CHD were higher in the second group with the lower prevalence of autosplenectomy in the present study.

As a conclusion, the sickled or just hardened RBCs-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood. Although RBCs suspensions and corticosteroids in acute, and aspirin with an anti-inflammatory dose plus low-dose warfarin plus hydroxyurea both in acute and chronic phases decrease severity, survivals are still shortened in both genders, dramatically. In contrast to the lower prevalence of autosplenectomy, painful crises per year, digital clubbing, COPD, leg ulcers, stroke, CRD, and CHD were all higher in the second group. So there may be an inverse relationship between prevalence of autosplenectomy and severity of SCDs, and spleen may act as a chronic inflammatory focus as a filter of blood for these abnormally hardened RBCs.

References

1. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol 2003; 42(7): 1149-60.
2. Helvaci MR, Tuncsezen UK, Seckin K, Piral K, Seyhan S, Karabacak AD, et al. Fasting plasma glucose may behave as a positive in mild but as a negative acute phase reactant in moderate and severe inflammatory disorders. World Family Med 2023; 21(6): 36-45.
3. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365(9468): 1415-28.
4. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106(25): 3143-421.
5. Helvaci MR, Aydin LY, Aydin Y. Digital clubbing may be an indicator of systemic atherosclerosis even at microvascular level. HealthMED 2012; 6(12): 3977-81.
6. Anderson RN, Smith BL. Deaths: leading causes for 2001. Natl Vital Stat Rep 2003; 52(9): 1-85.
7. Helvaci MR, Gokce C, Davran R, Akkucuk S, Ugur M, Oruc C. Mortal quintet of sickle cell diseases. Int J Clin Exp Med 2015; 8(7): 11442-8.
8. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994; 330(23): 1639-44.
9. Helvaci MR, Yaprak M, Abyad A, Pocock L. Atherosclerotic background of hepatosteatosis in sickle cell diseases. World Family Med 2018; 16(3): 12-8.
10. Helvaci MR, Kaya H. Effect of sickle cell diseases on height and weight. Pak J Med Sci 2011; 27(2): 361-4.
11. Helvaci MR, Aydin Y, Ayyildiz O. Hydroxyurea may prolong survival of sickle cell patients by decreasing frequency of painful crises. HealthMED 2013; 7(8): 2327-32.
12. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013; 187(4): 347-65.
13. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009; 179(7): 615-21.
14. Mankad VN, Williams JP, Harpen MD, Manci E, Longenecker G, Moore RB, et al. Magnetic resonance imaging of bone marrow in sickle cell disease: clinical, hematologic, and pathologic correlations. Blood 1990; 75(1): 274-83.
15. Vandemergel X, Renneboog B. Prevalence, aetiologies and significance of clubbing in a department of general internal medicine. Eur J Intern Med 2008; 19(5): 325-9.
16. Schamroth L. Personal experience. S Afr Med J 1976; 50(9): 297-300.
17. Helvaci MR, Aydin Y, Ayyildiz O. Clinical severity of sickle cell anemia alone and sickle cell diseases with thalassemias. HealthMED 2013; 7(7): 2028-33.
18. Parfrey NA, Moore W, Hutchins GM. Is pain crisis a cause of death in sickle cell disease? Am J Clin Pathol 1985; 84: 209-12.
19. Helvaci MR, Camlibel M, Yuksek B, Sevinc A, Camci C, Abyad A, et al. Acute painful crises may be causes of sudden deaths in sickle cell diseases. World Family Med 2023; 21(5): 37-49.
20. Helvaci MR, Ayyildiz O, Gundogdu M. Red blood cell transfusions and survival of sickle cell patients. HealthMED 2013; 7(11): 2907-12.
21. Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ, et al. Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med 2000; 342: 83-9.
22. Helvaci MR, Atci N, Ayyildiz O, Muftuoglu OE, Pocock L. Red blood cell supports in severe clinical conditions in sickle cell diseases. World Family Med 2016; 14(5): 11-8.
23. Balkaran B, Char G, Morris JS, Thomas PW, Serjeant BE, Serjeant GR. Stroke in a cohort of patients with homozygous sickle cell disease. J Pediatr 1992; 120: 360-6.
24. Cole TB, Sprinkle RH, Smith SJ, Buchanan GR. Intravenous narcotic therapy for children with severe sickle cell pain crisis. Am J Dis Child 1986; 140: 1255-9.
25. Yawn BPs, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 2014; 312(10): 1033-48.
26. Helvaci MR, Ayyildiz O, Gundogdu M. Hydroxyurea therapy and parameters of health in sickle cell patients. HealthMED 2014; 8(4): 451-6.
27. Helvaci MR, Tonyali O, Yaprak M, Abyad A, Pocock L. Increased sexual performance of sickle cell patients with hydroxyurea. World Family Med 2019; 17(4): 28-33.
28. Miller BA, Platt O, Hope S, Dover G, Nathan DG. Influence of hydroxyurea on fetal hemoglobin production in vitro. Blood 1987; 70(6): 1824-9.
29. Platt OS. Is there treatment for sickle cell anemia? N Engl J Med 1988; 319(22): 1479-80.
30. Helvaci MR, Aydogan F, Sevinc A, Camci C, Dilek I. Platelet and white blood cell counts in severity of sickle cell diseases. HealthMED 2014; 8(4): 477-82.
31. Charache S. Mechanism of action of hydroxyurea in the management of sickle cell anemia in adults. Semin Hematol 1997; 34(3): 15-21.
32. Charache S, Barton FB, Moore RD, Terrin ML, Steinberg MH, Dover GJ, et al. Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive "switching" agent. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Medicine (Baltimore) 1996; 75(6): 300-26.
33. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMA 2003; 289(13): 1645-51.
34. Lebensburger JD, Miller ST, Howard TH, Casella JF, Brown RC, Lu M, et al; BABY HUG Investigators. Influence of severity of anemia on clinical findings in

infants with sickle cell anemia: analyses from the BABY HUG study. Pediatr Blood Cancer 2012; 59(4): 675-8.
35. Toghi H, Konno S, Tamura K, Kimura B, Kawano K. Effects of low-to-high doses of aspirin on platelet aggregability and metabolites of thromboxane A2 and prostacyclin. Stroke 1992; 23(10): 1400-3.
36. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 373(9678): 1849-60.
37. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol 2012; 13(5): 518-27.
38. Schrör K. Aspirin and Reye syndrome: a review of the evidence. Paediatr Drugs 2007; 9(3): 195-204.
39. Pugliese A, Beltramo T, Torre D. Reye's and Reye's-like syndromes. Cell Biochem Funct 2008; 26(7): 741-6.
40. Hurwitz ES. Reye's syndrome. Epidemiol Rev 1989; 11: 249-53.
41. Macdonald S. Aspirin use to be banned in under 16 year olds. BMJ 2002; 325(7371): 988.
42. Meremikwu MM, Okomo U. Sickle cell disease. BMJ Clin Evid 2011; 2011: 2402.
43. Poncz M, Kane E, Gill FM. Acute chest syndrome in sickle cell disease: etiology and clinical correlates. J Pediatr 1985; 107(6): 861-6.
44. Helvaci MR, Tuncsezen UK, Seckin K, Piral K, Seyhan S, Karabacak AD, et al. An exaggerated capillary endothelial edema may be the cause of sudden deaths in sickle cell diseases. World Family Med 2023; 21(6): 23-35.
45. Sprinkle RH, Cole T, Smith S, Buchanan GR. Acute chest syndrome in children with sickle cell disease. A retrospective analysis of 100 hospitalized cases. Am J Pediatr Hematol Oncol 1986; 8(2): 105-10.
46. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med 1995; 332(20): 1317-22.
47. Vichinsky E, Williams R, Das M, Earles AN, Lewis N, Adler A, et al. Pulmonary fat embolism: a distinct cause of severe acute chest syndrome in sickle cell anemia. Blood 1994; 83(11): 3107-12.
48. Charache S, Scott JC, Charache P. ''Acute chest syndrome'' in adults with sickle cell anemia. Microbiology, treatment, and prevention. Arch Intern Med 1979; 139(1): 67-9.
49. Gordeuk VR, Castro OL, Machado RF. Pathophysiology and treatment of pulmonary hypertension in sickle cell disease. Blood 2016; 127(7): 820-8.
50. Simonneau G, Gatzoulis MA, Adantia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J American College Cardiol 2013; 62(25): 34-41.
51. Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, et al. A global view of pulmonary hypertension. Lancet Respir Med 2016; 4(4): 306-22.
52. Naeije R, Barbera JA. Pulmonary hypertension associated with COPD. Crit Care 2001; 5(6): 286-9.
53. Peinado VI, Barbera JA, Abate P, Ramirez J, Roca J, Santos S, et al. Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999; 59: 1605-11.
54. Helvaci MR, Arslanoglu Z, Celikel A, Abyad A, Pocock L. Pathophysiology of pulmonary hypertension in sickle cell diseases. Middle East J Intern Med 2018; 11(2): 14-21.
55. Castro O. Systemic fat embolism and pulmonary hypertension in sickle cell disease. Hematol Oncol Clin North Am 1996; 10(6): 1289-303.
56. Cunningham CM, Li M, Ruffenach G, Doshi M, Aryan L, Hong J, et al. Y-chromosome gene, Uty, protects against pulmonary hypertension by reducing proinflammatory chemokines. Am J Respir Crit Care Med 2022; 206(2): 186-96.
57. Duffels MG, Engelfriet PM, Berger RM, van Loon RL, Hoendermis E, Vriend JW, et al. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. Int J Cardiol 2007; 120(2): 198-204.
58. Oudiz RJ. Classification of pulmonary hypertension. Cardiol Clin 2016; 34(3): 359-61.
59. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 2004; 350(9): 886-95.
60. Helvaci MR, Erden ES, Aydin LY. Atherosclerotic background of chronic obstructive pulmonary disease in sickle cell patients. HealthMED 2013; 7(2): 484-8.
61. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: definition, assessment, and prevention. Lancet 2015; 385(9979): 1778-88.
62. Schoepf D, Heun R. Alcohol dependence and physical comorbidity: Increased prevalence but reduced relevance of individual comorbidities for hospital-based mortality during a 12.5-year observation period in general hospital admissions in urban North-West England. Eur Psychiatry 2015; 30(4): 459-68.
63. Singh G, Zhang W, Kuo YF, Sharma G. Association of Psychological Disorders With 30-Day Readmission Rates in Patients With COPD. Chest 2016; 149(4): 905-15.
64. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998; 279(18): 1477-82.
65. Mannino DM, Watt G, Hole D, Gillis C, Hart C, McConnachie A, et al. The natural history of chronic obstructive pulmonary disease. Eur Respir J 2006; 27(3): 627-43.
66. Mapel DW, Hurley JS, Frost FJ, Petersen HV, Picchi MA, Coultas DB. Health care utilization in chronic obstructive pulmonary disease. A case-control study in a health maintenance organization. Arch Intern Med 2000; 160(17): 2653-58.

67. Anthonisen NR, Connett JE, Enright PL, Manfreda J; Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002; 166(3): 333-9.
68. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA; TORCH Clinical Endpoint Committee. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. Thorax 2007; 62(5): 411-5.
69. Myers KA, Farquhar DR. The rational clinical examination. Does this patient have clubbing? JAMA 2001; 286(3): 341-7.
70. Toovey OT, Eisenhauer HJ. A new hypothesis on the mechanism of digital clubbing secondary to pulmonary pathologies. Med Hypotheses 2010; 75(6): 511-3.
71. Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. Adv Skin Wound Care 2004: 17(8); 410-6.
72. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg ulcers in sickle cell disease. Am J Hematol 2010; 85(10): 831-3.
73. Bhatia LS, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? Eur Heart J 2012; 33(10): 1190-1200.
74. Pacifico L, Nobili V, Anania C, Verdecchia P, Chiesa C. Pediatric nonalcoholic fatty liver disease, metabolic syndrome and cardiovascular risk. World J Gastroenterol 2011; 17(26): 3082-91.
75. Mawatari S, Uto H, Tsubouchi H. Chronic liver disease and arteriosclerosis. Nihon Rinsho 2011; 69(1): 153-7.
76. Bugianesi E, Moscatiello S, Ciaravella MF, Marchesini G. Insulin resistance in nonalcoholic fatty liver disease. Curr Pharm Des 2010; 16(17): 1941-51.
77. Helvaci MR, Aydin LY, Aydin Y. Chronic obstructive pulmonary disease may be one of the terminal end points of metabolic syndrome. Pak J Med Sci 2012; 28(3): 376-9.
78. Mostafa A, Mohamed MK, Saeed M, Hasan A, Fontanet A, Godsland I, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors. Gut 2010; 59(8): 1135-40.
79. Helvaci MR, Ayyildiz O, Gundogdu M, Aydin Y, Abyad A, Pocock L. Hyperlipoproteinemias may actually be acute phase reactants in the plasma. World Family Med 2018; 16(1): 7-10.
80. Levin A, Hemmelgarn B, Culleton B, Tobe S, McFarlane P, Ruzicka M, et al. Guidelines for the management of chronic kidney disease. CMAJ 2008; 179(11): 1154-62.
81. Nassiri AA, Hakemi MS, Asadzadeh R, Faizei AM, Alatab S, Miri R, et al. Differences in cardiovascular disease risk factors associated with maximum and mean carotid intima-media thickness among hemodialysis patients. Iran J Kidney Dis 2012; 6(3): 203-8.
82. Xia M, Guerra N, Sukhova GK, Yang K, Miller CK, Shi GP, et al. Immune activation resulting from NKG2D/ligand interaction promotes atherosclerosis. Circulation 2011; 124(25): 2933-43.
83. Hall JE, Henegar JR, Dwyer TM, Liu J, da Silva AA, Kuo JJ, et al. Is obesity a major cause of chronic kidney disease? Adv Ren Replace Ther 2004; 11(1): 41-54.
84. Nerpin E, Ingelsson E, Risérus U, Helmersson-Karlqvist J, Sundström J, Jobs E, et al. Association between glomerular filtration rate and endothelial function in an elderly community cohort. Atherosclerosis 2012; 224(1): 242-6.
85. Stengel B, Tarver-Carr ME, Powe NR, Eberhardt MS, Brancati FL. Lifestyle factors, obesity and the risk of chronic kidney disease. Epidemiology 2003; 14(4): 479-87.
86. Bonora E, Targher G. Increased risk of cardiovascular disease and chronic kidney disease in NAFLD. Nat Rev Gastroenterol Hepatol 2012; 9(7): 372-81.
87. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006; 17(7): 2034-47.
88. Helvaci MR, Aydin Y, Aydin LY. Atherosclerotic background of chronic kidney disease in sickle cell patients. HealthMED 2013; 7(9): 2532-7.
89. Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. Nat Rev Cardiol 2014; 11(5): 276-89.
90. Kontos MC, Diercks DB, Kirk JD. Emergency department and office-based evaluation of patients with chest pain. Mayo Clin Proc 2010; 85(3): 284-99.
91. Dai X, Wiernek S, Evans JP, Runge MS. Genetics of coronary artery disease and myocardial infarction. World J Cardiol 2016; 8(1): 1-23.
92. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388(10053): 1459-544.
93. Prevalence of coronary heart disease--United States, 2006-2010. MMWR Morb Mortal Wkly Rep 2011; 60(40): 1377-81.
94. Wang HX, Leineweber C, Kirkeeide R, Svane B, Schenck-Gustafsson K, Theorell T, et al. Psychosocial stress and atherosclerosis: family and work stress accelerate progression of coronary disease in women. The Stockholm Female Coronary Angiography Study. J Intern Med 2007; 261(3): 245-54.
95. DeBaun MR, Gordon M, McKinstry RC, Noetzel MJ, White DA, Sarnaik SA, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med 2014; 371(8): 699-710.
96. Gueguen A, Mahevas M, Nzouakou R, Hosseini H, Habibi A, Bachir D, et al. Sickle-cell disease stroke throughout life: a retrospective study in an adult referral center. Am J Hematol 2014; 89(3): 267-72.
97. Majumdar S, Miller M, Khan M, Gordon C, Forsythe A, Smith MG, et al. Outcome of overt stroke in sickle cell anaemia, a single institution's experience. Br J Haematol 2014; 165(5): 707-13.
98. Kossorotoff M, Grevent D, de Montalembert M. Cerebral vasculopathy in pediatric sickle-cell anemia. Arch Pediatr 2014; 21(4): 404-14.

99. Helvaci MR, Gokce C, Sahan M, Hakimoglu S, Coskun M, Gozukara KH. Venous involvement in sickle cell diseases. Int J Clin Exp Med 2016; 9(6): 11950-7.
100. Kaminsky A, Sperling H. Diagnosis and management of priapism. Urologe A 2015; 54(5): 654-61.
101. Anele UA, Le BV, Resar LM, Burnett AL. How I treat priapism. Blood 2015; 125(23): 3551-8.
102. Bartolucci P, Lionnet F. Chronic complications of sickle cell disease. Rev Prat 2014; 64(8): 1120-6.
103. Broderick GA. Priapism and sickle-cell anemia: diagnosis and nonsurgical therapy. J Sex Med 2012; 9(1): 88-103.
104. Ballas SK, Lyon D. Safety and efficacy of blood exchange transfusion for priapism complicating sickle cell disease. J Clin Apher 2016; 31(1): 5-10.
105. Mohamed S, Fong CM, Ming YJ, Kori AN, Wahab SA, Ali ZM. Evaluation of an initiation regimen of warfarin for international normalized ratio target 2.0 to 3.0. J Pharm Technol 2021; 37(6): 286-92.
106. Chu MWA, Ruel M, Graeve A, Gerdisch MW, Ralph J, Damiano Jr RJ, Smith RL. Low-dose vs standard warfarin after mechanical mitral valve replacement: A randomized trial. Ann Thorac Surg 2023; 115(4): 929-38.
107. Crowther MA, Douketis JD, Schnurr T, Steidl L, Mera V, Ultori C, et al. Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneously vitamin K in the treatment of warfarin-associated coagulopathy. A randomized, controlled trial. Ann Intern Med 2002; 137(4): 251-4.
108. Brown DG, Wilkerson EC, Love WE. A review of traditional and novel oral anticoagulant and antiplatelet therapy for dermatologists and dermatologic surgeons. J Am Acad Dermatol 2015; 72(3): 524-34.
109. Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. CMAJ 2007; 177(4): 347-51.
110. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-analysis of observational studies. Chest 2016; 149(4): 951-9.
111. Chai-Adisaksopha C, Lorio A, Hillis C, Siegal D, Witt DM, Schulman S, et al. Warfarin resumption following anticoagulant-associated intracranial hemorrhage: A systematic review and meta-analysis. Thromb Res 2017; 160: 97-104.
112. Ferro JM, Coutinho JM, Dentali F, Kobayashi A, Alasheev A, Canhao P, et al. Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: A randomized clinical trial. JAMA Neurol 2019; 76(12): 1457-65.
113. Meade TW. Low-dose warfarin and low-dose aspirin in the primary prevention of ischemic heart disease. Am J Cardiol 1990; 65(6): 7C-11C.
114. Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, Maraventano SW, et al. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990; 323(22): 1505-11.
115. Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanya A, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. Lancet 1994; 343(8902): 886-9.
116. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014; 383(9921): 955-62.
117. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. BMJ 2018; 362: k2505.
118. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361(12): 1139-51.
119. Chan YC, Valenti D, Mansfield AO, Stansby G. Warfarin induced skin necrosis. Br J Surg 2000; 87(3): 266-72.
120. Swirski FK, Nahrendorf M, Etzrodt M, Wildgruber M, Cortez-Retamozo V, Panizzi P, et al. Identification of splenic reservoir monocytes and their deployment to inflammatory sites. Science 2009; 325(5940): 612-6.
121. Jia T, Pamer EG. Immunology. Dispensable but not irrelevant. Science 2009; 325(5940): 549-50.
122. Robinette CD, Fraumeni Jr JF. Splenectomy and subsequent mortality in veterans of the 1939-45 war. Lancet 1977; 2(8029): 127-9.

The clinical significance of thyroid antibodies in non-thyroid diseases

Almoutaz Alkhier Ahmed Abdulrahman

Senior Family Medicine Specialist .
Nad alhamar Health Center, Dubai Academic and Health Corporation

Correspondence:
Dr. Almoutaz Alkhier Ahmed Abdulrahman
Senior Family Medicine Specialist .FRCGP[int],MSc diabetes, MSc endocrinology ,
Pg Cer medical education, FASLM.
Nad alhamar Health Center.
Dubai Academic and Health Corporation
Email: Khier2@yahoo.com

Received: July 2023. Accepted: August 2023; Published: September 1, 2023.
Citation: Almoutaz Alkhier Ahmed Abdulrahman. The clinical significance of thyroid antibodies in non-thyroid diseases. World Family Medicine. August 2023; 21(8): 33-43. DOI: 10.5742/MEWFM.2023.95256178

Abstract

Background: Epidemiological studies showed that the population has a high immune disease prevalence, and thyroid immune diseases are among the top autoimmune disorders seen in clinical practice. Investigators noticed an association between some non-thyroidal conditions with thyroid autoantibodies, and some of the outcomes of these non–thyroid diseases may be affected by the presence of these thyroid antibodies.

Objective: To investigate the association of thyroid autoantibodies with non-thyroidal diseases and their clinical significance, such as the positive or negative impact on the disease outcome.

Methods: A systematic literature review was done using selection criteria with the help of search questions. Multiple search engines were searched for eligible articles. Articles were filtered based on the inclusion and exclusion criteria. Data were extracted and analysed for clinical or statistical significance between case and control groups in selected studies.

Results: Eighteen (18) articles fulfilled the inclusion and exclusion criteria; 44.4% were analytical cross-section studies, 5% were prospective studies, 5.5% were meta-analysis studies, 5.5% were case-control studies, and 16.7% were retrospective studies. The included studies aimed to find an association between TPO-Ab, TG-Ab, and some non-thyroidal diseases such as Vitamin D deficiency, Allergic diseases, mood disorders, women's reproductive system diseases, abortion, systemic lupus erythematosus, rheumatoid disease, Celiac disease, Type 1 diabetes, and breast cancer. The ORs in the included studies were > 1, and the confidence intervals did not cross 1, which means both clinical (favour positivity in case groups) and statistical (existing difference between case and control groups) significance. The "I^2 value", which is an indicator for heterogeneity of the studies included in the meta-analysis, was high in the included research (>50%), which indicates heterogeneity of the included study. TPO-Ab was a favourable prognostic indicator in cases of breast cancer. Relative risk (RR) was used to assess the disease-free survival rate in subjects with breast carcinoma. The survival rate between patients with TPO-Ab > 0.3u/ml and <0.3u/ml was statistically significant (P value 0.016), and relative risk = 3.46.

Conclusion: Thyroid autoantibodies are not exclusively markers of thyroid autoimmune diseases but can also be markers and indicators of non-thyroidal illnesses. Their presence could be either a favourable prognostic indicator, as with breast carcinoma cases or unfavourable prognostic indicator, as with abortion. Further studies are recommended to explore more associations.

Key words: Thyroid, thyroid autoantibodies, thyroid diseases, non-thyroidal diseases.

Introduction

Thyroid hormones are the end products of the thyroid gland, which are transferred to the different parts of the body where different enzymes known as deiodinase enzymes work to form the active or inactive form of the thyroid hormones needed to regulate different human metabolic actions (1). The thyroid gland contains different antigens, which could be the site of autoimmune reactions and form specific antibodies (2). These antibodies may act within the thyroid gland and affect its function either as hypo or hyper-function or be found in the blood associated with other non-autoimmune thyroid diseases (2).

Three essential thyroid antigens are involved in thyroid autoimmunity: thyroglobulin, thyroid stimulating hormone receptor, and thyroid peroxidase (TPO).

Thyroglobulin is a protein of 670KDa composed of two polypeptide chains from which the thyroid hormones (T3 and T4) are produced. Scientists discovered about 40 antigenic epitopes on human thyroglobulin; 4-6 epitopes are believed to be recognized by B cells and involved in antibody response to thyroglobulin (3). There is evidence that the iodination of thyroglobulin results in the reconfiguration of the molecule and change in antigenic epitopes. The presence of these multi-configuration, iodine, TPO, and hydrogen peroxide is thought to be the thyroid autoimmune response trigger (4).

Thyroid Peroxidase is the second antigen (5). It was known as the thyroid microsomal antigen. It was identified as TPO in 1985. It is composed of 107KDa; 933 amino acid residue glycoprotein presents as a dimer on the apical surface of thyroid follicular cells and cytoplasm. Multiple B cell reactive epitopes are present in human TPO, and they are genetically determined and remain staple within each patient.

The third antigen is the Thyroid Stimulating Hormone – receptor protein. It is a 74 amino acids glycoprotein. It has two subunits, the extracellular ‘’A’’ subunit and the transmembrane ‘’B’’ subunit. There is controversy about whether specific epitopes exist for these antibodies (6). However, the majority believe there are no specific epitopes for the interaction of these antibodies on the protein. This antigen is exclusively associated with thyroid diseases. There are other antigens, but fewer will be described, like the sodium–iodide symporter. The aim of this review is to find the clinical significance of these antibodies’ presence in conditions unrelated to thyroid diseases.

Methodology

A systematic literature review was conducted. This review discussed thyroid autoantibodies’ presence and clinical significance in non-thyroidal diseases. A personal computer was used to search using the search question to select studies based on the inclusion criteria. A constructed search strategy using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) model was followed. PRISMA flow diagram (Figure 1) delineates the number of studies found in the search, included and excluded, and the reasons for exclusions (7). PubMed, Google scholar and Cochrane Library were used as search engines. PubMed was the leading search engine used. The second step was to list the detected articles to remove duplicated titles and filter them based on selection criteria. In articles with titles irrelevant to the search question, abstracts were screened for any relation to the question; if not, the articles were excluded. Articles were then downloaded to review the full text. The third step was to review the full text to determine if the inclusion and exclusion criteria were satisfied. A double review was conducted if there was any doubt about the inclusion or exclusion criteria in any article. The following were the inclusion criteria; studies published in English without limited publication date, studies that involved human participants, studies that included only patients with euthyroid function not in current treatment for thyroid dysfunction, studies with free access to full text, studies with Systematic reviews, meta-analysis, case-control, cohort, and cross-section study designs. The following were the exclusion criteria; studies not showing details such as conference abstracts, studies included patients with thyroid diseases or receiving medicine for thyroid dysfunction, review articles, case studies, or case series studies, as these types of studies do not investigate association or correlation (8). Data from the included studies were extracted and discussed in studies’ summaries.

Results

Eighteen (n=18) studies were included after they met the selection criteria. Eight (n=8) were analytical cross-section studies, one (n=1) was a case-control study, one (n=1) was a meta-analysis study, five (n=5) were prospective, three (n=3) were retrospective, and one (n=1) was a case-control study (Table 1). All studies included patients with euthyroid function assessed by triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) or known to be euthyroid by researchers. The studies included 7063 patients (case groups) and 3966 healthy participants (control groups) (P <0.001) (Table 1). Five studies (n=5) included children only, and thirteen (n=13) included adults > 12 years (Table 1). Six (n=6) studies included only females, and twelve (n=12) included males and females (Table 1). No studies included only males (Table 1). One study compared populations from different geographical zones (Table 1). All studies used Thyroid peroxidase antibodies (TPO-ab) and thyroglobulin antibodies (TG-Ab) as thyroid autoimmunity markers. All studies included only patients with euthyroid

Figure 1: PRISMA Flow Diagram

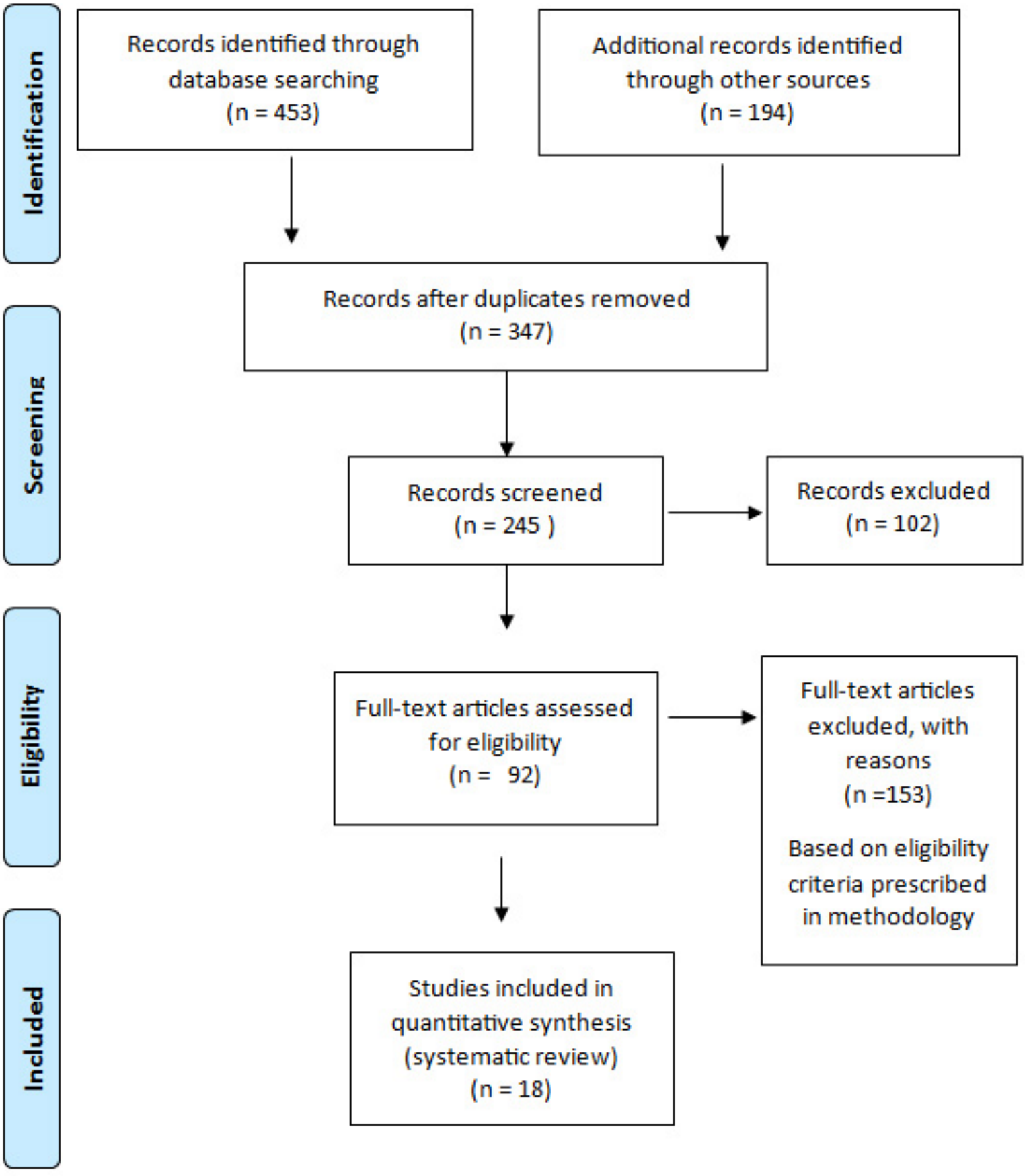


Table 1: Studies included in the review

Study	type	Date of publication	Population	Disease investigated	Statistical tool(s)
Carta et al (9)	Analytic Cross-sectional study	2004	222 adults	Mood disorders	Prevalence , OR,CI95%, P value, MVLR
Snijders et al (19)	Analytic Cross-sectional study	2020	1021 case group ,373 control group. Adults	Bipolar disorders	OR, P value
Shin et al (11)	Retrospective study	2014	304 participants. adults	Vit D deficiency	P value, correlation (r)
Darban et al (12)	Analytic cross section study	2022	35 case group, 35 control group. Adults	Vit D deficiency	OR, CI 95%, P value
Zhang et al (13)	Analytic cross sectional study	2022	217 case group, 217 control group. Adults	Allergic diseases	P value, CI 95%
Ismaeil et al (14)	Case control study	2020	25 case group, 25 control group. Children	Bronchial asthma	P value, correlation (r).
Levy et al (15)	Cohort prospective study	2003	187. Children	Chronic urticaria	Incidence rate
Zhang et el (16)	Analytic cross sectional study	2022	1100 case group, 1100 control group	Chronic spontaneous urticaria	OR, P value, correlation (r)
Singh et al (17)	Cohort retrosepctive study	1995	487 participants. Adult women	Reproductive failure	P value
Janssen et al (18)	Cohort prospective study	2004	175 case group, 168 control group.	Polycystic ovary	Incidence rate, P value
Wang et al (19)	Cohort retrospective study	2018	121 case group, 408 control group. Adult women	Female infertility	Incidence rate, P value
Stagnaro et al (20)	Cohort Retrospective study	1990	552 adult women	Miscarriage in at risk pregnancy	Prevalence, P value
Smyth et al (23)	Analytic cross sectional study	1998	478 case group, 222 control group	Breast cancer	P value, RR
Sharifi,Ghasemi and Mousavinasab (24)	Analytic cross sectional study	2008	91 case ,163 controls	Type 1 diabetes	P value, r, 95% CI
Kalyoncu and Urganci (25)	Cohort prospective study	2015	67 cases. children	Celiac disease	P value
Roldan et al (26)	Analytical cross sectional study	2012	800 cases. Adult	Rheumatoid disease	OR, P value, 95% CI

function, not in treatment for thyroid dysfunction. All studies used the correlation coefficient (r) had positive r values > 0, which means a positive correlation. Some studies used logistic regression to test the association between multiple factors and an outcome, such as age and sex, with thyroid autoantibodies. In the meta-analysis study included, the I^2 index assesses the heterogeneity. In this study, the I^2 for studies looks for the TG-Ab and TPO-Ab with patients with SLE; the higher the I^2, the more heterogenic the study will affect the study's strength. In the study, I^2 > 50% (50.4% and 62.5%, respectively). All studies were hospital-based studies except one study, which was a community-based study.

Summaries of included studies

Carta et al (2004).
This is a cross-sectional community-based study. It found that 16.6% of the overall sample had a TPO-Ab value above the standard cut-off. Multivariate logistic regression for TPO- Ab on the risk of one mood diagnosis considering age and gender showed a positive relation to anti-TPO (OR 2.89, CI 95% years (38), and there was no relation with positive TPO-Ab, age and sex (gender F vs. M – OR 1.38, CI 95% 0.68 – 2.82), age (<44 vs.>44 years, OR 1.14 CI95% 0.57 – 2.30), for anxiety disorder, positive vs. negative TPO-Ab risk was 4.5, CI 95% 2.02 -10-04), while for gender F vs. M, OR 1.58, CI 95% 0.75 – 3.31 and for age (<44 vs.>44 years) OR 1.91, CI 95% 0.92 -3.96.

Limitation: the study included a small size, which increases the bias of including the actual number of rare psychiatric diagnoses less frequently observed in the general population, such as panic disorder (lifetime prevalence 2.7%).

Sneijders et al (2020).
This is a cross-sectional study which found that TPO-Ab significantly increased in bipolar patients versus controls and more in women than men (11% versus 5.3%, P<0.001). It was higher in subjects with ages above 45 than those below 45 (9.7% versus 6.8%) P= 0.07, which was not statistically significant. TPO-Ab did not differ between bipolar patients (8.4%) and controls (9.1%) P= 0.964, which confirms the absence of an association of BP with TPO-Ab. Even after adjusting for age and sex, no significant association was found (P=0.123). For the first-degree relatives' group, the TPO-Ab level did not differ compared to the bipolar control groups (P=0.538, P=0.402, respectively) even after adjustment for age and sex. Investigators combined meta-analysis with their study to support their findings. The meta-analysis results showed that the overall odds ratio was 1.3 (95% CI 0.7-2.3, P=0.3), which is mildly clinically significant but not statistically significant as the CI crosses the 1.

Limitation: cross-sectional design, hospital-based, measuring TPO-Ab years after disease onset and inclusion of controls from two different studies. The combined meta-analysis showed moderate heterogeneity (I^2 =63%).

Shin et al (2014).
This is a retrospective study which found that Patients with elevated TPO-Ab had lower Vit D than those who did not (12.6 +/- 5.5ng/ml vs. 14.5+/- 7.3 ng/ml respectively (P <0.001) after adjusting for age, sex, and BMI, a negative correlation was recognized between Vit D3 and TPO-Ab levels (r = - 0.252, P <0.001). This correlation did not exist in the non-AITD (r=0.117, P= 0.127); the P value > 0.05. Vit D level was a significant determinant for the presence of TPO-Ab (OR 0.917, 95% CI 0.858 – 0.953 , P=0.039).

Limitations: this is a retrospective study with a relatively small sample size and was hospital-based. The study did not measure Thyroglobulin and TG-Ab, so the association with Vit D was not tested.

Darban et al (2022).
This is a cross-sectional study. TPO-Ab was high (>40iu/ml) in 31.4% of patients with Vit D deficiency and 11.4% of the control group (P=0.041). Logistic regression analysis showed the chance of positive TPO-Ab in people with vitamin D (Vit D) deficiency was 3.55% in comparison with the subjects without Vit D deficiency (OR 3.55, CI 95% 1.01 -12.55, P = 0.049).

Limitation: the study neglects the effect of confounders such as season and gender on Vit D and thyroid function. The study had a small sample size, most participants were females, and it was hospital-based.

Zhang et al (2022).
This case-control study explored the relationship between allergies and autoimmune diseases; Allergic Rhinitis (AR), Atopic Dermatitis (AD), and Chronic Spontaneous Urticaria (CSU). TG-Ab positivity was identified as a risk factor for AR, CSU, and AD in Chinese children (OR 2.333, CI 95% 1.243 – 4.378). Multivariate regression analysis also confirmed that TG-Ab (P=0.004) rather than TPO-Ab (P=0.0468) significantly impacted the occurrence of allergic disease.

Limitations: it is a hospital-based study, retrospective, with a small sample size. The study did not correlate between the level of thyroid autoantibodies and allergic diseases. The study could not identify the roles of TG-Ab and TPO-Ab in the pathogenesis of atopic autoimmune reactions.

Ismaeil et al (2020).
This is a case-control study. The study found that there was no significant difference between case and control groups regarding levels of T3 (P=0.131), T4 (P=0.49), TSH (P=0.504), TPO-Ab (P=0.345), and TG-Ab (P 0.307). The correlation was not significant between asthma severity and TPO-Ab (r=0.139, P=0.394) and TG-Ab (r=0.164, P=0.311); the P value was > 0.05.

Limitations: hospital-based study, with a small sample size. Statistic methods needed to be explained clearly within the study.

Levy et al (2003).
This is a cohort study. The study found only 4.3% (8 participants) had increased antithyroid antibodies. All positive were females, 4 with increased TPO-Ab, 2 with increased TG-Ab, and 2 with both increased. The duration of urticaria was four months to 7 years. Five patients were euthyroid, and one was found to have increased antithyroid antibodies five years from the onset of urticaria.

Limitation: small-size study, hospital-based. Researchers ignore factors that may aggravate urticaria and thyroid function.

Zhang et al (2022).
This is a multicentre, analytic cross-sectional study that explored the relationship between allergies and autoimmune diseases; allergic rhinitis (AR), Chronic spontaneous urticaria (CSU), and/or atopic dermatitis (AD). They found that the prevalence rates of TPO-Ab IgE and IgG, TG-b IgE, or TG-Ab IgG in patients were significantly higher than in controls. Significant correlations were observed between prevalence rates of TPO-Ab IgE and TPO-Ab IgG (r=0.297, P<0.001) and between TG-Ab IgE and IgG in patients (r=0.137, P<0.001). Positive anti-TPO-Ab IgE, positive TPO-Ab IgG, and total IgE<40iu/ml were independent predictors of refractory antihistamine cases.

Limitation: Chinese health system differs from western health systems as it allows multiple visits within a hospital to the same specialty, reflecting bad patient compliance. It was challenging to encourage patients to stop antihistamine use seven days before; this created difficulty in assessing the number of wheals in a patient in the last week.

Singh et al (1995).
This is a cohort study. Researchers found that about 22% of patients were positive for TG-Ab, TPO-Ab, or both while 78% were negative. In the antibody-positive group, there was a 32% spontaneous abortion rate versus 16% in the antibody-negative group. In all antibody-positive groups, 26% miscarried versus 13% in the negative group (P=0.002). In biochemical abortion, the association was not significant. The distribution of aetiology of infertility in the positive antibody group was 33% tubal–pelvic factor, 24% male factor, 23% unexplained, and 20% ovulatory dysfunction. In the negative group, it was 34% tubal–pelvic, 27% male factor, 19% unexplained and 18% ovulatory dysfunction, and 2% uterine-cervical factor. Interestingly, researchers found that none of the thyroid antibody-positive groups had any clinical evidence of thyroid disease; only 18 patients had a history of thyroid disease on replacement therapy, and 50% had thyroid autoantibodies.

Limitation: This is a small-size study, hospital-based, and does not involve a control group.

Janssen et al (2004).
This is a prospective, multicentre case-control study. Researchers found Elevated TPO-Ab or TG-Ab in 8.3% of the control group and 26.9% in the PCOS group (P<0.001). The thyroid ultrasound in the PCOS (42.3%) group showed a picture of autoimmune thyroiditis more than the control group (6.5%) with P <0.001. TSH was normal in both groups. Researchers studied the influence of thyroid antibodies on the characteristics of PCOS patients, and they found that only the age, the pattern of ultrasound (hypoechoic), and the LH to FSH ratio were statistically significant (P value <0.05, <0.001, and <0.05, respectively).

Limitations: This is a hospital-based study with a small sample size.

Wang et al (2018).
This is an analytic cross-sectional study. Researchers found that among patients with positive TPO-Ab, the incidence rate of endometriosis was 28.1% and 18.6% in the negative group (P<0.005). The incidence rate of Polycystic ovary syndrome (PCOS) in the positive group was 37.1% and 19.4% in the controls (P<0.001). The difference was not statistically significant for primary ovarian failure and tubal obstruction (P>0.05). The difference in the percentage of positive simple TPO-Ab among age groups was statistically significant (P value = 0.035). The age group, 28-35 years with infertile PCOS, was noticed to be influenced by TPO-Ab positivity.

Limitations: small-size study, hospital-based.

Stagnaro-Green et al (1990).
This is a retrospective, multicentre study. The outcome was defined as:
1) elective abortion,
2) spontaneous abortion in either the first or second trimester
3) successful pregnancy. 80.4% of participants were negative for IgG thyroid antibodies, while 19.6% were positive for TG-Ab and/or TPO-Ab. The overall abortion incidence was 10.2%. Spontaneous abortion occurred in 17% of the thyroid autoantibodies positive group and 8.4% of the negative group (P=0.011). Second-trimester abortion occurred in 29% of the thyroid autoantibodies-positive group and 24% of the antibody-negative group. Miscarriage was not related to the presence of any specific IgG subclass of thyroid autoantibody.

Limitations: relatively small study, hospital-based, and retrospectively designed.

Pan et al (2015).
This is a meta-analysis study. The study found TG-Ab OR=2.99,95% CI=1.83- 4.89. TPO-Ab OR =2.20, 95% CI= 1.27 – 3.82. The study went further and analysed the demographical association with thyroid autoimmunity. The association was positive between TG-Ab and SLE in both

American and European populations (OR 4.03, 95% CI 2.08 – 7.8, OR 1.81, 95% CI= 1.23 -2.65) but not in Asian or African populations (OR=5.43,95% CI = 0.76 – 39.1, OR 2.44, 95% CI0.36 – 10.7). The association was positive between TPO-Ab and SLE in African and European populations (OR=4.55,95% 1.33 -15.49; OR=2.32,95% CI 1.62 -3.32) but not observed in either Asian or American populations (OR=0.66,95% CI=0.16-2.76, OR=1.10,95% CI=0.55-2.24).

Limitations: studies included were relatively small. A study was done in different parts of the world, so time and methodology were different, carrying risk heterogeneity (I^2 for studies targeted TG-Ab was 50.4% and TPO-Ab 62.5%).

Sieiro Netto et al (2004).
This is a prospective study. A total of 5.4% were TPO-Ab positive (95% CI 3.7 -707). TSH was found high in TPO-Ab positive group compared with TPO-Ab negative group (13.8% vs. 2.4%, P value 0.017). The overall risk of abortion was 2.4% (95% CI 1.3 -4.1). The risk of abortion was higher among women >= 35 years (7.7%, CI 95% 1.6 -20.9), TPO-Ab positive (10.3%, CI 95% 2.1 -27.3), and presenting a high level of TSH (12.5%, CI 95% 1.5 -38.3). These factors remain independently associated with the risk of abortion in a complete multivariate analysis.

Limitations: this is a hospital-based study with a risk of selection bias. The sample size is relatively small. Investigators use self-filled questionnaires to collect the history of participants with the risk of information bias.

Smyth et al (1998).
This is a case-control study. TPO-Ab was detected in 34% of carcinoma patients compared to 18.5% in their control group (P <0.001) and 28.7% in the benign breast disease group compared to their control group 13.6% (P<0.05). In survival group analysis, patients with high TPO-Ab titre (>=0.3 U/ml) were associated with a significantly better disease–free period (Relative risk RR 3.46, P<0.02) compared with those who were negative. The positive effect of TPO-Ab was noticed when the thyroid volume was within the intermediate range (10.1 -18.8ml).

Limitations: the study had a relatively small sample size and was hospital-based.4.2.10.

Roldan et al (2012).
This is a cross-sectional, analytical study. The prevalence of AITD was 9.8%. The presence of autoantibodies was 37.8% for TPO-Ab and 20.8% for TG-Ab. Type 2 diabetes (OR 13.61; 95% CI 1.61 – 111.96; P= 0.016), thrombosis (OR 24.4; 95%CI 2.72- 218.42; P=0.004), abnormal BMI (OR 4.22;95% CI 1.19-14.93; P=0.025) were positively associated with patients with RA and AITD (P value <0.05).

Limitation: hospital-based study, risk of information bias as only patients with thyroid dysfunction tested for thyroid antibodies while others were not tested.

Sharifi, Ghasemi and Mousaviasab (2008).
This is an analytic cross-sectional study. TPO-Ab was detected in 39.6% of patients and 6.7% of controls (P=0.001). 38.2% of male diabetics had positive TPO-Ab, and 40.4% of female diabetics had positive TPO-Ab (P=0 .8). 39.3% of female diabetics had positive TG-Ab, and 14.7% of males had positive TG-Ab (P=0.14). The correlation was positive between age and TPO-Ab but not for TG-Ab among people with diabetes (r=0.29, P=0.006) as well as the duration of diabetes and the level of TPO-Ab (r=0.33, P 0.004), but there was no correlation with TG-Ab. Approximately 22.4 % of diabetic patients were positive for both TPO-Ab and TG-Ab. There was no difference between males and females regarding TSH level and the frequency of abnormal thyroid function (P =0.5).

Limitations: small-size study, hospital-based, regional (conducted in a city in the northwest of Iran).

Kalyoncu and Urganci (2015).
This is a descriptive cross sectional study. About 16.4% of patients had antithyroid antibodies, which became positive after 2-3 years from celiac disease diagnosis. No other immune diseases among patients except two patients with type 1 diabetes were diagnosed before the celiac disease. Age was significantly different between the positive antithyroid group and the negative group (P=0.004), with no difference with gender, weight, height, clinical presentation, and compliance to a gluten-free diet (P value >0.05). In patients with positive antibodies, 72.7% remained euthyroid during the follow-up time (8.05 +/- 3.6 years).

Limitations: Small size study, hospital-based, cross-sectional design did not allow researchers to assess the correlation. All patients had a severe histopathological degree which did not allow researchers to assess the association of different classes to thyroid antibodies.

Discussion

Autoimmune thyroid diseases are common endocrine diseases associated with detecting thyroid autoantibodies. These autoantibodies are frequently found in patients with autoimmune thyroid diseases and individuals without thyroid dysfunction manifestations. Circulating thyroid autoimmune antibodies are not restricted to autoimmune thyroid diseases but can also be detected in other common autoimmune diseases.

Vitamin D deficiency is one of the non-thyroidal diseases found to be associated with thyroid autoantibodies. Shin et al. (11) showed the association between Vit D deficiency and thyroid autoantibodies, particularly with TPO-Ab. Tamer et al. (27) argued that Vit D deficiency could be a sign of autoimmune thyroid disease. Darban et al. (12) found that there was no significant correlation between Vit d deficiency and thyroid function in both case and control groups. However, there was a significant statistical association between TPO-ab and level of Vit D. The odds ratio in this study to have Vit D deficiency in subjects with

TPO-ab >= 40iu was 3.55, (95% CI 1.12 -1.55, P=049), which indicates clinical and statistical significance. Kivity et al. (28) studied the presence of antithyroid antibodies and abnormal thyroid function and Vit D. They found a statistically significant correlation between the presence of antithyroid antibodies and Vit d deficiency (P= 0.01) but not with thyroid function (P=0.059).

Many researchers studied the association between mood disorders and symptomless Autoimmune thyroid diseases (AITDs). Carta et al. (9) showed an association between mood disorders and positive TPO-Ab in a community-based study. They found that age and gender were independent risk factors for this association. Major depressive episodes (OR 2.7, 95%CI 1,1 -6.7, P = 0.033), depressive disorder not otherwise specified (OR 4.4, 95% CI 1.1-9.3, P = 0.049), and anxiety disorders not otherwise specified (OR 4, 95% CI 1.1 -15.5, P = 0.045) were the most associated disorders to positive TPO-Ab. Snijders et al. (10) investigated the association between TPO-Ab and bipolar disorder; interestingly, this study found no association of TPO-Ab with bipolar disorder even after adjusting to age and gender (P= 0.709, after adjusting 0.123).

Zhang et al. (13) compared thyroid autoantibodies levels among Chinese patients with allergic diseases and their age and sex-matched controls. The study found a significant association between the presence of TG-Ab rather than TPO-Ab on the occurrence of allergic disease. This phenomenon can be explained by forming immune complexes in AITD patients; these complexes can further bind to the Fc receptor on mast cells (29). El Shabrawy et al. (30) showed that TPO-Ab was more related to allergic diseases than TG-Ab (30). Ismaeil et al. (14) studied the association between some allergic diseases and bronchial asthma with thyroid antibodies; interestingly, they did not find any association between TPO-Ab and TG-Ab and bronchial asthma. The relationship between chronic urticaria and autoimmune thyroid disease has recently been frequently reported in the literature. The prevalence in adult series ranges from 14 -33% (31). Levy et al. (15) studied this association in children (6-18 years). They found a prevalence of about 4.8%, lower than the adult prevalence but higher than that found by Marwaha et al. (32) and Rallison et al. (33). Although the study included 187 participants, 90 were males. However, participants with chronic urticaria and thyroid autoimmunity were females. This is comparable with other researchers who noticed a more predominant association among females (34). The deposition of thyroid immune complexes on the skin could trigger an allergic reaction, but the exact mechanism is not yet precise.

Women's reproductive system is another target for thyroid autoimmune. Singh et al. (17) studied the association of thyroid antibodies to pregnancy loss in a particular population (women who conceived with assisted reproductive techniques) who were euthyroid. The study found a high prevalence of miscarriage in patients with positive thyroid antibodies (32%) compared to those with negative thyroid antibodies (P =0.002). Stagnaro-Green et al. (20) and Glinoer et al. (35) found a significant correlation between thyroid antibodies and the risk of abortion; in both studies; >98% of participants were euthyroid. The mechanism involved the thyroid autoimmunity and pregnancy loss could be related to the interaction between thyroid antibodies and the several thyrotropin-like hormones produced by the placenta (36).

Wang et al. (19) studied the association between thyroid antibodies and pregnancy loss. They found that the association was more positive in patients with endometriosis and polycystic ovary syndrome. The positive rate of TPO-Ab in infertile females with PCOS ages 28-35 years was increased significantly (P=0.035); these findings made the authors recommend screening females with PCOS aged 28-35 years for thyroid antibodies. Janssen et al. (18) found the exact relation of thyroid antibodies in patients with PCOS, but they did further thyroid ultrasound assessment. They found that in patients with PCOS, their thyroid ultrasound showed a picture of autoimmune thyroiditis in 42.3% compared to the control group (6.5%); P<0.001. Thyroid autoimmune antibodies could affect the outcome of pregnancy as well. Stagnaro -Green et al. (20) observed that the abortion rate was higher among women with positive thyroid antibodies. 92.7% of participants in this study were <35 years, and autoimmunity was associated with higher abortion risk; it is significant because this population has a low risk of abortion that becomes higher when associated with thyroid autoantibodies (37). The presence of thyroid autoantibodies may reflect minimal thyroid dysfunction. Some studies postulated that the association of abortion with thyroid autoantibodies could be related to this minimal dysfunction, not to the antibodies themself (38). Geva et al. (39) postulated that the absence of TPO-Ab could strongly predict success in women submitted to assisted reproduction.

The meta-analysis by Pan et al. (21) tried to find an association between SLE and thyroid antibodies. Researchers found an association between thyroid antibodies (TPO-Ab and TG-Ab) and SLE. The study dug deep and analysed the occurrence of association based on demographical distribution. They compare the American, European, Asian, and African populations for the presence of TPO-Ab among SLE patients. TG-Ab was associated with SLE in the American and European populations but not in Africans and Asians. TPO-Ab was positively associated with SLE in the African and European populations but not in the American and Asian populations.

A lengthy debate about thyroid and breast diseases was running between researchers. A higher prevalence of TPO-Ab in breast carcinoma patients than in controls was reported (40). Smyth et al. (23) demonstrated a high TPO-Ab positivity (34%) in patients with breast carcinoma compared with 18.5% inappropriate female control, even in patients with benign breast diseases was higher than their control (28.7% vs. 13,6%). The association suggested

the presence of subclinical autoimmune thyroid disease. Higher TSH, even within the normal range, may indicate the tendency to hypothyroid function in such patients (41). The TPO-Ab positivity was associated with better disease outcomes. Also, the size of the thyroid gland (=<10ml, >=18ml) is associated with a better outcome. Fukutomi, Nanasawa, and Yamamoto (42) shared the same finding regarding the positive prognostic of TPO-Ab in a patient with breast carcinoma. The mechanism that high TPO-Ab can positively affect the outcome of breast carcinoma is not yet precise; it could be through an effect on mammary receptors affecting the cytotoxicity of the cancer cell; still, it is a matter of research.

Rheumatoid Disease was another autoimmune disease that underwent investigation for the possibility of the occurrence of thyroid antibodies within its pathophysiology. Roldan et al. (26) worked to determine the prevalence and impact of autoimmune thyroid disease in patients with rheumatoid arthritis. The worldwide prevalence of Autoimmune Thyroid Disease (AITD) in rheumatoid arthritis varies considerably, ranging from 0.5% in Morocco to 27% in Slovakia (43). Type 1 diabetes was another disease brought under focus. Sharifi, Ghasemi, and Mousavinasab (24) investigated the prevalence of TPO-Ab, and TG-Ab in patients with type 1 and compared the effect of age and sex on patients with AITD with type 1 diabetes. Type 1 diabetes was considered an autoimmune disease (44) associated strongly with other organ-specific diseases such as AITDs. Also, thyroid antibodies are more prevalent with type 1 diabetes and AITD (45). Chang et al. (46) reported that 10-24% of type 1 diabetic patients who were clinically euthyroid had been reported to be positive for TPO-Ab. Sharifi, Ghasemi, and Mousavinasab (24) reported a 39.6% prevalence of positive TPO-Ab among type 1 diabetics. Researchers found a tendency for TPO-Ab to occur with increasing age; this finding comes with what Verge et al. (47) reported. Kalyoncu and Urganci (25) investigated the association of Celiac disease with thyroid autoimmune antibodies. The association between celiac disease and other autoimmune disorders, such as type 1 diabetes, is well established (48). The prevalence of antithyroid antibodies has been reported to be high in patients with celiac disease (25), and some reported low prevalence (49). Researchers only observed a significant difference between the observed antithyroid antibodies and younger age in patients with celiac disease. The frequency of antithyroid antibodies did not correlate with the duration of gluten intake and compliance with a gluten-free diet.

Conclusion

Thyroid autoantibodies are frequently found in patients with AITDs and subjects without manifest thyroid dysfunction. Thyroid antibodies can be detected in a group of non-thyroidal illnesses and participate in the pathogenesis of these diseases. These antibodies could be a trigger for inflammatory or allergic reactions. The association of these antibodies with the illness could be a positive or negative correlation. These antibodies could be a prognostic indicator to increase disease-free survival, as in the case of breast carcinoma. Thyroid autoantibodies were not an exclusive indicator for thyroid diseases. However, they became clinical indicators of other non-thyroidal diseases, and their clinical significance must be assessed and followed.

Conflict of interest:
I had declared that I have no conflict of interest. Also, I had no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work and any other relationships or activities that could appear to have influenced the submitted work.

Acknowledgement
The author would like to thank Mrs Mayada Abubakr Alsaeed for her valuable help in editing and organizing this paper.

References

1) Bouknight, A.L., 2003. Thyroid physiology and thyroid function testing. Otolaryngologic Clinics of North America, 36(1), pp.9-15.
2) LiVOLSI, V.A., 1994. The pathology of autoimmune thyroid disease: a review. Thyroid, 4(3), pp.333-339.
3) DUNN, J.T. and RAY, S.C., 1978. Variations in the structure of thyroglobulins from normal and goitrous human thyroids. The Journal of Clinical Endocrinology & Metabolism, 47(4), pp.861-869.
4) McLachlan, S.M. and Rapoport, B., 2004. Why measure thyroglobulin autoantibodies rather than thyroid peroxidase autoantibodies?. Thyroid, 14(7), pp.510-520.
5) McLachlan, S.M. and Rapoport, B., 1992. The molecular biology of thyroid peroxidase: cloning, expression and role as autoantigen in autoimmune thyroid disease. Endocrine reviews, 13(2), pp.192-206.
6) Chazenbalk, G.D., Latrofa, F., McLachlan, S.M. and Rapoport, B., 2004. Thyroid stimulation does not require antibodies with identical epitopes but does involve recognition of a critical conformation at the N terminus of the thyrotropin receptor A-subunit. The Journal of Clinical Endocrinology & Metabolism, 89(4), pp.1788-1793.
7) Moher, D., Liberati, A., Tetzlaff, J. and Altman, D.G., 2009. Group TP, Oxman A, Cook D, Guyatt G, Swingler G, Volmink J, Ioannidis J, Young C, Horton R, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. Public Library of Science, 6, p.e1000097.
8) Ranganathan, P. and Aggarwal, R., 2018. Study designs: Part 1–An overview and classification. Perspectives in clinical research, 9(4), p.184.
9) Carta, M.G., Loviselli, A., Hardoy, M.C., Massa, S., Cadeddu, M., Sardu, C., Carpiniello, B., Dell'Osso, L. and Mariotti, S., 2004. The link between thyroid autoimmunity (antithyroid peroxidase autoantibodies) with anxiety and mood disorders in the community: a field of interest for public health in the future. BMC psychiatry, 4(1), pp.1-5.

10) Snijders, G.J.L.J., de Witte, L.D., van Den Berk, D., van Der Laan, C., Regeer, E., Begemann, M.J.H., van Berlekom, A.B., Litjens, M., Boks, M.P., Ophoff, R.A. and Kahn, R.S., 2020. No association between anti-thyroidperoxidase antibodies and bipolar disorder: a study in the Dutch Bipolar Cohort and a meta-analysis. Psychoneuroendocrinology, 112, p.104518.

11) Shin, D.Y., Kim, K.J., Kim, D., Hwang, S. and Lee, E.J., 2014. Low serum vitamin D is associated with anti-thyroid peroxidase antibody in autoimmune thyroiditis. Yonsei medical journal, 55(2), pp.476-481.

12) Darban, M., Mohamadian, S.D., Mahmoodifar, S. and Ghorbani, R., 2022. Predicting positive anti-thyroid peroxidase antibody chance in vitamin D deficient patients.

13) Zhang, C., Hong, C., Lian, X., Wen, L., Xu, K., Tian, Z., Si, W. and Li, Y., 2022. Correlations of thyroid autoantibodies with allergic diseases: A case-control study of 434 Chinese patients. Medicine, 101(30).

14) Ismaeil, N.Y., Hemeda Moustafa, A. and Farouk Mosa, M., 2020. ASSESMENT OF THYROID PROFILE AND AUTO ANTIBODIES IN CHILDREN WITH ASTHMA AT AL-HUSSEIN UNIVERSITY HOSPITAL. Al-Azhar Journal of Pediatrics, 23(3), pp.1038-1047.

15) Levy, Y., Segal, N., Weintrob, N. and Danon, Y.L., 2003. Chronic urticaria: association with thyroid autoimmunity. Archives of disease in childhood, 88(6), pp.517-519.

16) Zhang, L., Qiu, L., Wu, J., Qi, Y., Wang, H., Qi, R., Yao, X., Zhu, H., Li, Y., Hao, S. and Lu, Q., 2022. IgE and IgG Anti-Thyroid Autoantibodies in Chinese Patients With Chronic Spontaneous Urticaria and a Literature Review. Allergy, asthma & immunology research, 14(1), p.131.

17) Singh, A., Dantas, Z.N., Stone, S.C. and Asch, R.H., 1995. Presence of thyroid antibodies in early reproductive failure: biochemical versus clinical pregnancies. Fertility and sterility, 63(2), pp.277-281.

18) Janssen, O.E., Mehlmauer, N., Hahn, S., Offner, A.H. and Gartner, R., 2004. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. European journal of endocrinology, 150(3), pp.363-370.

19) Wang, X., Ding, X., Xiao, X., Xiong, F. and Fang, R., 2018. An exploration on the influence of positive simple thyroid peroxidase antibody on female infertility. Experimental and Therapeutic Medicine, 16(4), pp.3077-3081.

20) Stagnaro-Green, A., Roman, S.H., Cobin, R.H., El-Harazy, E., Alvarez-Marfany, M. and Davies, T.F., 1990. Detection of at-risk pregnancy by means of highly sensitive assays for thyroid autoantibodies. Jama, 264(11), pp.1422-1425.

21) Pan, X.F., Gu, J.Q. and Shan, Z.Y., 2015. Patients with systemic lupus erythematosus have higher prevalence of thyroid autoantibodies: a systematic review and meta-analysis. PloS one, 10(4), p.e0123291.

22) Sieiro Netto, L., Medina Coeli, C., Micmacher, E., Mamede Da Costa, S., Nazar, L., Galvão, D., Buescu, A. and Vaisman, M., 2004. Influence of thyroid autoimmunity and maternal age on the risk of miscarriage. American Journal of Reproductive Immunology, 52(5), pp.312-316.

23) Smyth, P.P.A., Shering, S.G., Kilbane, M.T., Murray, M.J., McDermott, E.W.M., Smith, D.F. and O'Higgins, N.J., 1998. Serum thyroid peroxidase autoantibodies, thyroid volume, and outcome in breast carcinoma. The Journal of Clinical Endocrinology & Metabolism, 83(8), pp.2711-2716.

24) Sharifi, F., Ghasemi, L. and Mousavinasab, S., 2008. Thyroid function and anti-thyroid antibodies in Iranian patients with type 1 diabetes mellitus: influences of age and sex. Iran J Allergy Asthma Immunol ;7(1): 31-36

25) Kalyoncu, D. and Urganci, N., 2015. Antithyroid antibodies and thyroid function in pediatric patients with celiac disease. International Journal of Endocrinology, 2015.

26) Roldan, J.C., Amaya-Amaya, J., Castellanos-De La Hoz, J., Giraldo-Villamil, J., Montoya-Ortiz, G., Cruz-Tapias, P., Rojas-Villarraga, A., Mantilla, R.D. and Anaya, J.M., 2012. Autoimmune thyroid disease in rheumatoid arthritis: a global perspective. Arthritis, 2012.

27) Tamer, G., Arik, S., Tamer, I. and Coksert, D., 2011. Relative vitamin D insufficiency in Hashimoto's thyroiditis. Thyroid, 21(8), pp.891-896.

28) Kivity, S., Agmon-Levin, N., Zisappl, M., Shapira, Y., Nagy, E.V., Dankó, K., Szekanecz, Z., Langevitz, P. and Shoenfeld, Y., 2011. Vitamin D and autoimmune thyroid diseases. Cellular & molecular immunology, 8(3), pp.243-247.

29) Altrichter, S., Peter, H.J., Pisarevskaja, D., Metz, M., Martus, P. and Maurer, M., 2011. IgE mediated autoallergy against thyroid peroxidase–a novel pathomechanism of chronic spontaneous urticaria?. PloS one, 6(4), p.e14794.

30) El Shabrawy, R.M., Atta, A.H. and Rashad, N.M., 2016. Serum Anti-TPO and TPO Gene Polymorphism as a Predictive Factor for Hidden Autoimmune Thyroiditis in Patient with Bronchial Asthma and Allergic Rhinitis. The Egyptian journal of immunology, 23(1), pp.77-86.

31) Zauli, D., Deleonardi, G., Foderaro, S., Grassi, A., Bortolotti, R., Ballardini, G. and Bianchi, F.B., 2001, March. Thyroid autoimmunity in chronic urticaria. In Allergy and Asthma Proceedings (Vol. 22, No. 2, p. 93). OceanSide Publications.

32) Marwaha, R.K., Tandon, N., Karak, A.K., Gupta, N., Verma, K. and Kochupillai, N., 2000. Hashimoto's thyroiditis: countrywide screening of goitrous healthy young girls in postiodization phase in India. The Journal of Clinical Endocrinology & Metabolism, 85(10), pp.3798-3802.

33) Rallison, M.L., Dobyns, B.M., Meikle, A.W., Bishop, M., Lyon, J.L. and Stevens, W., 1991. Natural history of thyroid abnormalities: prevalence, incidence, and regression of thyroid diseases in adolescents and young adults. The American journal of medicine, 91(4), pp.363-370.

34) Gaig, P., Garcia-Ortega, P., Enrique, E. and Richart, C., 2000. Successful treatment of chronic idiopathic urticaria associated with thyroid autoimmunity. Journal of investigational allergology & clinical immunology, 10(6), pp.342-345.

35) Glinoer, D., Soto, M.F., Bourdoux, P., Lejeune, B., Delange, F., Lemone, M., Kinthaert, J., Robijn, C., GRUN, J.P. and NAYER, P.D., 1991. Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. The Journal of Clinical Endocrinology & Metabolism, 73(2), pp.421-427.
36) Mariotti, S., Chiovato, L., Vitti, P., Marcocci, C., Fenzi, G.F., Del Prete, G.F., Tiri, A., Romagnani, S., Ricci, M. and Pinchera, A., 1989. Recent advances in the understanding of humoral and cellular mechanisms implicated in thyroid autoimmune disorders. Clinical immunology and immunopathology, 50(1), pp.S73-S84.
37) Andersen, A.M.N., Wohlfahrt, J., Christens, P., Olsen, J. and Melbye, M., 2000. Maternal age and fetal loss: population based register linkage study. Bmj, 320(7251), pp.1708-1712.
38) VAQUERO, E., DE CAROLIS, C.A.T.E.R.I.N.A., VALENSISE, H., ROMANINI, C., LAZZARIN, N. and MORETTI, C., 2000. Mild Thyroid Abnormalities and Recurrent Spontaneous Abortion: Diagnostic and Therapeutical Approach 1. American Journal of Reproductive Immunology, 43(4), pp.204-208.
39) Geva, E., Vardinon, N., Lessing, J.B., Lerner-Geva, L., Azem, F., Yovel, L., Burke, M., Yust, I., Grunfeld, R. and Amit, A., 1996. Immunology: Organ-specific autoantibodies are possible markers for reproductive failure: a prospective study in an in-vitro fertilization—embryo transfer programme. Human Reproduction, 11(8), pp.1627-1631.
40) Giani, C., Fierabracci, P.A.O.L.A., Bonacci, R.O.S.A.N.N.A., Gigliotti, A.G.O.S.T.I.N.O., Campani, D., De Negri, F.E.R.D.I.N.A.N.D.O., Cecchetti, D.E.N.I.S.E., Martino, E.N.I.O. and Pinchera, A.L.D.O., 1996. Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy. The Journal of Clinical Endocrinology & Metabolism, 81(3), pp.990-994.
41) Vanderpump, M.P.J., Tunbrldge, W.M.G., French, J., Appleton, D., Bates, D., Clark, F., Evans, J.G., Hasan, D.M., Rodgers, H., Tunbridge, F. and Young, E.T., 1995. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clinical endocrinology, 43(1), pp.55-68.
42) Fukutomi, T., Nanasawa, T. and Yamamoto, H., 1989. Influences from the treatment of thyroid disease and diabetes mellitus on breast cancer prognosis. Gan no rinsho. Japan Journal of Cancer Clinics, 35(5), pp.575-579.
43) Benamour, S., Zeroual, B., Fares, L., El Kabli, H. and Bettal, S., 1992. Rheumatoid arthritis in Morocco. Apropos of 404 observations. Revue du rhumatisme et des maladies osteo-articulaires, 59(12), pp.801-807.
44) Kawasaki, E., Takino, H., Yano, M., Uotani, S., Matsumoto, K., Takao, Y., Yamaguchi, Y., Akazawa, S. and Nagataki, S., 1994. Autoantibodies to glutamic acid decarboxylase in patients with IDDM and autoimmune thyroid disease. Diabetes, 43(1), pp.80-86.
45) Okten, A.Y.Ş.E., Akcay, S.A.L.İ.H.A., Cakir, M.U.R.A.T., Girisken, I., Kosucu, P.O.L.A.T. and Deger, O.R.H.A.N., 2006. Iodine status, thyroid function, thyroid volume and thyroid autoimmunity in patients with type 1 diabetes mellitus in an iodine-replete area. Diabetes & metabolism, 32(4), pp.323-329.
46) Chang, C.C., Huang, C.N. and Chuang, L.M., 1998. Autoantibodies to thyroid peroxidase in patients with type 1 diabetes in Taiwan. European journal of endocrinology, 139(1), pp.44-48.
47) Verge, C.F., Howard, N.J., Rowley, M.J., Mackay, I.R., Zimmet, P.Z., Egan, M., Hulinska, H., Hulinsky, I., Silvestrini, R.A., Kamath, S. and Sharp, A., 1994. Anti-glutamate decarboxylase and other antibodies at the onset of childhood IDDM: a population-based study. Diabetologia, 37(11), pp.1113-1120.
48) Volta, U., Ravaglia, G., Granito, A., Forti, P., Maioli, F., Petrolini, N., Zoli, M. and Bianchi, F.B., 2001. Coeliac disease in patients with autoimmune thyroiditis. Digestion, 64(1), pp.61-65.
49) Ansaldi, N., Palmas, T., Corrias, A., Barbato, M., D'Altiglia, M.R., Campanozzi, A., Baldassarre, M., Rea, F., Pluvio, R., Bonamico, M. and Lazzari, R., 2003. Autoimmune thyroid disease and celiac disease in children. Journal of pediatric gastroenterology and nutrition, 37(1), pp.63-66.

Vitamin B-12 deficiency in type 2 diabetes patients on metformin therapy – A narrative review

Amir Tauqir Chaudhary [1], Shiraz Ali A [2]

(1)Specialist Family Medicine Norway, Tutor Family Medicine Norway, Consultant Family Medicine PHCC Qatar,
(2) A&E GP Clinical Lead BTHFT, Bradford Royal Infirmary, Duckworth Lane, BD9 6RJ, England, Consultant Family Medicine PHCC Qatar

Corresponding author:
Dr. Amir Tauqir Chaudhary, MBBS (Pak), MD (Equivalence exam with UiO Norway),
Specialist Family Medicine Norway,
Tutor Family Medicine Norway,
Consultant Family Medicine PHCC Qatar
Mobile: 00974 51094681
Email: amirtauqeernw@hotmail.com

Received: July 2023. Accepted: August 2023; Published: September 1, 2023.
Citation: Amir Tauqir Chaudhary, Shiraz Ali. Vitamin B-12 deficiency in type 2 diabetes patients on metformin therapy – A narrative review. World Family Medicine. August 2023; 21(8): 44-54. DOI: 10.5742/MEWFM.2023.95256179

Abstract

Due to its increased incidence and related complications, T2DM (Type 2 diabetes mellitus) is becoming an issue of public health concern. This narrative review elucidates association between metformin therapy in T2DM and cobalamin (Vit. B12) deficiency. According to various studies, diabetic patients receiving metformin medication had a higher risk of Vit. B12 (vitamin B12) deficiency than those T2DM patients not receiving metformin therapy, ranging from 14% to 22.4% in those taking metformin and from 6% to 10% in those not taking metformin. Odds ratios for Vit. B12 deficiency associated with using metformin ranged from 2.2 to 2.7, indicating a moderate to high risk. The management of Vit. B12 deficiency in T2DM involves a combination of accurate diagnosis, appropriate supplementation strategies, patient education, and interdisciplinary collaboration. Consensus and guidelines recommend routine monitoring of serum vitamin B12 levels, high-dose oral supplementation, intramuscular injections for severe deficiency, and consideration of alternative routes of administration, along with lifestyle modifications.

Keywords: Diabetes mellitus type 2, Metformin therapy, Vitamin B12, Management, and treatment

Introduction

1. Type 2 diabetes mellitus:
T2DM (Type 2 Diabetes Mellitus), a metabolic condition, is caused by decreased insulin secretion and/or insulin resistance. Due to its increasing prevalence and related complications, it is becoming a serious public health issue.

Global Prevalence: T2DM has reached epidemic proportions globally, posing substantial challenges to healthcare systems worldwide. According to recent data from 2022-2023, the global prevalence of T2DM continues to increase. According to the International Diabetes Federation (IDF), T2DM accounts for about 90% to 95% of cases of diabetes and affects 463 million persons globally between the ages of 20 and 79. This indicates a substantial increase over earlier projections and emphasises the urgent requirement for efficient preventative and management solutions (1, 2).

Prevalence in Qatar: Qatar, a rapidly developing country in the Arabian Gulf region, has witnessed a dramatic rise in T2DM prevalence over the past years. Qatar's high socioeconomic status, sedentary lifestyles, and changing dietary habits might have contributed to the increased prevalence of T2DM. Recent data from 2022-2023 indicates that T2DM remains a pressing health concern in Qatar (3).

According to the Qatar National Diabetes Registry (QNDR), the diabetes prevalence in Qatar was estimated to be 16.7% among persons aged 20-79. Furthermore, most diabetes cases in Qatar were attributed to T2DM. The QNDR also highlights the increased risk of diabetes among Qatari nationals compared to expatriate residents, emphasizing the need for targeted interventions within the local population (4).

T2DM represents a global health challenge, with its prevalence continuing to rise worldwide, including in Qatar. The alarming rates of T2DM in Qatar require immediate action from healthcare policymakers, public health professionals, and researchers to implement comprehensive prevention and management strategies. Given the significant burden T2DM imposes on individuals, families, and healthcare systems, it is crucial to prioritize early detection, lifestyle interventions, and access to quality healthcare services to mitigate the impact of this chronic disease (5). Future research must focus on monitoring and evaluating the effectiveness of interventions to reduce T2DM prevalence and associated complications in both global and Qatar-specific contexts.

2. Recent Advances in the Management of Type 2 Diabetes Mellitus:
Significant improvements in T2DM management have been made over time, with an emphasis on glycaemic control, avoiding complications, and raising the general quality of life for those who have the condition. Precision medicine is now possible in managing T2DM due to recent developments in genomics and molecular biology. The identification of genetic variants associated with T2DM susceptibility and treatment response has enabled personalized approaches. Tailoring treatment plans based on an individual's genetic profile, metabolic characteristics, and lifestyle factors allows for more effective and targeted interventions (6).

There are now more choices for treating T2DM because of the emergence of novel types of glucose-lowering drugs. GLP-1 RA (Glucagon-like peptide-1 receptor agonist) and SGLT-2 (sodium-glucose cotransporter-2) inhibitors have demonstrated exceptional effectiveness in improving glycemic management and lowering cardiovascular and renal consequences. These substances not only lower blood glucose levels but also provide other advantages like enhanced cardiovascular outcomes, weight loss, and lowered blood pressure (7).

The integration of artificial intelligence (AI) and digital health technologies has the potential to revolutionize T2DM management (8). AI-based algorithms can analyse large datasets, including electronic health records and wearable device data, to generate personalized treatment recommendations and predict individual responses to therapies (9). Mobile applications and wearable devices provide facilities for monitoring the levels of glucose in the blood real-time. They also encourage increased physical activity, and to change dietary patterns, empowering patients to actively participate in self-management and enabling healthcare providers to deliver personalized care (10).

For obese people with T2DM, bariatric surgery can be a successful therapy option. Recent research has demonstrated that sleeve gastrectomy and the Roux-en-Y surgical procedures not only cause significant weight reduction but also create significant and long-lasting improvements in glycaemic control and diabetes remission (11). Bariatric surgery should be considered for carefully chosen T2DM patients who meet certain requirements (12).

However, more investigations are required to confirm the efficacy, safety, and affordability of these therapies. Accepting these developments in clinical practise has the potential to revolutionise T2DM management, resulting in improved outcomes and a higher quality and better life for people with this condition.

3. Metformin in the Management of Type 2 Diabetes Mellitus:
Metformin is an oral drug that is widely prescribed and is essential in the treatment of T2DM. Metformin has several advantages as a first-line medication, including its ability to decrease blood sugar, good safety profile, and potential cardiovascular advantages. The purpose of this summary is to clarify the mechanism of action, ideal dosage, and most recent consensus treatment recommendations for metformin monotherapy in T2DM (6).

Modalities of action: Multiple pathways are used by metformin to produce its therapeutic benefits. Gluconeogenesis and glycogenolysis are mostly inhibited,

which lowers hepatic glucose synthesis. Metformin also improves skeletal muscle glucose absorption and utilisation, which increases peripheral insulin sensitivity. Additionally, it prevents the absorption of intestinal glucose and, albeit little, encourages weight loss. These combined efforts help people with T2DM have better glycemic control (7).

Optimal Dosage: Based on the characteristics and tolerance of the patient, the dosage of metformin should be adjusted. Initially, 500 mg or 850 mg should be taken orally once or twice daily with meals. Up to a daily dose of 2,000–2,550 mg, the dose can be gradually increased every 1-2 weeks based on glycemic response and tolerability. It is possible to use once-daily dosage with extended-release formulations, which may increase gastrointestinal tolerability (7).

Latest consensus management recommendations: Guidelines for the management and treatment of hyperglycemia in T2DM were developed jointly by the ADA (American Diabetes Association) and the EASD (European Association for the Study of Diabetes). The 2022 ADA/EASD guidelines state that metformin monotherapy, excluding contraindications or intolerance, continues to be the front-line pharmaceutical treatment for most people with T2DM. The guidelines recommend initiating metformin at the time of diagnosis alongside lifestyle modifications and maintaining treatment unless contraindications or intolerance develop (13).

Furthermore, the guidelines emphasize the importance of individualizing treatment targets and incorporating shared decision-making with patients. They recommend considering metformin continuation even when additional glucose-lowering medications are required to achieve glycaemic control. In certain cases, such as when metformin is contraindicated or not tolerated, alternative therapies may be initiated as the initial pharmacological treatment.

4. Adverse effects of metformin:
Metformin is frequently used for the management and treatment of T2DM, and the drug has a generally positive safety profile and is well tolerated. However, metformin has certain drawbacks as well.

Effects on the Gastrointestinal Tract: The gastrointestinal tract is where metformin side effects are most frequently observed. Diarrhoea, nausea, vomiting, and abdominal discomfort are a few of them. According to clinical research, gastrointestinal side effects might occur somewhere between 5% and 30% of the time (14, 15). However, most of these side effects are minor and brief and go away on their own or after a dose modification.

Vitamin B12 Deficiency: Metformin use has been linked to a possible risk of Vit. B12 insufficiency. Metformin therapy for longer duration has been shown in investigations to potentially lower Vit. B12 and increase the prevalence of Vit. B12 insufficiency (15, 16). It is advised to regularly check vitamin B12 levels and think about prescribing supplements, most importantly in people who are at the risk of insufficiency, such as those in the geriatric age or those who have malabsorption problems (17).

Lactic Acidosis: This can be a rare but dangerous side effect while using metformin. It is important to remember that lactic acidosis associated with metformin-usage is extremely uncommon, with just 3 occurrences being documented per 100,000 patient years (18). People who have comorbidities or illnesses that predispose them to metabolic abnormalities, renal impairment, or acute sickness are more likely to develop lactic acidosis. When receiving the proper dosage, people with normal renal function run a very minimal risk of developing lactic acidosis (19).

Other Adverse Effects: Less commonly reported adverse effects of metformin include metallic taste, rash, reduced absorption of vitamin B12, and, rarely, hepatotoxicity. However, the occurrence of these adverse effects is infrequent, and the overall safety profile of metformin is favourable.

Overall, the benefits of metformin in achieving glycaemic control and in reducing the complications associated with T2DM far outweigh the potential adverse effects. The safety profile and metformin effectiveness in people with T2DM can be enhanced by regular monitoring, specific patient assessment, and appropriate dose adjustments.

5. Vitamin B12 – Biological functions and ADME:
Cobalamin, sometimes referred to as vitamin B-12, is important for several vital biological processes that occur in the human body. The production of DNA, RNA, and proteins, which are necessary for healthy cell division and growth, depends on Vit. B12. Furthermore, it also contributes in the development and maintenance of myelin sheaths, which safeguard nerve cells and support healthy brain activity. Additionally, it is involved in red blood cell formation, fatty acid metabolism, and amino acid metabolism (20).

The small intestine is where vitamin B-12 is largely absorbed. For effective absorption, an intrinsic factor released by the parietal cells in the gastric mucosa is needed. After being absorbed, Vit. B12 is carried to different tissues and organs via transcobalamin II, a transport protein that it interacts with. Vitamin B-12 is metabolised and transformed within the tissues into its active forms, methylcobalamin and adenosylcobalamin. A big part of storing vitamin B-12 for later use is the liver. Extra vitamin B-12 is removed through faeces and bile (20).

Role of Vitamin B12 in diabetic patients: In accordance with several studies, people living with diabetes have an increased risk of Vit. B12 insufficiency, than people without the disease (21, 22). Although the underlying causes of this connection are not entirely understood, they may include things like changed absorption, compromised transport proteins, and usage of the diabetes drug metformin. Diabetes patients with Vit. B12 deficiencies have an

increased probability of developing diabetic neuropathy, retinopathy, and cardiovascular problems.

Vitamin B12 insufficiency has been linked in clinical research to diabetic neuropathy, a common consequence of diabetes characterised by nerve damage. Due to the vitamin's significance in the production of myelin and the operation of the nervous system, Vit. B12 deficiency may contribute to the onset and progression of neuropathy. In a study involving diabetic patients with peripheral neuropathy, vitamin B12 supplementation improved nerve conduction velocity and neuropathic symptoms (21).

Diabetes-related vitamin B12 insufficiency has also been associated with increased risk of cardiovascular problems. In those with T2DM, Sato Y et al. showed that Vit. B12 treatment decreased cardiovascular risk factors such as homocysteine levels (22).

To effectively control diabetes and its consequences, Vit. B12 is essential. The incidence of Vit. B12 insufficiency in diabetic patients and its possible impact on diabetic neuropathy and cardiovascular consequences have been noted in clinical research. The consequences of Vit. B12 supplementation on neuropathic symptoms and risk markers of the cardiovascular system, have been encouraging. To better understand the mechanisms driving vitamin B12 insufficiency in diabetes and to identify the best preventative and care practises, more study is required.

Clinicians can optimise diabetes management and enhance patient outcomes by understanding of the importance of Vit. B12 in diabetes and its potential implications. Future research should concentrate on extensive clinical trials to determine the best vitamin B12 dosage, duration, and timing for diabetic patients and assess its long-term benefits on problems associated with diabetes.

6. General causes of Vitamin B12 deficiency in type 2 diabetes mellitus:

In comparison to the general population, Vit. B12 deficiency appears to be more prevalent in those with T2DM. The use of metformin, changed stomach physiology, and poor dietary practises are some of the many factors that contribute to vitamin B12 insufficiency in T2DM.

Utilisation of metformin: Vitamin B12 insufficiency has been linked to metformin, the first-line treatment for T2DM. Various research has found that taking metformin will decrease the absorption of Vit. B12 in the gut and hinders B12 transport through the intestinal epithelium. Long-term metformin medication, particularly at high doses, may cause a gradual drop in vitamin B12 levels (23).

Altered gastric physiology: Individuals with T2DM often exhibit changes in gastric physiology, such as delayed gastric emptying and reduced gastric acid secretion. These alterations can disrupt the normal release of vitamin B12 from food sources and impair its subsequent absorption. Additionally, reduced production of intrinsic factor, a protein necessary for B12 absorption in the ileum, can further contribute to vitamin B12 deficiency in T2DM (24).
Dietary factors: Poor dietary intake of vitamin B12-rich foods is another common cause of deficiency in both T2DM and the general population. The use of animal derived B12 sources, such as dairy products, fish, and meat, may be restricted for T2DM patients due to dietary limitations or food preferences (25).

To optimise their management and enhance clinical results, physicians should be made aware of these potential causes, and they may consider routine screening and Vit. B12 supplementation in T2DM patients at risk of deficiency.

7. Metformin induced vitamin B12 deficiency in T2DM:

Metformin, which is frequently recommended for T2DM (type 2 diabetic mellitus), was found to be associated with deficiency of Vit. B12. Vitamin B12 cannot be absorbed properly in the gut and cannot pass the intestinal epithelium when taken with metformin. Long-term metformin use, particularly at high doses, can cause a progressive drop in vitamin B12 levels. Clinically, vitamin B12 insufficiency can cause neurological and haematological problems, deteriorating the metabolic disorders already present in T2DM. For addressing this potential unwanted side effect of metformin, regular monitoring of Vit. B12 levels and consideration of supplemental solutions are essential (22).

Pathophysiology of Metformin-induced Vitamin B12 deficiency in T2DM:

New research has shed light on the pathophysiology of Vit. B12 insufficiency because of metformin in people with T2DM (type 2 diabetic mellitus). Ting et al. (25) in their research studied the fundamental mechanisms. They discovered metformin usage was linked to changes in gastrointestinal physiology, such as a reduction in stomach acid output and a delay in gastric emptying. These modifications may hinder Vit. B12 absorption and decrease its availability from dietary protein sources. Additionally, Ting et al. (25) recognised the influence of metformin on Vit. B12's intestinal transit. They found that metformin inhibited cubilin expression, which is a protein involved in the absorption of the intrinsic factor-Vit. B12 combination into enterocytes from the gut lumen. This decrease in cubilin expression can prevent vitamin B12 from being absorbed, which might result in a shortage.
In T2DM patients, Almatrafi et al. discovered a link between Vit. B12 levels and metformin usage. They discovered a highly significant negative connection, indicating that longer-term metformin medication was linked to decreased levels of Vit. B12. This finding backs up the idea that prolonged metformin usage can gradually worsen Vit. B12 insufficiency (26).

Impaired absorption: Metformin has been found to interfere with the gastrointestinal tract's ability to absorb vitamin B12, leading to impaired absorption. It is believed to disrupt the binding of Vit. B12 to the intrinsic factor in the stomach necessary for its absorption. Metformin's

interference with this binding process can result in a reduced availability of vitamin B12 for absorption, leading to deficiency (25).

Altered Intestinal Transport: The movement of vitamin B12 across the intestinal epithelium may also be impaired by metformin. According to studies, metformin inhibits the production and operations of proteins that are involved in the transportation of Vit. B12, such as cubilin and transcobalamin receptors. The intrinsic factor-Vit. B12 combination is taken up by cubilin from the gut lumen into enterocytes, and transcobalamin receptors help the vitamin B12 cross the enterocytes' basolateral membrane and enter the bloodstream. Metformin can affect these transport proteins' ability to function properly or downregulate them, which prevents the absorption and enterohepatic circulation of Vit. B12 and lead to insufficiency (23).

Gastric Physiology: Altered gastric physiology observed in T2DM, such as delayed gastric emptying and reduced gastric acid secretion, can also play a role in metformin-induced vitamin B12 deficiency. Delayed gastric emptying may prolong the contact time between metformin and the stomach, potentially increasing its interaction with the intrinsic factor and affecting its binding to Vit. B12. The release of Vit. B12 from food sources containing protein can be hampered by decreased stomach acid output, which is frequently seen in T2DM patients. Additionally, T2DM may result in decreased production of intrinsic factor in the gastric mucosa, further impairing Vit. B12 absorption (23).

Complex pathophysiological processes, such as reduced intestinal absorption, changed intestinal transport, and disturbed gastric physiology, contribute to metformin-induced Vit. B12 insufficiency in T2DM (Figure 1). To reduce the risk of consequences caused by Vit. B12 insufficiency, physicians should be made aware of this link, and consider routine monitoring of Vit. B12 levels and implement appropriate supplementing measures.

8. Metformin-induced Vitamin B12 deficiency – latest clinical evidence:

Metformin usage is associated with Vit. B12 deficit, according to many recent studies. According to Bell's 2010 research, 30% of individuals taking metformin on a chronic basis had vitamin B12 deficiencies, which might manifest as peripheral neuropathy (21). A favourable association of metformin use with Vit. B12 insufficiency was discovered by Khattab 2022 after conducting a systematic evaluation of 19 bodies of research, with higher metformin doses being closely linked to lower vitamin B12 levels (24). In individuals on metformin, Kang, 2014, discovered that sulfonylurea usage was a substantial independent risk factor for B12 insufficiency (27). The duration and dose of treatment with metformin were clinically significant risk factors for developing Vit. B12 deficiency, according to Ting's nested case-control study from 2006 (25). To avoid consequences from Vit. B12 deficiency, regular monitoring of Vit. B12 levels is advised during prolonged metformin administration.

Western Studies:

There is a wide variation in the incidence of Vit. B12 deficiency among metformin users that depends on the length and dosage of metformin therapy, and the population characteristics. As per recent meta-analysis, patients who used metformin had a prevalence of Vit. B12 deficiency that was 19.6% higher than that of non-users (9.5%) (28). However, studies from various nations and eras were included in this study, which could have had varied dietary customs and screening procedures.

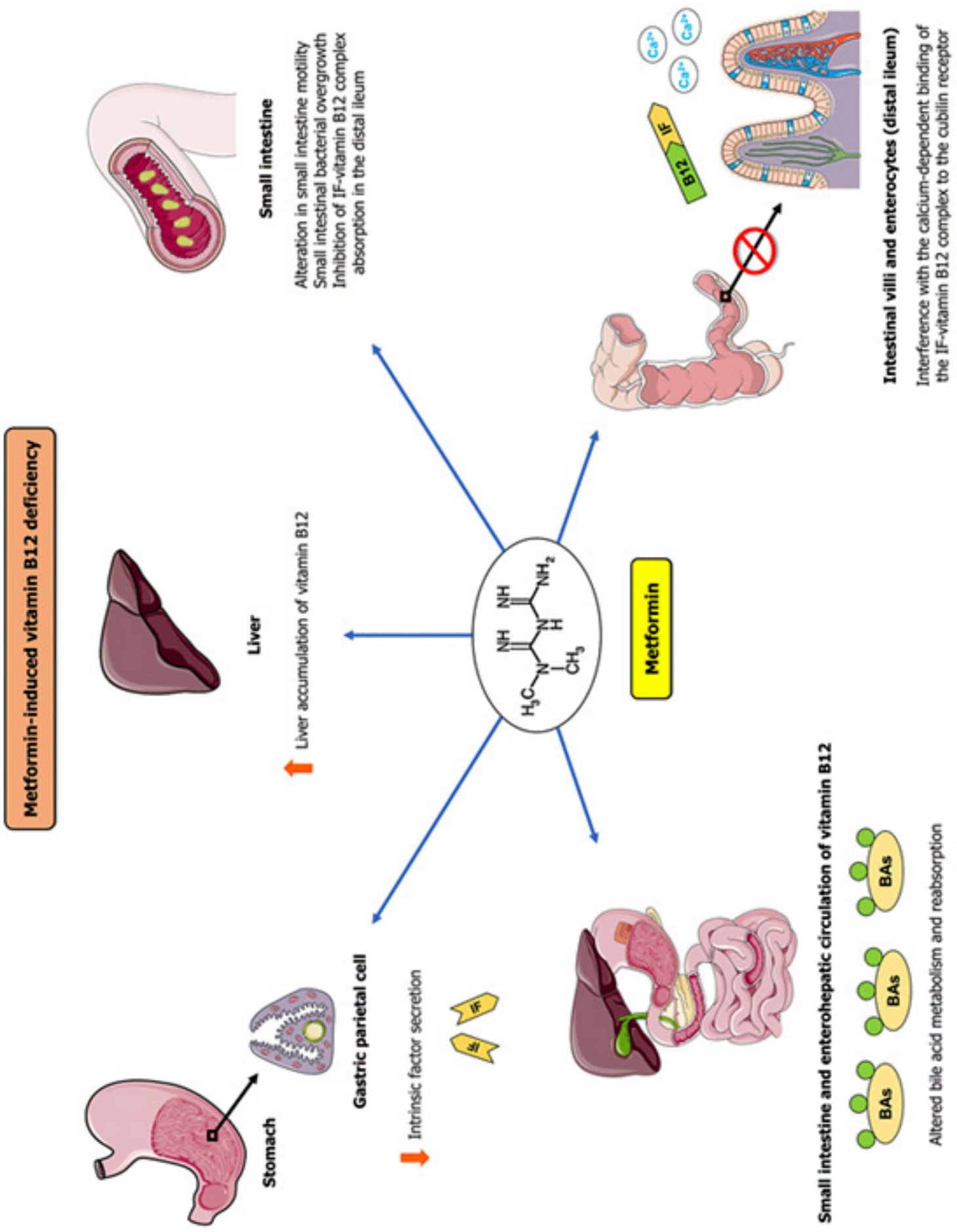
In a retrospective cohort analysis, Lee AK et al. (29) examined data from 14,623 type 2 diabetes patients who were recruited in a major Californian healthcare system between 2011 and 2017. According to the study, metformin users had a 6.3% prevalence of Vit. B12 insufficiency (200 pg/mL), while it was 2.4% in non-users. With higher dosages and longer treatment periods, the prevalence rose. Only 37% of metformin users checked their Vit. B12 levels during the study period, which points to a lower prevalence of screening for Vit. B12 deficiency.

Data from 1,621 T2DM patients who were a part of NHANES (National Health and Nutrition Examination Survey) between 2011 and 2016 were analysed by Kim JY et al. (30). According to this study, metformin users had Vit. B12 deficiency (200 pg/mL) higher than the non-users (5.8% vs. 2.4%). The frequency was higher in non-Hispanic females, older people (>60 years), , and those who had lower income and educational levels. Only 22% of metformin users checked their Vit. B12 levels in the previous year, according to the study's findings, which points to a lack of awareness of, and screening for, vitamin B12 deficiency.

Data from 4,368 type 2 diabetes patients who received care at a Texas Veterans Affairs Medical Centre between 2013 and 2018 were examined by Martin D et al. (31). The prevalence of Vit. B12 deficiency (200 pg/mL) was 7.4% among those using metformin, and 4.8% in non-users, according to the study. Higher metformin therapy doses led to an increase in prevalence, but no longer treatment times. Only 16% of metformin users had their vitamin B12 levels checked during the study period, according to the study's findings, indicating a low rate of vitamin B12 deficiency screening.

These three investigations demonstrate that metformin-induced vitamin B12 insufficiency is a prevalent and underreported condition among T2DM individuals in the United States. Depending on other characteristics and the dosage of metformin medication, the prevalence ranges from 5.8% to 7.4%. Despite recommendations from the American Diabetes Association and other organisations to frequently check vitamin B12 levels among metformin users, the screening rates for vitamin B12 deficiency are relatively low, ranging from 16% to 37%. This could result in missed opportunities for vitamin B12 deficient early detection and treatment, which can stop or reverse its effects.

Figure 1: Pathophysiology of Metformin induced Vitamin B12 deficiency in T2DM.



Note: Illustration obtained from Infante M et al. (23)

American individuals with type 2 diabetes frequently experience underdiagnosed metformin-induced vitamin B12 insufficiency. For these individuals' health and quality of life, it may have detrimental effects. Therefore, it is crucial to raise awareness of this issue, conduct more screenings, and offer suitable treatment and preventative measures.

Numerous studies have demonstrated that prolonged metformin treatment causes malabsorption of Vit. B12, with a drop in blood Vit. B12 content from 30% to 14%. It was discovered that patients who used higher dosages of metformin for longer periods of time had an increased chance of acquiring Vit. B12 insufficiency. Early identification of Vit. B12 deficiency in these patients is crucial to prevent further neurological and haematological symptoms (34).

In another cross-sectional study done in Spain, 312 people with T2DM who had used metformin for a period of six months were included. According to the study, 29.5% of the patients had borderline Vit. B12 deficiency (200-300 pg/mL) and 17.6% of the patients had severe deficiency (200 pg/mL). Patients who used greater metformin dosages (> 2000 mg/day) and for prolonged periods of time (> 5 years) had increased rates of vitamin B12 insufficiency. Additionally, the study discovered that lower levels of methylmalonic acid and homocysteine, indicators of poor Vit. B12 metabolism, were linked to vitamin B12 insufficiency (35).

There were 121 type 2 diabetics in an Italian prospective cohort research who had been on metformin for a period of one year. According to the study, 32.2% of the patients had borderline shortage of vitamin B12 (221–300 pmol/L), and 11.6% of the patients had severe deficiency (221 pmol/L). Patients who took metformin at larger doses (> 1500 mg/day) and for longer periods of time (> 10 years) had increased rates of vitamin B12 insufficiency. Additionally, the study discovered that low levels of haemoglobin and haematocrit, two markers of anaemia, were linked to Vit. B12 deficiency (36).

About 390 study participants with T2DM receiving metformin medication for a period of 4 months were enrolled in a randomised controlled trial from the Netherlands. In this experiment, blood vitamin B12 levels and clinical outcomes were examined after 52 weeks of oral vitamin B12 supplementation (850 mcg/day) against placebo. According to the research, vitamin B12 supplements significantly raised serum Vit. B12 levels by 55% as compared with placebo and stopped future Vit. B12 level reduction in individuals receiving metformin treatment. However, compared to placebo, vitamin B12 supplementation had no positive impact on homocysteine, haemoglobin, or quality of life scores (37).

These studies demonstrate that metformin medication in European patients with T2DM frequently results in Vit. B12 insufficiency, which may be a significant side effect. Additionally, they contend that lengthier use of metformin at higher doses and durations increases the chance of developing a vitamin B12 deficiency. These studies do, however, have several drawbacks, including small sample sizes, heterogeneity in the definition and measurement of Vit. B12 deficiency, a lack of confounding factor adjustment, and brief follow-up times.

Therefore, more investigation is required to establish the most effective screening frequency, cut-off values, and modes and dosages of Vit. B12 supplementation for individuals receiving metformin therapy. Furthermore, it's critical to examine the effects of Vit. B12 insufficiency and supplementation in metformin-treated patients, including anaemia, neuropathy, cognitive function, and cardiovascular risk.

Asian studies:

The association between metformin usage with Vit. B12 deficiency in various groups, including Asian individuals with T2DM has been examined in a number of systematic reviews and meta-analyses.

In a meta-analysis conducted by Khattab et al. (24), 19 studies that examined the impact of metformin on Vit. B12 levels in type 2 diabetes mellitus patients without Vit. B12 supplementation, were included (15 observational studies and 4 randomised controlled trials). The pooled odds ratio between metformin usage and Vit. B12 deficiency was found to be 2.23 (95% CI: 1.77 to 2.80), indicating a positive association between the two. Additionally, they noted that treatment duration was not highly correlated with Vit. B12 levels, although higher metformin doses were. The authors advised taking therapeutic Vit. B12 pills or injections together with a diet high in Vit. B12 to minimise consequences from Vit. B12 insufficiency. They also advised routine monitoring of Vit. B12 levels throughout long-term metformin use.

In another systematic review done by Infante et al. (23), 16 research (seven randomised controlled trials and nine observational) studies that examined the relationship of metformin medication with Vit. B12 deficiency in people with prediabetes or T2DM were included. In comparison to placebo or other antidiabetic medications, the authors discovered that treatment with metformin was related with a significant decrease in serum Vit. B12 levels, with a mean difference of -52.4 pmol/L (95% CI: -64.5 to -40.3). They added that elevated homocysteine and decreased folate levels were associated with metformin-induced vitamin B12 insufficiency, which may have detrimental effects on cardiovascular health. The authors recommended that people with prediabetes or T2DM who are using metformin for treatment should be evaluated for Vit. B12 deficiency, particularly if they had risk factors including advanced age, a vegetarian diet, or pernicious anaemia.

About 11 research (6 observational studies and 5 randomised controlled trials) that examined the impact of metformin on serum Vit. B12 levels in patients with prediabetes and T2DM in China were included in a meta-analysis done by Li et al. (38). When compared to those who did not take metformin, the researchers discovered a substantial drop in serum vitamin B12 levels, with a

mean difference of -55.6 pmol/L (95% CI: -74.9 to -36.4). They also noticed a link between lower serum levels of Vit. B12 and larger doses and longer periods of metformin treatment. The authors advised continuous monitoring of serum Vit. B12 levels in type 2 diabetes mellitus patients using metformin and, if necessary, Vit. B12 supplementation.

Studies from the Middle East region:
In several regions of the world, investigations have investigated the incidence of Vit. B12 insufficiency in diabetes patients and how it affects their response to metformin therapy. Additionally, metformin use has been linked to a 9%–52% drop in serum vitamin B12 levels, according to randomised control trials and cross-sectional investigations (39). However, there is a dearth of information on this subject throughout the Middle East, particularly in Qatar.

As shown in Table 1, the prevalence of Vit. B12 deficiency was found to be higher in diabetic patients receiving metformin therapy than in those not receiving it, ranging from 12.5% to 30.7% in individuals taking metformin and around 10% in individuals not using metformin, according to all five investigations. Metformin usage is found to have a moderate to high risk of Vit. B12 deficiency, according to odds ratios that ranged from 2.2 to 2.7.

The disparate approaches of the research and thresholds for identifying Vit. B12 deficiency, may make it difficult to interpret the findings. However, most of the research used a cut off value of < 150 pg/mL, which is consistent with the World Health Organization criteria for vitamin B12 deficiency. The studies also used different doses of metformin, but the mean doses were similar and within the recommended range of 1.5 to 2 g/day for T2DM patients. The length of metformin medication, another significant factor that may affect the likelihood of Vit. B12 deficiency, was not reported in the trials.

The clinical effects of Vit. B12 insufficiency in diabetic patients on metformin therapy, such as anaemia, neuropathy, or cognitive impairment, were not evaluated in the research. However, other studies found that individuals with Vit. B12 deficiency also had higher homocysteine and lower levels of haemoglobin and hematocrit, which may influence their hematopoietic and cardiovascular health.

9. Diagnosis of Vitamin B12 deficiency in T2DM:
Due to the potential consequences linked to a deficiency, the diagnosis of Vit. B12 deficiency in T2DM requires rigorous investigation. In the early assessment of Vit. B12 deficiency, clinical assessment is extremely important. It is important to look for signs and symptoms of deficiency in T2DM patients, such as fatigue, weakness, neuropathy, glossitis, and macrocytic anaemia. However, these clinical manifestations are non-specific and can overlap with other conditions, making a definitive diagnosis based on symptoms alone challenging.

Laboratory Testing:
Serum Vit. B12 Levels: The diagnosis of Vit. B12 deficiency is frequently made using serum vitamin B12 levels. The common reference range lies in the 200–900 pg/mL range. The ideal limit for identifying insufficiency in T2DM patients is still being debated, though. According to certain studies, concentrations below 300 pg/mL or even 350 pg/mL should be taken as a sign that this population is deficient (45).

Serum Folate and Homocysteine Levels: Since vitamin B12 deficiency can lead to elevated homocysteine and decreased serum folate levels, measuring these markers can provide supportive evidence. Elevated homocysteine levels (>15 µmol/L) and decreased serum folate levels can indicate impaired vitamin B12 metabolism (46).

Holotranscobalamin (holoTC): A portion of vitamin B12 that is biologically active and involved in cellular absorption is called holoTC. Assessing holoTC levels might offer a more precise evaluation of tissue B12 status. Even in the face of adequate total B12 levels, some studies contend that low holoTC levels (35 pmol/L) are a sign of functional vitamin B12 deficiency (47).

Methylmalonic Acid (MMA) and Homocysteine: MMA is a metabolite that accumulates in vitamin B12 deficiency. Elevated MMA levels (>0.37 µmol/L) can indicate impaired B12 metabolism. Combined measurement of MMA and homocysteine levels can improve diagnostic accuracy (48).

Table 1: Studies on metformin-induced vitamin B12 deficiency in the Middle East region

Study	Country	Sample size	Vit. B12 cutoff	Prevalence of Vit. B12 deficiency
Yousef Khan F et al. (40)	Qatar	3124	< 145 pg/ mL	30.7%
Alharbi TJ et al. (41)	Saudi Arabia	412	< 132.8 pg/ mL	Metformin group -9.4% Non-metformin group – 2.2%
Mohammed B et al. (42)	Saudi Arabia	347	< 145 pg/ mL	10.4%
Al Saeed RR et al. (43)	Saudi Arabia	307	< 150 pg/ mL	Deficiency -3.6% Borderline – 66.1%
Alshammari et al. (44)	Saudi Arabia	363	< 150 pg/ mL	12.5%

Intrinsic Factor Antibody (IFA) Testing: IFA testing is useful in detecting pernicious anaemia, an autoimmune condition found in vitamin B12 deficiencies. The presence of IFA is indicative of autoimmune-mediated destruction of intrinsic factors, impairing B12 absorption. However, it is important to note that IFA testing has limitations, including false-positive results and a lack of sensitivity in some cases (49).

The diagnosis and management of Vit. B12 deficiency in T2DM requires a comprehensive approach, considering clinical assessment and laboratory testing. Serum vitamin B12 levels, supplemented by measurements of folate, homocysteine, holoTC, MMA, and IFA, can aid in diagnosing deficiency and evaluating the functional status of vitamin B12. Additionally, considering the individual patient's clinical presentation, medical history, and response to supplementation is crucial for accurate diagnosis and appropriate management.

10. Management of Vitamin B12 deficiency in T2DM: To avoid potential problems and enhance patient outcomes, Vit. B12 deficiency in T2DM must be properly managed. It's critical to get an early and precise diagnosis of Vit. B12 insufficiency in T2DM. According to the most recent recommendations, serum levels of Vit. B12 should be measured along with other indicators such holotranscobalamin, methylmalonic acid (MMA), and homocysteine (50). In T2DM patients taking metformin or who have clinical signs of a vitamin B12 deficit, routine monitoring of Vit. B12 status is advised.

Oral Vit. B12 Supplementation: Oral Vit. B12 supplementation is a convenient and effective option for patients with T2DM. It is recommended to use high-dose oral B12 supplements (1,000 to 2,000 µg/day) due to the impaired absorption associated with T2DM. This high-dose approach compensates for the reduced absorption efficiency and ensures adequate vitamin B12 levels (51).
Intramuscular Vitamin B12 Injection: In cases of severe deficiency or malabsorption, intramuscular injection of vitamin B12 is the preferred route of administration. The initial treatment typically involves a series of injections (1,000 µg/day) for several days or weeks, followed by maintenance injections (1,000 µg/month) (52).

Subcutaneous or Intranasal Vitamin B12: Emerging evidence suggests that subcutaneous or intranasal administration of vitamin B12 may be a viable alternative to intramuscular injection. These approaches are more practical and might be preferred by patients. To determine their effectiveness and safety in T2DM, however, more research is required (51).

Patient education: Treatment of vitamin B12 insufficiency in T2DM includes patient education as a key component. Healthcare professionals should stress the value of consistent observation, adherence to supplementation plans, and knowledge of dietary sources of vitamin B12. It can also assist to promote a balanced diet that includes foods high in vitamin B12, such as dairy products, eggs, poultry, meat, and fish (52).

Interdisciplinary Collaboration: For the best therapy of vitamin B12 deficiency in T2DM, collaboration amongst healthcare professionals, including endocrinologists, primary care doctors, nutritionists, and pharmacists, is crucial. Comprehensive evaluation, appropriate supplements, routine monitoring, and continuous patient assistance are all made possible by an interdisciplinary approach (52).

Accurate diagnosis, sensible supplementation plans, patient education, and interdisciplinary cooperation all go into managing vitamin B12 deficiency in T2DM. Consensus and recommendations urge routine vitamin B12 level monitoring, high-dose oral supplementation, intramuscular injections for severe deficiency, and thought of alternate administration methods. Long-term management requires patient education and lifestyle changes. Healthcare providers can optimise the treatment of T2DM patients with vitamin B12 insufficiency and enhance their general health outcomes by putting these recommendations into practise.

Conclusion

One noticeable and potentially harmful adverse effect of metformin therapy in persons with T2DM is metformin-induced Vit. B12 deficiency. It may result in several clinical problems, including anaemia, neuropathy, memory loss, and cardiovascular disease. Therefore, to avoid the detrimental effects of this illness, regular screening and appropriate management are crucial. Measurement of serum Vit. B12 levels and other indicators, supplementation with oral or parenteral Vit. B12, and dietary changes are all part of the screening and management techniques for metformin-induced Vit. B12 insufficiency.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: International Diabetes Federation. (2019). Accessed: June 28, 2023: https://www.diabetesatlas.org.
2. American Diabetes Association; 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2020. Diabetes Care 1 January 2020; 43 (Supplement_1): S14–S31. 10.2337/dc20-S002.
3. Bener A, Zirie M, Janahi IM, et al. Prevalence of diagnosed and undiagnosed diabetes mellitus and its risk factors in a population-based study of Qatar. Diabetes Res Clin Pract. 2009;84(1):99-106. 10.1016/j.diabres.2009.02.003.
4. Alhyas L, McKay A, Balasanthiran A, et al. Prevalences of overweight, obesity, hyperglycaemia, hypertension and dyslipidaemia in the Gulf: systematic review. JRSM Short Rep. 2011 Jul;2(7):55. 10.1258/shorts.2011.011019.
5. Al-Kaabi J, Al-Maskari F, Saadi H, et al. Assessment of dietary practice among diabetic patients in the United arab emirates. Rev Diabet Stud. 2008 Summer;5(2):110-5. 10.1900/RDS.2008.5.110.

6. American Diabetes Association. Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45 (Supplement 1): S1-S232. 10.2337/dc22-SINT
7. American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45 (Supplement 1):S125-S143. 10.2337/dc22-S009.
8. Bonoto BC, de Araújo VE, Godói IP, et al. Efficacy of mobile apps to support the care of patients with diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. JMIR Mhealth Uhealth. 2017;5(3):e4. 10.2196/mhealth.6309.
9. Kitsiou S, Paré G, Jaana M, et al. Effectiveness of mHealth interventions for patients with diabetes: an overview of systematic reviews. PLoS One. 2017;12(3): e0173160. 10.1371/journal.pone.0173160.
10. Wang J, Cai C, Padhye N, et al. A behavioral lifestyle intervention enhanced with multiple-behavior self-monitoring using mobile and connected tools for underserved individuals with type 2 diabetes and comorbid overweight or obesity: pilot comparative effectiveness trial. JMIR Mhealth Uhealth. 2018;6(4):e92. 10.2196/ mhealth.4478.
11. Schauer PR, Bhatt DL, Kirwan JP. Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes. N Engl J Med. 2017;376(7):641-651. 10.1056/NEJMoa1600869.
12. Rubino F, Nathan DM, Eckel RH. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care. 2016;39(6):861-877. 10.2337/dc16-0236.
13. Buse JB, Wexler DJ, Tsapas A, et al. 2022 update to: Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022;45(1):4-36. 10.2337/dci19-0066.
14. Bailey CJ, Turner RC. Metformin. N Engl J Med. 1996;334(9):574-579. 10.1056/NEJM199602293340906.
15. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ. 2010;340:c2181. 10.1136/bmj. c2181.
16. Wulffelé MG, Kooy A, Lehert P, et al. Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial. J Intern Med. 2003;254(5):455-463. 10.1046/j.1365-2796.2003.01213.x.
17. Pflipsen MC, Oh RC, Saguil A, et al. The prevalence of vitamin B(12) deficiency in patients with type 2 diabetes: a cross-sectional study. J Am Board Fam Med. 2009;22(5):528-534. 10.3122/jabfm.2009.05.090044.
18. Misbin RI. The phantom of lactic acidosis due to metformin in patients with diabetes. Diabetes Care. 2004 Jul;27(7):1791-3. 10.2337/diacare.27.7.1791.
19. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients: prognostic value of arterial lactate levels and plasma metformin concentrations. Drug Saf. 1999 Mar;20(3):377-84. 10.2165/00002018-199920040-00006.
20. Reynolds E. Vitamin B12, folic acid, and the nervous system. Lancet Neurol. 2006;5(11):949-60. 10.1016/S1474-4422(06)70598-1.
21. Bell DS. Metformin-induced vitamin B12 deficiency presenting as a peripheral neuropathy. South Med J. 2010 Mar;103(3):265-7. 10.1097/SMJ.0b013e3181ce0e4d.
22. Sato Y, Ouchi K, Funase Y, et al. Relationship between metformin use, vitamin B12 deficiency, hyperhomocysteinemia and vascular complications in patients with type 2 diabetes. Endocr J. 2013;60(12):1275-80. 10.1507/endocrj.ej13-0332.
23. Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin B12 deficiency: An association to bear in mind. World J Diabetes 2021; 12(7): 916-931. 10.4239/wjd.v12.i7.916.
24. Khattab R, Albannawi M, Alhajjmohammed D, et al. Metformin-Induced Vitamin B12 Deficiency among Type 2 Diabetes Mellitus' Patients: A Systematic Review. Curr Diabetes Rev. 2023;19(4):1-10. 10.2174/157339981 8666220418080959.
25. Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM. Risk factors of vitamin B12 deficiency in patients receiving metformin. Arch Intern Med. 2006;166(18):1975-1979. 10.1001/archinte.166.18.1975.
26. Almatrafi SB, Bakr EH, Almatrafi AA, et al. Prevalence of vitamin B12 deficiency and its association with metformin-treated type 2 diabetic patients: A cross sectional study. Human Nutrition & Metabolism, 2022;27, 200138. 10.1016/j.hnm.2022.200138.
27. Kang D, Yun JS, Ko SH, et al. Higher prevalence of metformin-induced vitamin B12 deficiency in sulfonylurea combination compared with insulin combination in patients with type 2 diabetes: a cross-sectional study. PLoS One. 2014 Oct 9;9(10):e109878. 10.1371/journal. pone.0109878.
28. Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency. Diabetes Res Clin Pract. 2012;97(3):359-367. 10.1016/j.diabres.2012.06.001.
29. Lee AK, Lee CJ, Huang ES, et al. Risk of hypoglycemia following intensification of metformin treatment with insulin versus sulfonylurea. CMAJ. 2016;188(4):E98-E106. 10.2337/dc17-0819.
30. Kim J, Ahn CW, Fang S, et al. Association between metformin dose and vitamin B12 deficiency in patients with type 2 diabetes. Medicine (Baltimore). 2019 Nov;98(46): e17918. 10.1097/MD.0000000000017918.
31. Martin D, Thaker J, Shreve M, et al. Assessment of vitamin B12 deficiency and B12 screening trends for patients on metformin: a retrospective cohort case review. BMJ Nutr Prev Health. 2021 Jan 4;4(1):30-35. 10.1136/ bmjnph-2020-000193.
32. American Diabetes Association. Standards of medical care in diabetes-2020 abridged for primary care providers. Clin Diabetes. 2020;38(1):10-38. 10.2337/cd20-as01.
33. Qaseem A, Barry MJ, Humphrey LL, et al. Clinical Guidelines Committee of the American College of Physicians; Fitterman N, Horwitch C, Kansagara D, McLean RM, Wilt TJ. Oral Pharmacologic Treatment of

Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med. 2017 Feb 21;166(4):279-290. 10.7326/M16-1860.
34. Al-Hamdi A, Al-Gahhafi M, Al-Roshdi S, et al. Vitamin B12 Deficiency in Diabetic Patients on Metformin Therapy: A cross-sectional study from Oman. Sultan Qaboos Univ Med J. 2020 Feb;20(1):e90-e94. 10.18295/squmj.2020.20.01.013.
35. Calvo Romero JM, Ramiro Lozano JM. Vitamin B (12) in type 2 diabetic patients treated with metformin. Endocrinol Nutr. 2012 Oct;59(8):487-90. 10.1016/j.endonu.2012.06.005.
36. Sayedali E, Yalin AE, Yalin S. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes. World J Diabetes. 2023 May 15;14(5):585-593. 10.4239/wjd.v14.i5.585.
37. van Wijngaarden JP, Swart KM, Enneman AW, et al. Effect of daily vitamin B-12 and folic acid supplementation on fracture incidence in elderly individuals with an elevated plasma homocysteine concentration: B-PROOF, a randomized controlled trial. Am J Clin Nutr. 2014 Dec;100(6):1578-86. 10.3945/ajcn.114.090043.
38. Yang W, Cai X, Wu H, et al. Associations between metformin use and vitamin B12 levels, anemia, and neuropathy in patients with diabetes: a meta-analysis. J Diabetes. 2019 Sep;11(9):729-743. 10.1111/1753-0407.12900.
39. Chapman LE, Darling AL, Brown JE. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab. 2016 Nov;42(5):316-327. 10.1016/j.diabet.2016.03.008.
40. Yousef Khan F, Yousif AB, Suliman A, et al. Association of vitamin B12 deficiency with metformin use in patients with type 2 diabetes treated in the largest tertiary care hospital in Qatar. Qatar Med J. 2021 Sep 9;2021(2):39. 10.5339/qmj.2021.39.
41. Alharbi TJ, Tourkmani AM, Abdelhay O, et al. The association between metformin therapy and vitamin B12 deficiency: a cross-sectional study. J Family Community Med. 2019;26(3):206-211. 10.1371/journal.pone.0204420.
42. Mohammad B. Jajah, Amjad A. Althagafi, Norah M, et al. Prevalence of vitamin B12 deficiency in type 2 diabetes patient treated with metformin. World Family Medicine. 2020; 18(1): 54-59. 10.5742MEWFM.2020.
43. Al Saeed RR, Baraja MA. Vitamin B12 deficiency in patients with type 2 diabetes mellitus using metformin and the associated factors in Saudi Arabia. Saudi Med J. 2021 Feb;42(2):161-165. 10.15537/smj.2021.2.25693.
44. Alshammari AN, Iqbal R, Baksh IP. Vitamin B12 deficiency and the knowledge and practice of physicians regarding screening for vitamin B12 deficiency among type 2 diabetic patients on metformin in selected hospitals in Riyadh, Saudi Arabia. J. Fam. Med. Prim. Care. 2019;8:2306–2311. 10.4103/jfmpc.jfmpc_416_19.
45. Carmel R. How I treat cobalamin (vitamin B12) deficiency. Blood. 2008 Sep 15;112(6):2214-21. 10.1182/blood-2008-03-040253.
46. Allen LH. Vitamin B-12. Adv Nutr 2012;3:54-55. 10.3945/an.111.001370.
47. Nexo E, Hoffmann-Lücke E. Holotranscobalamin, a marker of vitamin B-12 status: analytical aspects and clinical utility. Am J Clin Nutr. 2011 Jul;94(1):359S-365S. 10.3945/ajcn.111.013458.
48. Langan RC, Goodbred AJ. Vitamin B12 deficiency: Recognition and management. Am Fam Physician 2017;96:384-9. Accessed: June 29, 2023: https://www.aafp.org/pubs/afp/issues/2017/0915/p384.html
49. Mineva EM, Sternberg MR, Zhang M, Aoki Y, Storandt R, Bailey RL, et al. Age-specific reference ranges are needed to interpret serum methylmalonic acid concentrations in the US population. Am J Clin Nutr 2019;110:158-68. 10.1093/ajcn/nqz045.
50. Hannibal L, Lysne V, Bjørke-Monsen A-L, Behringer S, Grünert SC, Spiekerkoetter U, et al. Biomarkers and algorithms for the diagnosis of vitamin B12 deficiency. Front Mol Biosci 2016;3:27. 10.3389/fmolb.2016.00027.
51. Devalia V, Hamilton MS, Molloy AM British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014;166:496–513. 10.1111/bjh.12959.
52. Andrès E, Noel E, Goichot B. Metformin-associated vitamin B12 deficiency. Arch Intern Med. 2002;162:2251–2252. 10.1001/archinte.162.19.2251-a.

Robot-Assisted Versus Laparoscopic Radical Nephrectomy: A Systematic Review and Meta-Analysis

Hazim Mohammed alsufyani [1], Mohammed Adel Mohammed Shami [2], Ahmed abdelazim abdelaziz haty [3], Mohammed Mutlaq Hamdan Althobaiti [4], Ayman Khalid Kurdi [5], Ahmed Faisal Siraj [6], Abdulaziz M Althaqafi [7], Hussain A Albarqi [8]

(1) Consultant of Adult and Pediatric Urology, Department of Urology, King Faisal medical complex, Taif
(2) Bachelor in Medicine and Surgery, Urology Department, King Abdulaziz Specialist Hospital, Taif
(3) Higher academic degree : Doctorate degree of medicine, Urology department, King Faisal Medical Complex
(4) Bachelor in Medicine and Surgery, Urology department, King faisal medical complex
(5) Bachelor's Degree of Medicine, Urology Department King Saud Bin Abdulaziz University, Jeddah, King Faisal Complex, Taif
(6) Bachelor of medicine and surgery, Taif University College of Medicine, Makkah Region
(7) Urology resident, Department of urology, King Faisal medical complex, Taif
(8) Bachelor in Medicine & Surgery, Urology Department, King Faisal Medical complex, Saudi Arabia

Corresponding author:
Hazim Mohammed alsufyani
Consultant of Adult and Pediatric Urology, Department of Urology, King Faisal medical complex, Taif, Saudi Arabia

Received: July 2023. Accepted: August 2023; Published: September 1, 2023.
Citation: Hazim Mohammed alsufyani et al. Robot-Assisted Versus Laparoscopic Radical Nephrectomy: A Systematic Review and Meta-Analysis. World Family Medicine. August 2023; 21(8): 55-69. DOI: 10.5742/MEWFM.2023.95256180

Abstract

Background: For the treatment of renal cell carcinoma, robotic-assisted radical nephrectomy (RARN) has been developed as an alternative to laparoscopic radical nephrectomy (LRN) (RCC). The objective of this systematic review and meta-analysis was to compare the perioperative results of RARN and LRN in the treatment of RCC.

Methodology: An exhaustive search of electronic databases from their inception until May 2023 was done. The meta-analysis comprised nine trials with a total of 13,676 individuals who underwent either RARN or LRN. Estimated blood loss, length of hospital stay, conversion rate, transfusion rate, and perioperative complications were evaluated as surgical outcomes.

Results: The meta-analysis revealed no statistically significant demographic differences between the two surgical techniques. There were no significant differences between RARN and LRN in terms of predicted blood loss, length of hospital stay, conversion rate, or transfusion rate. The meta-analysis of complications revealed no significant differences between the two surgical methods for intraoperative or postoperative problems.

Conclusion: This comprehensive review and meta-analysis suggests that RARN and LRN had comparable perioperative results when used to treat RCC. Although RARN may give prospective benefits in the form of enhanced visibility and dexterity, the clinical significance of these benefits remains unknown. Further high-quality studies with long-term follow-up are required to further comprehend the possible advantages and disadvantages of RARN against LRN in the treatment of RCC.

Key words: Robot assisted laparoscopic radical nephrectomy, meta-analysis

Introduction

Robson described radical nephrectomy as the usual treatment for localized renal cell cancer in 1963 [1]. The intact kidney covered by Gerota's fascia, as well as the ipsilateral adrenal gland and proximal ureter, are routinely removed. Concomitant excision of renal hilar lymph nodes is controversial and is not regularly performed in most facilities. Laparoscopic nephrectomy, which can be performed by a transperitoneal or retroperitoneal technique, has grown in popularity in recent years for both benign and malignant illness [2]. Clayman et al. initially described laparoscopic transperitoneal nephrectomy for an oncocytoma in 1990 [3]. Laparoscopic uncomplicated nephrectomy is currently recognized as a safe treatment with several benefits, including improved cosmesis, reduced analgesic needs, shorter hospital stays, and quicker recovery [4]. Nephron-sparing surgery has been positioned as the gold standard for the treatment of T1 tumours, bilateral renal masses, or renal neoplasms in single-kidney patients [5], to preserve renal function, compared to radical nephrectomy. However, part of the reason for this advancement in minimally invasive surgical techniques was due to an increase in the incidence of renal cancer [6], which led to the development of these techniques. Robotic-assisted partial nephrectomy is now a safe procedure that has a shorter warm ischemia time (WIT) than the laparoscopic method because of recent advancements in minimally invasive surgery [7]. The robotic technique is employed in numerous other urological procedures, such as prostatectomy, and it has seen significant development in several other specialties, such as breast cancer and reconstruction surgery [8]. Due to the progress of vascular reconstruction using 3D technology for preoperative planning and surgical simulation, since the first RAPN was carried out by Gettman et al. in 2002, this approach has advanced to be able to treat patients with T2 tumors or complex masses [9]. For bigger and/or locally advanced renal malignancies that are ineligible for partial nephrectomy (PN), current recommendations prescribe radical nephrectomy (RN). Due to similar oncological results, but reduced perioperative morbidity, guidelines also favour laparoscopic RN (LRN) over open RN (ORN) [10]. Robot-assisted nursing (RRN) is being used more frequently thanks to technological advancements and widespread adoption of robot-assisted surgery. Studies have revealed a consistent drift in favour of RRN as a result in recent years. Robotic surgery has not yet been shown to be superior to traditional laparoscopy for the treatment of clinically localized renal cell carcinoma (RCC), and no randomized controlled trial comparing the efficacy of RRN and LRN has been conducted [11]. While there are some undeniable advantages of robot-assisted surgery over laparoscopy, such as three-dimensional vision, degrees of freedom, elimination of the fulcrum effect, suppression of physiological tremor, and improved dexterity, they might not always translate into a definite advantage in the case of RN. Additionally, possible drawbacks (lack of tactile input, extended setup times, and higher total expenses) could offset the advantages of the minimally invasive nature shared by RRN and LRN (shorter hospital stays, faster recovery) [12]. In difficult procedures including the management of big tumours, aberrant anatomy, or higher tumour stages involving contiguous organ invasion that are often managed with ORN, some unique features of robot-assisted surgery may be helpful. RN and thrombectomy are typically used in the treatment of locally advanced non-metastatic RCC with venous tumour thrombosis. Only a few cases of pure laparoscopy or a combination procedure with hand help or open conversion have been described thus far; most of these cases have been carried out utilizing an open approach. By minimizing caval manipulation and facilitating simpler vascular reconstruction, the robotic technique may reduce the chance of accidental embolization, which is a common cause of perioperative death in these circumstances [13]. In patients having RN for kidney cancer, the aim of this systematic analysis is to assess the outcomes of robotic surgery and compare them to those of laparoscopic and open surgery.

Methodology

Search Techniques and Selection of Studies

The authors did a systematic search of MEDLINE, PubMed, Google scholar, CINAHL, EMBASE, and Scopus from 1 January 2000 to 30 May 2023. The following search terms were used: (Robotics or Robot-Assisted) AND (Laparoscopic or Laparoscopy) AND Radical Nephrectomy AND (Kidney neoplasms or carcinoma or cancer). The search was limited to English-language publications only. The titles and abstracts of the discovered papers were independently reviewed by two researchers to determine their eligibility for inclusion in the study. Then, the complete texts of possibly eligible publications were examined to determine if they matched the inclusion criteria. Any disagreements between the two researchers were handled through consensus or by a third researcher.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Studies comparing robot-assisted radical nephrectomy (RARN) and laparoscopic radical nephrectomy (LRN) in patients with kidney cancer; (2) studies reporting at least one of the following outcomes: operative time, estimated blood loss, length of hospital stay, conversion rate to open surgery, complication rate, or oncologic outcomes; (3) English-language studies; and (4) studies published between 1 January 2000 and 30 May 2023.

Exclusion criteria included (1) studies that did not compare RARN and LRN, (2) studies that did not provide any of the outcomes of interest, (3) studies published in languages other than English, and (4) studies published prior to January 1, 2000.

Extraction of data and quality evaluation

Two separate researchers independently extracted data from the eligible studies. Authors, publication year, study design, sample size, patient characteristics, kind of surgery, outcomes of interest, and findings were retrieved. Any data extraction conflicts were resolved by consensus or a third investigator.

Using the Cochrane Risk of Bias tool for randomised controlled trials and the Newcastle-Ottawa Scale for non-randomized research, the quality of the included studies was evaluated. Discrepancies in the evaluation of quality were handled by consensus or a third investigator.

Analytical Statistics

The meta-analysis was performed using the software Review Manager (version 5.4). Continuous outcomes were summarised using the mean difference (MD) and 95 percent confidence interval (CI), while dichotomous outcomes were summarised using the odds ratio (OR) and 95 percent CI. Using the I2 statistic, heterogeneity between studies was determined. When sufficient heterogeneity was evident (I2 > 50%), a random-effects model was utilised to combine the data. In the absence of significant heterogeneity (I2 50%), a fixed-effects model was employed.

Synthesis of Data and Reporting

Using forest plots, the results of the meta-analysis were given. A narrative summary of the systematic review's findings was provided. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, the study was reported.

Results

Study Selection and Characteristics:

A thorough search of electronic databases, including PubMed, Embase, and Cochrane Library, was done from inception to May 2023. "robotic-assisted radical nephrectomy," "laparoscopic radical nephrectomy," "renal cell carcinoma," and "kidney cancer" were the search phrases utilised. Initial research revealed 1,056 potentially relevant studies. After deleting duplicates and screening titles and abstracts, the eligibility of 39 full-text publications was evaluated. 30 papers were removed for a variety of reasons, including non-comparative studies, case reports, and studies that did not report results of interest.

This systematic review and meta-analysis included nine trials with a total of 13,676 patients who underwent robotic-assisted radical nephrectomy (RARN) or laparoscopic radical nephrectomy (LRN). The research designs were prospective, retrospective, and matched by propensity score. The surgical procedures employed were RARN and LRN. Table 1 presents the baseline characteristics of the included studies, whereas Table 2 provides an evaluation of the research' quality. In every study, the patient's age, gender, BMI, tumour size, and duration of follow-up were recorded.

Figure 1: The PRISMA figures showing the steps to choose the studies for systematic review

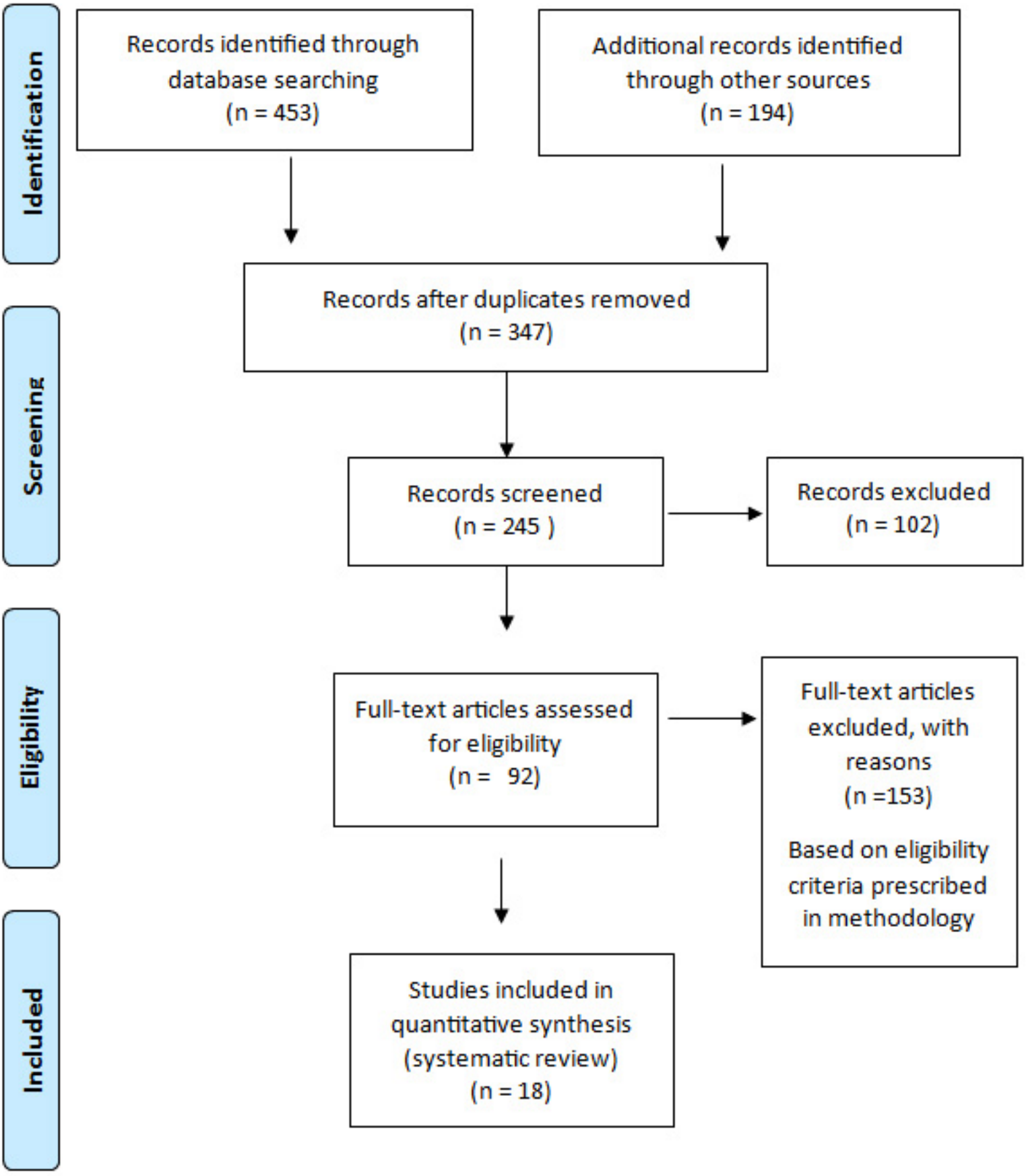


Table 1: Baseline characteristics of included studies and methodological assessment.

Authors	Year	Study Design	Surgical Method	Patients (N)	Age (years)	BMI	Tumour Size (cm)	Follow-up (months)	Quality Score	Level of Evidence
Nazemi et al. [14]	2006	Prospective	RARN	6	63.2 ± 32.4	27.1 ± 11.4	4.3 ± 2.6	4 (1–10)	7	4
			LRN	12	62.7 ± 27.7	28.9 ± 17.3	7.1 ± 10.7	7 (1–21)		
Hemal et al. [15]	2009	Prospective	RARN	15	50.3 ± 10.2	28.3 ± 4.5	6.7 ± 2.3	8.3 (1–12)	7	4
			LRN	15	52.7 ± 11.8	29.1 ± 3.4	6.9 ± 2.1	9.1 (2–12)		
White et al. [16]	2011	Retrospective	RARN	10	66 ± 17.2	29.4 ± 6	5.5 ± 2.2	10.5	7	2b
			LRN	10	66.5 ± 11.2	30.5 ± 8.2	7 ± 2.9	10.5		
Helmers et al. [17]	2016	Prospective	RARN	76	62 ± 11.5	27.8 ± 6.3	5.6 ± 2.9	NR	7	4
			LRN	243	62.1 ± 13.1	28.9 ± 5.4	6 ± 3	NR		
Jeong et al., [18]	2017	Retrospective	RARN	5180	60.87 ±21.98	NA	NA	NA	7	4
			LRN	18573	60.87 ± 21.98	NA	NA	NA		
Li et al. [19]	2017	Retrospective	RARN	21	59.1 ± 13.4	25.8 ± 3.5	NR	5.1 (3–10)	6	4
			LRN	23	59.4 ± 5.5	24.8 ± 3.5	NR	3.9 (3–9)		
Golombos et al. [20]	2017	Propensity Score Match	RARN	230	73.7 ± 6.0	NR	4.8 ± 2.6	3.2*	7	2b
			LRN	230	74.2 ± 6.2	NR	4.8 ± 2.3	3.2		
Anele et al. [21]	2019	Retrospective	RARN	404	62.6 ± 12.3	27.8 ± 4.7	8.7 ± 2.1	14.9 (6–34)	8	2b
			LRN	537	63.3 ± 11.2	26.9 ± 5.6	8.9 ± 1.5	20.2 (7–43.2)		
Gershman et al [22]	2020	Retrospective comparison	RARN	4926	59.6 ± 12.5	NA	NA	NA	7	2b
			LRN	3390	62.6 ± 12.5	NA	NA	NA		

Table 2: Quality assessment of included studies

Study	Selection				Comparability		Exposure			Total points
	REC	SNEC	AE	DO	SC	AF	AO	FU	AFU	
Nazemi et al.	1	1	1	1	1		1		1	7
Hemal et al.	1	1	1	1	1		1		1	7
White et al.	1	1	1	1	1		1		1	7
Helmers et al.	1	1	1	1	1		1		1	7
Golombos et al.	1	1	1	1	1		1		1	7
Jeong et al	1	1	1	1	1		1		1	7
Li et al.	1	1	1	1	1		1			6
Anele et al.	1	1	1	1	1		1	1		8
Gershman	1	1	1	1	1		1		1	7

Demographics of the Studies:

Table 3 displays the findings of the meta-analysis of the demographics of the studies. There were a total of 10,868 patients who received RARN and 23,033 patients who underwent LRN throughout nine investigations. There was no significant difference between the two groups in terms of age (weighted mean difference (WMD), -0.56; 95 % CI, -1.30 to 0.35; p=0.213), sex (odds ratio (OR), 1.01; 95 R CI, 0.72 to 1.32; p=0.98), BMI (WMD, 0.55; 95 % CI, -0.17 to 0.88; p=0.19), or tumour size (WMD, -0.07; 95 % CI, -0.58 to 0.13; p=0.53).

Table 3: The demographics of the studies.

Outcomes	No. of studies	No. of patients RARN/LRN	WMD or OR (95% CI)	*P*-value	Heterogeneity			
					Chi^2	df	*P*	I^2 (%)
Age	9	10,868/23,033	−0.55 [−1.40, 0.30]	0.21	0.35	6	1.00	0
Sex	7	762/1,070	1.00 [0.82, 1.22]	0.98	3.44	6	0.75	0
BMI	6	532/840	0.45 [−0.07, 0.98]	0.09	5.78	5	0.33	13
Tumor size	6	741/1,047	−0.08 [−0.28, 0.12]	0.43	3.11	5	0.68	0

Sensitivity Analysis and Publication Bias:

After performing a sensitivity analysis on OT, EBL, and LOS, it was determined that the results were unaffected by eliminating any of the studies. The evaluation of publication bias using the ROBINS-I instrument revealed a modest probability of bias in all comparable studies.

Length of Hospital Stay:

The meta-analysis of hospital length of stay (LOS) included seven trials with 1,832 participants in total. The research revealed that there was no significant difference between RARN and LRN in terms of LOS (WMD, -0.24; 95% CI, -0.78 to 0.01; p=0.65) (Figure 1).

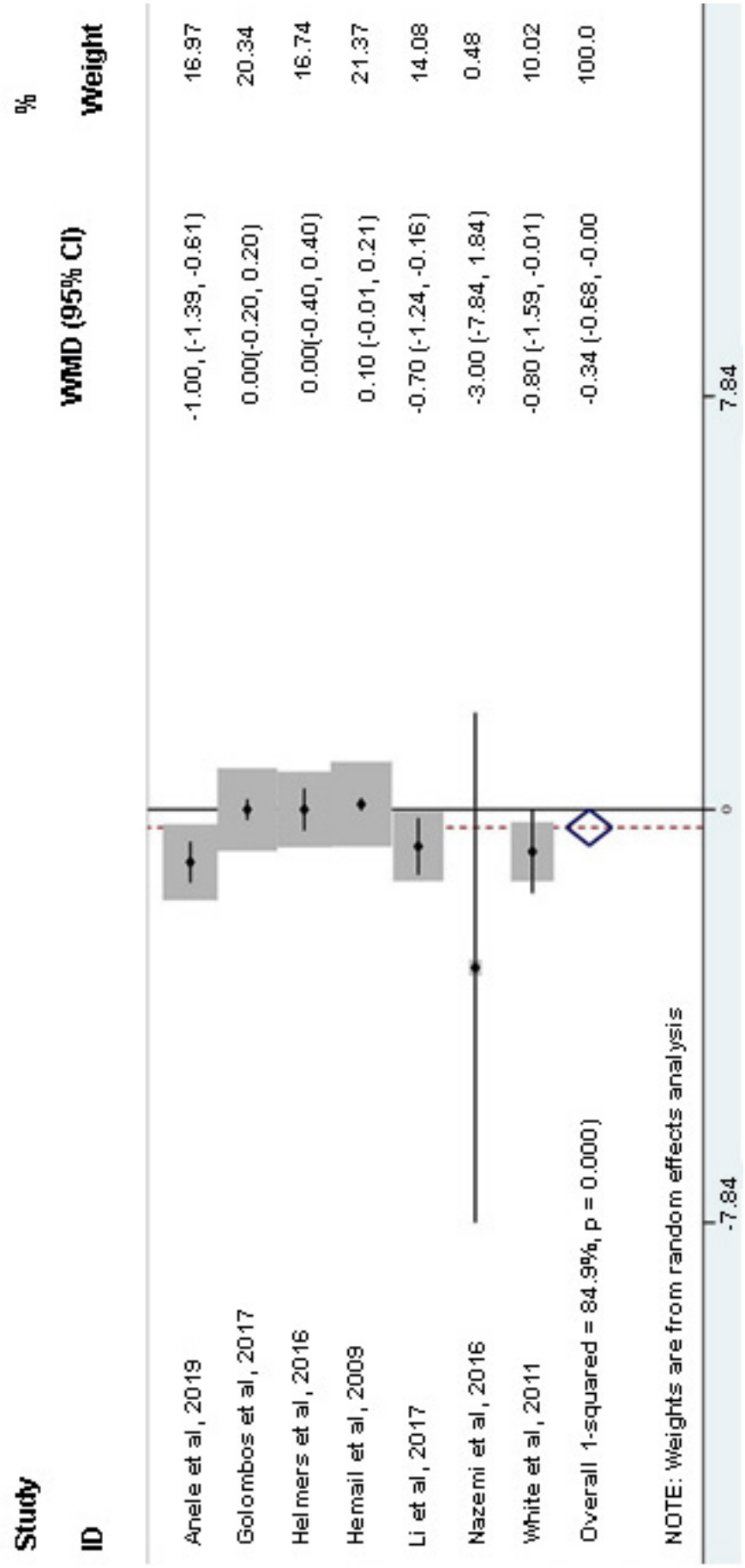


Figure 1: Forest plots of length of hospital stay

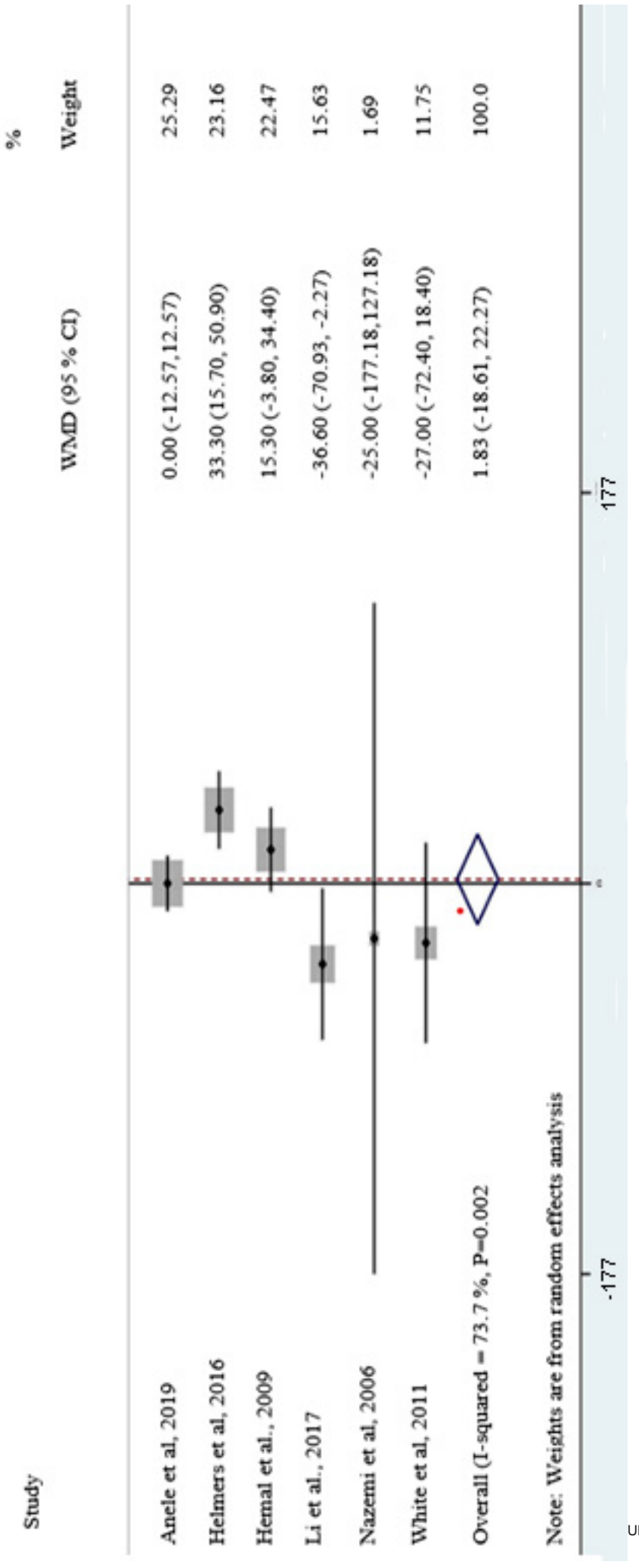


Figure 2: Forest plots of estimated blood loss

Estimated Blood Loss:
The estimated blood loss (EBL) meta-analysis includes six investigations with a total of 1,372 subjects. The research revealed that there was no significant difference between RARN and LRN in terms of EBL (WMD = 1.73; 95% CI = -18.11 to 22.37; p = 0.89) (Figure 2).

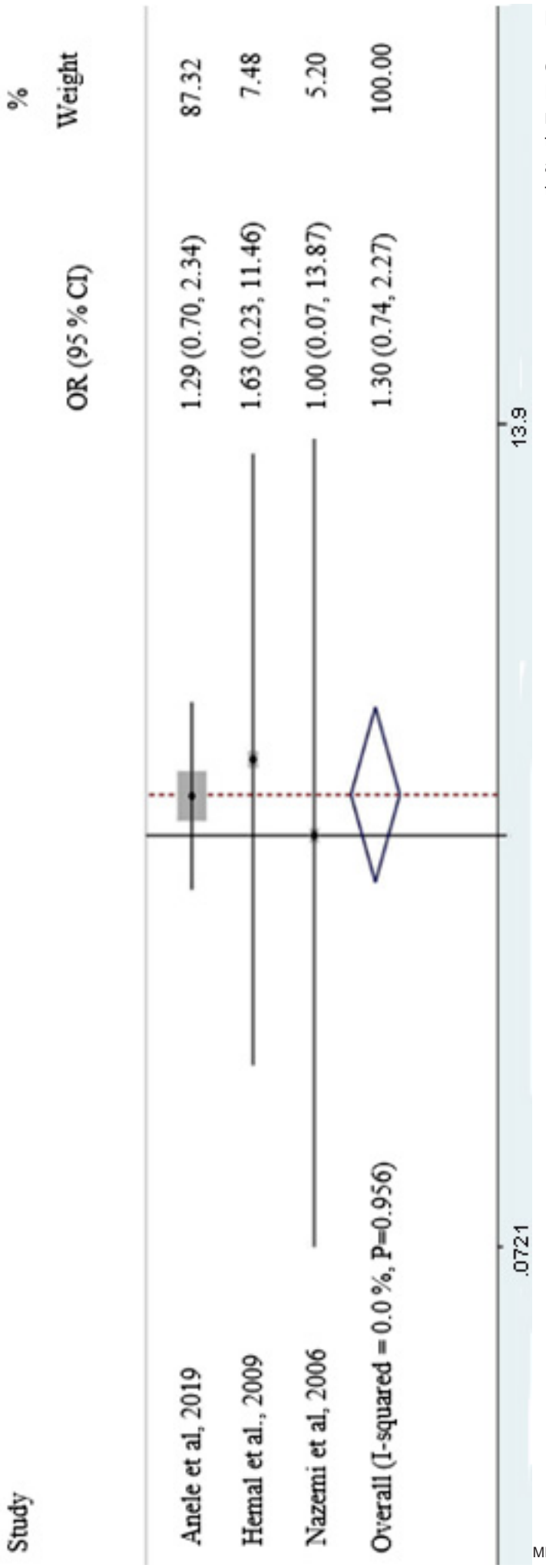


Figure 3: Forest plots of conversion rate

Conversion Rate:
Four trials involving 1,334 patients were included in the meta-analysis of conversion rate. The research revealed that there was no significant difference between RARN and LRN conversion rates (WMD = 2.89; 95% CI = 0.59 to 11.23; p = 0.15) (Figure 3).

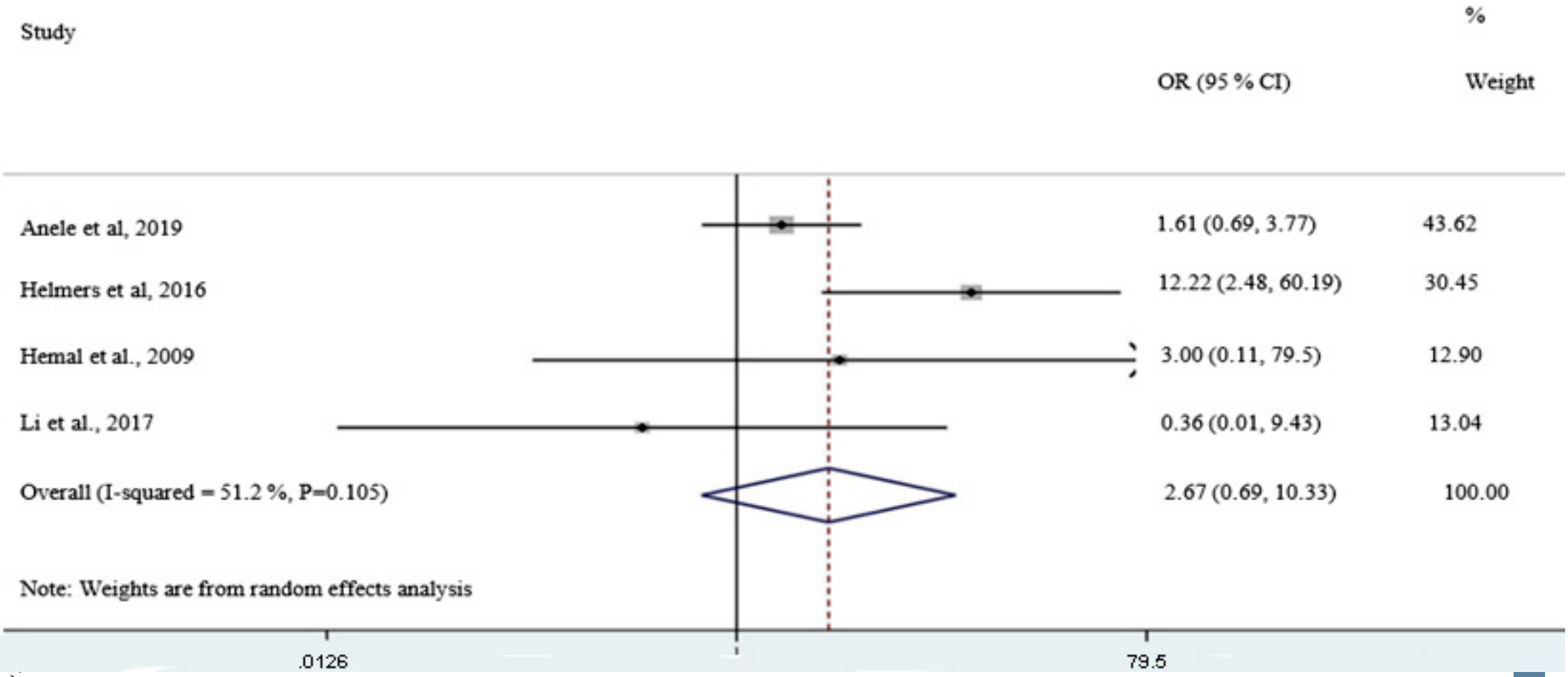


Figure 4: Forest plots of transfusion rate

Transfusion Rate:
The transfusion rate meta-analysis included three studies with a total of 989 individuals. The analysis revealed that there was no significant difference between RARN and LRN transfusion rates (OR, 1.25; 95% CI, 0.64 to 2.30; p=0.37) (Figure 4)

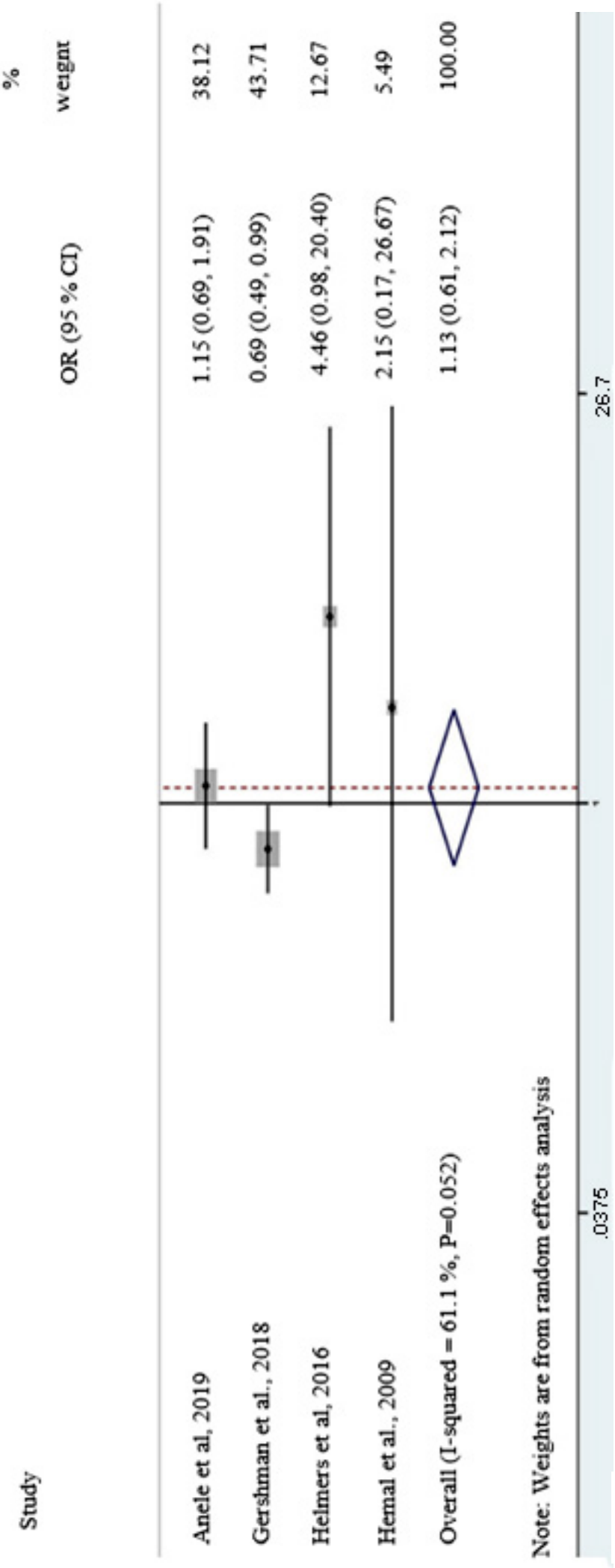


Figure 5: Forest plots of intraoperative complications

Complications:
The complications meta-analysis comprised nine trials with a total of 13,676 patients. The analysis revealed that intraoperative complications (OR, 1.15; 95 % CI, 0.71 to 2.30; p=0.58) (Figure 5) and postoperative complications (OR, 1.17; 95 R CI, 0.53 to 1.69; p=0.69) did not differ significantly between RARN and LRN (Figure 6)

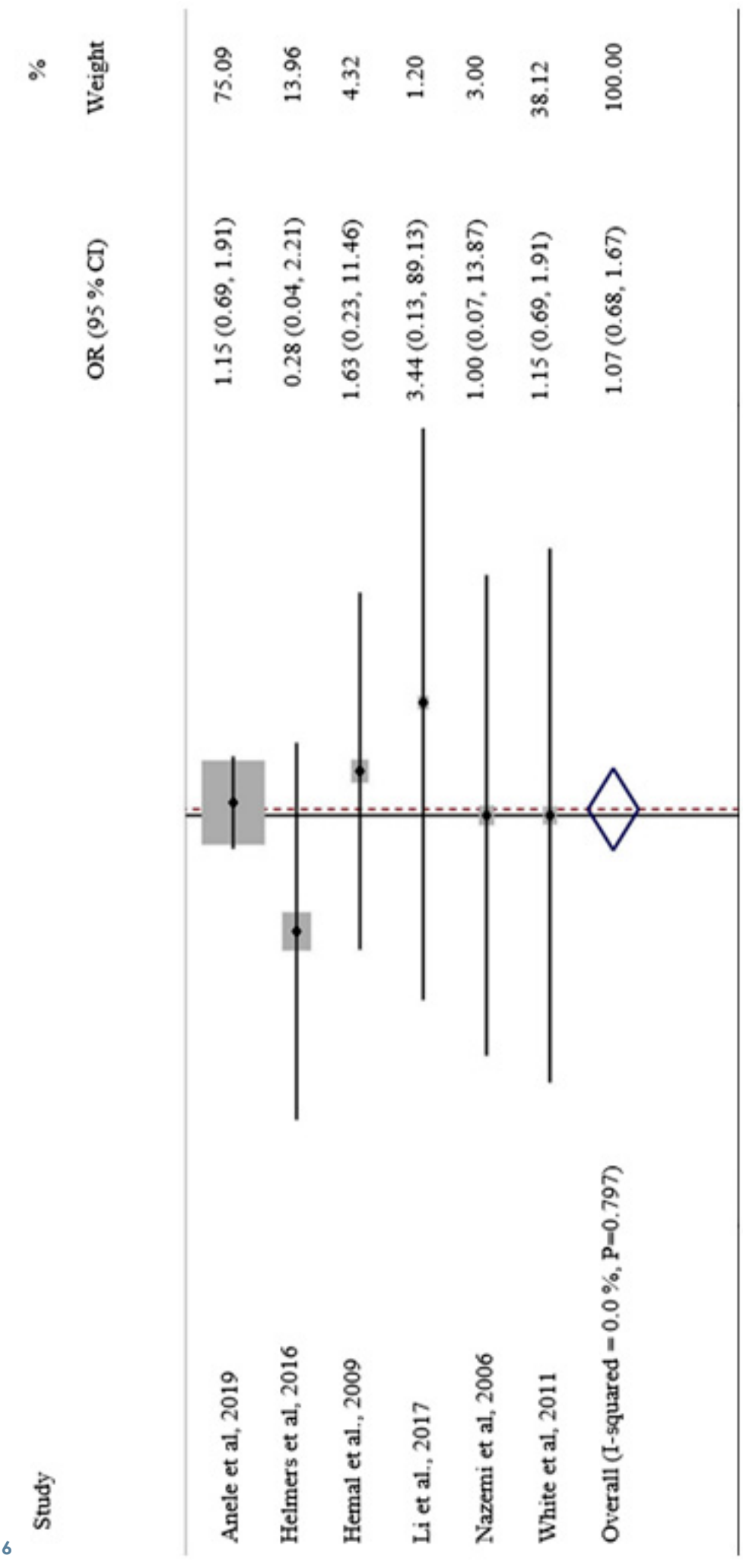


Figure 6: Forest plots of postoperative complications

Discussion

Renal cell carcinoma (RCC) is a frequent urological cancer that frequently necessitates surgery [23,24]. In the past decade, minimally invasive treatments have been utilized to treat RCC [25]. Laparoscopic and robotic surgical techniques are alternatives to open surgery [26]. Several decades ago, laparoscopic radical nephrectomy (LRN) became the standard surgical treatment for RCC [27]. In recent years, robotic-assisted radical nephrectomy (RARN) has arisen as an alternative surgical technique with potential advantages over laparoscopic radical nephrectomy (LRN), including enhanced visibility, dexterity, and ergonomics [17,28,29]. The objective of this systematic review and meta-analysis was to compare the perioperative and postoperative results of RARN and LRN in the treatment of RCC.

Several studies have evaluated the clinical parameters of RARN and conventional LRN, although the relative merits of these two technologies remain disputed [12,16,22].
The meta-analysis includes nine trials with a total of 13,676 patients who received RARN or LRN. The data revealed no statistically significant demographic differences between the two surgical techniques. There were no significant differences between RARN and LRN in terms of predicted blood loss, length of hospital stay, conversion rate, or transfusion rate. The meta-analysis of complications revealed no significant differences between the two surgical methods for intraoperative or postoperative problems.

In a retrospective cohort study by Jeong et al., the rate of prolonged operation time (OT) (>4 h) was higher in patients receiving RARN than in those having traditional LRN [18]. Using the multi-institutional renal masses database, Anele et al. observed that the time of surgery for RARN was significantly longer than that for LRN, with a median OT increase of almost 60 minutes (median = 185 min for RARN and 126 min for LRN, respectively) [21]. Our data indicate that OT was equivalent between RARN and LRN, contrary to the findings of both trials. In actuality, differing perspectives existed over the preferable OT strategy. There may be a correlation between the length of an operation and the surgeon's technical skill, and centers with less experience in robotic procedures may have longer OTs [30]. After 180 cases, Jaffe et al. discovered that the OT of robotic surgery may be lowered from the initial 240 minutes to 120 minutes [31]. Similarly, Wolanski et al. showed that as robotic surgery experience increased, operative length decreased dramatically [32]. They found that the robot-assisted operation may have offered considerable console time advantages over conventional laparoscopic surgery. As previously indicated, disparities in physician expertise may result in significant variations in surgery time, particularly the time required for suturing [33]. In addition, varying definitions of surgery time across the included studies may have contributed to varying results.
The possible advantages of RARN over LRN include enhanced vision and dexterity [34]. However, the meta-analysis did not reveal any significant changes in estimated blood loss, suggesting that the better visualization and dexterity did not translate into a meaningful clinical advantage in terms of blood loss. Our findings were congruent with those of previous research [15,16,21]. Helmers et al. conducted a retrospective analysis of 319 cases (243 RARN and 76 LRN). The RARN group exhibited a significantly higher EBL than the LRN group (median = 100 vs. 50 mL, p 0.05) [35].

Similarly, the meta-analysis did not reveal any statistically significant differences in hospital length of stay, conversion rate, or transfusion rate, showing that the two surgical techniques had comparable clinical results for these parameters. Considering hospital stay duration, in contrast, one prospective study found that the LOS for RARN was considerably shorter than that for LRN (4.4 versus 5.1 days, p 0.05) [19]. Anele et al. discovered that RARN had a significantly shorter median LOS (3 days in the RARN group versus 5 days in the LRN group, p 0.001) [21]. In addition, the robotic method's flexible operation may boost the surgeon's trust in the anastomosis' quality [36,37]. This may shorten the drainage tube's retention period, hence decreasing the LOS. Moreover, Helmers et al. indicated that RARN was linked with a higher conversion rate than traditional LRN (10.3 vs. 1%, p 0.01) [17], which contradicts our findings. There was no significant difference between RARN and LRN in terms of blood transfusion rate, which is consistent with the findings of previous comparative studies [14,15,21]. To corroborate our findings, prospective randomised controlled trials are required.

Complications are a crucial metric for assessing the safety of surgical procedures [38,39]. The meta-analysis of complications revealed no significant differences between RARN and LRN for intraoperative or postoperative problems. The findings are consistent with earlier meta-analyses that compared the two surgical procedures and found comparable incidence of complications between RARN and LRN [40]. Nevertheless, using data from the Nationwide Inpatient Sample from 2010 to 2013, Gershman et al. discovered that RARN was associated with lower perioperative morbidity (20.4% vs. 27.2%, p 0.001), and surgeons with extensive RARN experience can reduce or avoid collateral injuries during surgery [22]. Notably, the quality of the included research was moderate, and there was a moderate risk of bias in all comparison investigations, highlighting the need for caution when interpreting the results.

Since the launch of RARN, one of the primary concerns has been the high cost, which was anticipated to be the primary barrier to the widespread adoption of this technology. Jeong et al. found that the average direct hospital expenditures for RARN were considerably greater than those for LRN (US $19,530 vs. US $16,851, p = 0.004) [18]. Likewise, Gershman et al. discovered that RARN had higher overall hospital charges (US $16,207 vs. $15,037, p 0.001) [22]. In the single-institution analysis done by Helmers et al., there was no statistically significant difference in total inpatient expenses between

between the operations (median = US $14,913 vs. US $16,265; p = 0.171) [17]. According to Kates et al., the reduced LOS of the RARN technique may reduce hospital costs; however, additional prospective studies are necessary to understand this phenomenon [41].

As the first meta-analysis to explicitly evaluate the perioperative outcomes of RARN and LRN in patients with RCC, our study has clinical significance. This study is limited by the average quality of the included studies, the absence of long-term follow-up data, and the possibility of publication bias. Important aspects of the management of RCC, like recurrence rates and overall survival, were omitted from the analysis.

This systematic study and meta-analysis concludes that RARN and LRN had comparable perioperative outcomes in the treatment of RCC. Although RARN may give prospective benefits in the form of enhanced visibility and dexterity, the clinical significance of these benefits remains unknown. Further high-quality studies with long-term follow-up are required to further comprehend the possible advantages and disadvantages of RARN against LRN in the treatment of RCC.

References

1. Robson CJ. Radical Nephrectomy for Renal Cell Carcinoma. J Urol. 1963;89(1):37-42. doi:10.1016/S0022-5347(17)64494-X
2. Allan JDD, Tolley DA, Kaouk JH, Novick AC, Gill IS. Laparoscopic Radical Nephrectomy. Eur Urol. 2001;40(1):17-23. doi:10.1159/000049744
3. Clayman R V, Kavoussi LR, Soper NJ, et al. Laparoscopic Nephrectomy: Initial Case Report. J Urol. 1991;146(2 Part 1):278-282. doi:10.1016/S0022-5347(17)37770-4
4. Rassweiler JJ, Henkel TO, Potempa DM, Coptcoat M, Alken P. The Technique of Transperitoneal Laparoscopic Nephrectomy, Adrenalectomy and Nephroureterectomy. Eur Urol. 1993;23(4):425-430. doi:10.1159/000474647
5. Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2022 Update. Eur Urol. 2022;82(4):399-410. doi:10.1016/j.eururo.2022.03.006
6. Chow W-H. Rising Incidence of Renal Cell Cancer in the United States. JAMA. 1999;281(17):1628. doi:10.1001/jama.281.17.1628
7. Gul ZG, Tam A, Badani KK. Robotic partial nephrectomy: The current status. Indian J Urol. 2020;36(1):16-20. doi:10.4103/iju.IJU_174_19
8. Chen K, Beeraka NM, Zhang J, et al. Efficacy of da Vinci robot-assisted lymph node surgery than conventional axillary lymph node dissection in breast cancer – A comparative study. Int J Med Robot Comput Assist Surg. 2021;17(6). doi:10.1002/rcs.2307
9. Guerrero ER, Claro AVO, Cepero MJL, Delgado MS, Fernández JLÁ-O. Robotic versus Laparoscopic Partial Nephrectomy in the New Era: Systematic Review. Cancers (Basel). 2023;15(6):1793. doi:10.3390/cancers15061793
10. Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. Eur Urol. 2019;75(5):799-810. doi:10.1016/j.eururo.2019.02.011
11. Sterne JAC, Gavaghan D, Egger M. Publication and related bias in meta-analysis. J Clin Epidemiol. 2000;53(11):1119-1129. doi:10.1016/S0895-4356(00)00242-0
12. Yang DY, Monn MF, Bahler CD, Sundaram CP. Does Robotic Assistance Confer an Economic Benefit during Laparoscopic Radical Nephrectomy? J Urol. 2014;192(3):671-676. doi:10.1016/j.juro.2014.04.018
13. Hemal AK, Stansel I, Babbar P, Patel M. Robotic-assisted Nephroureterectomy and Bladder Cuff Excision Without Intraoperative Repositioning. Urology. 2011;78(2):357-364. doi:10.1016/j.urology.2010.12.075
14. Nazemi T, Galich A, Sterrett S, Klingler D, Smith L, Balaji KC. Radical nephrectomy performed by open, laparoscopy with or without hand-assistance or robotic methods by the same surgeon produces comparable perioperative results. Int braz j urol. 2006;32(1):15-22. doi:10.1590/S1677-55382006000100003
15. Hemal AK, Kumar A. A prospective comparison of laparoscopic and robotic radical nephrectomy for T1-2N0M0 renal cell carcinoma. World J Urol. 2009;27(1):89-94. doi:10.1007/s00345-008-0321-9
16. White MA, Autorino R, Spana G, et al. Robotic Laparoendoscopic Single-Site Radical Nephrectomy: Surgical Technique and Comparative Outcomes. Eur Urol. 2011;59(5):815-822. doi:10.1016/j.eururo.2011.02.020
17. Helmers M, Ball M, Gorin M, Pierorazio P, Allaf M. Robotic versus laparoscopic radical nephrectomy: Comparative analysis and cost considerations. Can J Urol. 2016;23:8435-8440.
18. Jeong IG, Khandwala YS, Kim JH, et al. Association of Robotic-Assisted vs Laparoscopic Radical Nephrectomy With Perioperative Outcomes and Health Care Costs, 2003 to 2015. JAMA. 2017;318(16):1561. doi:10.1001/jama.2017.14586
19. Li F Z, G SY, B L, L. S. Clinical effect of Da Vinci robot-assisted laparoscopic radical nephrectomy versus retroperitoneal laparoscopic radical nephrectomy inthetreatment of renal carcinoma: a comparative analysis. Med J Qilu. 2017;32:394-396. doi:10.13362/j.qlyx.201704006
20. Golombos DM, Chughtai B, Trinh Q-D, et al. Adoption of Technology and Its Impact on Nephrectomy Outcomes, a U.S. Population-Based Analysis (2008–2012). J Endourol. 2017;31(1):91-99. doi:10.1089/end.2016.0643
21. Anele UA, Marchioni M, Yang B, et al. Robotic versus laparoscopic radical nephrectomy: a large multi-institutional analysis (ROSULA Collaborative Group). World J Urol. 2019;37(11):2439-2450. doi:10.1007/s00345-019-02657-2
22. Gershman B, Bukavina L, Chen Z, et al. The Association of Robot-assisted Versus Pure Laparoscopic Radical Nephrectomy with Perioperative Outcomes and Hospital Costs. Eur Urol Focus. 2020;6(2):305-312. doi:10.1016/j.euf.2018.10.004

23. Krabbe L-M, Bagrodia A, Margulis V, Wood C. Surgical Management of Renal Cell Carcinoma. Semin Intervent Radiol. 2014;31(01):027-032. doi:10.1055/s-0033-1363840
24. Cairns P. Renal cell carcinoma. Srivastava S, Grizzle WE, eds. Cancer Biomarkers. 2011;9(1-6):461-473. doi:10.3233/CBM-2011-0176
25. Bragayrac LAN, Abbotoy D, Attwood K, et al. Outcomes of Minimal Invasive vs Open Radical Nephrectomy for the Treatment of Locally Advanced Renal-Cell Carcinoma. J Endourol. 2016;30(8):871-876. doi:10.1089/end.2016.0082
26. Asimakopoulos AD, Miano R, Annino F, et al. Robotic radical nephrectomy for renal cell carcinoma: a systematic review. BMC Urol. 2014;14(1):75. doi:10.1186/1471-2490-14-75
27. Nian X, Ye H, Zhang W, et al. Propensity-matched pair analysis of safety and efficacy between laparoscopic and open radical nephrectomy for the treatment of large renal masses (>10 cm): a retrospective cohort study. Transl Androl Urol. 2022;11(8):1148-1156. doi:10.21037/tau-22-449
28. Ashrafi AN, Gill IS. Minimally invasive radical nephrectomy: a contemporary review. Transl Androl Urol. 2020;9(6):3112-3122. doi:10.21037/tau-2019-suc-16
29. Crocerossa F, Carbonara U, Cantiello F, et al. Robot-assisted Radical Nephrectomy: A Systematic Review and Meta-analysis of Comparative Studies. Eur Urol. 2021;80(4):428-439. doi:10.1016/j.eururo.2020.10.034
30. Light A, Karthikeyan S, Maruthan S, Elhage O, Danuser H, Dasgupta P. Peri-operative outcomes and complications after laparoscopic vs robot-assisted dismembered pyeloplasty: a systematic review and meta-analysis. BJU Int. 2018;122(2):181-194. doi:10.1111/bju.14170
31. Jaffe J, Castellucci S, Cathelineau X, et al. Robot-Assisted Laparoscopic Prostatectomy: A Single-Institutions Learning Curve. Urology. 2009;73(1):127-133. doi:10.1016/j.urology.2008.08.482
32. Wolanski P, Chabert C, Jones L, Mullavey T, Walsh S, Gianduzzo T. Preliminary results of robot-assisted laparoscopic radical prostatectomy (RALP) after fellowship training and experience in laparoscopic radical prostatectomy (LRP). BJU Int. 2012;110:64-70. doi:10.1111/j.1464-410X.2012.11479.x
33. Birkmeyer JD, Reames BN, McCulloch P, Carr AJ, Campbell WB, Wennberg JE. Understanding of regional variation in the use of surgery. Lancet. 2013;382(9898):1121-1129. doi:10.1016/S0140-6736(13)61215-5
34. R. Sharma A. Operative Techniques and Outcomes in Laparoscopic Radical Nephrectomy. In: Current Concepts and Controversies in Laparoscopic Surgery [Working Title]. IntechOpen; 2022. doi:10.5772/intechopen.106475
35. Helmers MR, Ball MW, Gorin MA, Pierorazio PM, Allaf ME. Robotic versus laparoscopic radical nephrectomy: comparative analysis and cost considerations. Can J Urol. 2016;23(5):8435-8440. http://www.ncbi.nlm.nih.gov/pubmed/27705727
36. Kostakis ID, Sran H, Uwechue R, et al. Comparison Between Robotic and Laparoscopic or Open Anastomoses: A Systematic Review and Meta-Analysis. Robot Surg Res Rev. 2019;Volume 6:27-40. doi:10.2147/RSRR.S186768
37. Saeidi H, Opfermann JD, Kam M, et al. Autonomous robotic laparoscopic surgery for intestinal anastomosis. Sci Robot. 2022;7(62). doi:10.1126/scirobotics.abj2908
38. Christine B, Barbara B-A, Zehetmayer S, Wolfgang U. Comparing compliance with the WHO surgical safety checklist and complication rates in gynecologic surgery between day and night shifts. Arch Gynecol Obstet. 2022;306(4):1101-1106. doi:10.1007/s00404-022-06599-w
39. Blikkendaal MD, Driessen SRC, Rodrigues SP, et al. Measuring surgical safety during minimally invasive surgical procedures: a validation study. Surg Endosc. 2018;32(7):3087-3095. doi:10.1007/s00464-018-6021-7
40. Li J, Peng L, Cao D, et al. Comparison of Perioperative Outcomes of Robot-Assisted vs. Laparoscopic Radical Nephrectomy: A Systematic Review and Meta-Analysis. Front Oncol. 2020;10. doi:10.3389/fonc.2020.551052
41. Kates M, Ball MW, Patel HD, Gorin MA, Pierorazio PM, Allaf ME. The Financial Impact of Robotic Technology for Partial and Radical Nephrectomy. J Endourol. 2015;29(3):317-322. doi:10.1089/end.2014.0559

Rare Presentation of Aortic Aneurysm: A Diagnostic Challenge

Shiraz Ali [1], Amir Tauqir Chaudhary H [2]

(1) A&E GP Clinical Lead BTHFT, Bradford Royal Infirmary, Duckworth Lane, England, Consultant Family Medicine, PHCC Qatar
(2) Specialist Family Medicine Norway, Tutor Family Medicine Norway, Consultant Family Medicine PHCC Qatar

Corresponding author:
Dr. Shiraz Ali, MBBS MRCGP,
A&E GP Clinical Lead BTHFT,
Bradford Royal Infirmary,
Duckworth Lane, BD9 6RJ
England
Mobile: 07832236925
Email: dr.shirazali86@gmail.com

Received: July 2023. Accepted: August 2023; Published: September 1, 2023.
Citation: Shiraz Ali, Amir Tauqir Chaudhary. Rare Presentation of Aortic Aneurysm: A Diagnostic Challenge. World Family Medicine. August 2023; 21(8): 70-73 DOI: 10.5742/MEWFM.2023.95256181

Abstract

This case report highlights a rare presentation of abdominal aortic aneurysm, which posed a diagnostic challenge due to its atypical clinical manifestations. The patient initially presented with vague symptoms of renal colic and underwent a comprehensive evaluation, including imaging studies, to establish the diagnosis. Through a multidisciplinary approach and careful analysis of the diagnostic findings, a rare form of aortic aneurysm was identified. This case emphasizes the importance of considering unusual presentations of aortic aneurysms and the need for thorough investigation to ensure accurate diagnosis and appropriate management.

Keywords: aortic aneurysm, rare presentation, diagnostic challenge, multidisciplinary approach

Introduction

Abdominal aortic aneurysm refers to a condition characterized by abnormal enlargement or bulging of abdominal aorta, the main blood vessel supplying oxygenated blood to the lower body. This condition is often asymptomatic, until the patients experience pain when it becomes large or during rupture. Abdominal aortic aneurysm is a potentially life-threatening condition, and its diagnosis and treatment are essential to prevent complications (1).

Abdominal aortic aneurysm develops over time, with progressive expansion of arterial wall weakening. In many cases, the aneurysm remains small and poses little risk. However, when the size is enlarged, it elicits more stress on the arterial wall, and leads to complications such as rupture or dissection.

The typical clinical presentation of abdominal aortic aneurysm includes chest or back pain, but in some cases rare presentations occurs, which impose diagnostic challenges (2,3). Proper identification of these atypical manifestations is crucial to ensure timely diagnosis and appropriate management. Rupture of an abdominal aortic aneurysm is an emergency situation, which occurs during the rupture of weakened aneurysm arterial wall and causes severe internal bleeding. Abdominal aortic aneurysm rupture is a life-threatening condition which needs immediate emergency care and if not properly attended to, it leads to higher mortality rate (4).

The prompt diagnosis is done using imaging modalities such as computed tomography (CT) scan or ultrasound and also to evaluate the extent of the rupture. After diagnosis, immediate surgical approach is required to repair the rupture and to restrict the bleeding. Timely access to specialized facilities and expertise is crucial for successful treatment and optimal patient outcomes.

This case report describes a rare presentation of aortic aneurysm, highlighting the diagnostic approach and multidisciplinary efforts involved in establishing an accurate diagnosis and managing the condition.

Case Presentation

A 70-year-old male patient presented to an emergency care facility with a history of atraumatic, progressive lower back and left flank pain radiating towards the left groin. The pain was unresponsive to patient's home oral analgesia. There was no accompanying fever or bowel symptom. The patient reported nausea, inability to pass urine and distress due to pain. Vital signs at arrival were recorded as follows, blood pressure 140/88 mm Hg, pulse 100 beats per minute, and the patient was afebrile. The renal function test was done and it was normal and the point of care urine dip test showed trace protein.

Based on the clinical presentation, the initial working diagnosis was nephrolithiasis. He received intramuscular injection of Buscopan 20mg and Diclofenac 100mg PR for pain relief. The patient was subsequently discharged, with prescriptions for oral analgesia and a urology outpatient department follow up was instructed for further imaging as per local guidelines.

After 4-5 hours after discharge, the patient experienced increased pain, and an emergency ambulance was called. A new physician attended the patient and requested further investigations. A urine test was also requested but the patient was unable to provide it in this encounter. Urolithiasis with complete obstruction and possible hydronephrosis was suspected. The pain was controlled by administering IV Paracetamol followed by incremental doses of morphine. During transport, the patient's pulse increased to 105 bpm, and he became pale, with a blood pressure of 106/70 mmHg. Due to the patients' abrupt changes in vitals, paleness, ED was again contacted and advised to shift the patient to ED immediately and not to the Urology department.

Examination and findings at emergency department

Physical examination revealed clear lungs and a regular heart rate and rhythm. The abdomen was soft, tender, no guarding with a palpable pulsatile mass in central abdomen. Laboratory data revealed a normal haemogram, normal serum electrolytes, normal troponin-I (0.01ng/mL) and serum creatinine (1.2 mg/dl) respectively. Chest X-ray showed no abnormal findings.

An ECG was performed in the ambulance which revealed non-specific T-wave changes, raising concerns for a more severe condition.

The condition of the patient was informed to ED physician and the patient was immediately transferred to the radiology lab for a CT abdomen.

Diagnosis and Management

The CT abdomen revealed an expanding abdominal aortic aneurysm near rupture, causing an infra renal compression of the urinary tract. Urgent fluid resuscitation was initiated with surgical intervention by general surgical and vascular team.

Discussion

This present case report underscores the significance of recognizing rare presentations of aortic aneurysms, which can pose diagnostic challenges due to the absence of typical symptoms and physical examination findings. In this case, the patient's typical renal colic symptoms initially diverted attention from considering an aortic etiology. However, upon re-presentation an abdominal CT revealed an expanding abdominal aortic aneurysm near rupture, causing compression of the renal tract, requiring emergency surgical intervention.

In addition, the presence of frank haematuria or positive findings of blood in urine, point of care tests can support the diagnosis of renal or ureteric colic. However, specificity and positive predictive values are poor. In this case, the absence of haematuria does not exclude a diagnosis but should prompt consideration for other causes of pain (5).

Most of the abdominal aortic aneurysm cases are asymptomatic and they are usually detected as an incidental finding or in the routine medical screening on various imaging modalities. Further, it also overlaps with the common symptoms such as abdominal or back pain (6).

In rare instances, large abdominal aortic aneurysms (5-5.4cms) can compress or obstruct adjacent structures, including the ureters (7). Ureteral obstruction due to abdominal aortic aneurysms can cause symptoms such as flank pain, urinary tract infections, hydronephrosis, urinary retention or even acute kidney injury. However, aneurysmal rupture is notorious due to the atypical presentation and it is crucial to avoid misdiagnosis and ensure appropriate management (7). In our case, the patient's symptoms, clinical course, and initial response to analgesics contributed to the diagnostic delay. The subsequent deterioration and imaging findings highlighted the importance of considering abdominal aortic aneurysm early in the differential diagnosis of acute abdominal pain, even in the absence of typical risk factors or symptoms. Diagnostic delay in the management of abdominal aortic aneurysm can occur due to various factors and can have significant implications for patient outcomes (8). Atypical symptoms or presentations, such as referred pain to the groin, thigh, or testicles, may be misinterpreted as musculoskeletal or urological issues, leading to delays in considering abdominal aortic aneurysm as a potential diagnosis (8). In addition, more awareness must be created among the healthcare professionals about abdominal aortic aneurysm, and its risk factors, symptoms, and screening for early detection. Meanwhile, robust access to imaging analysis, clear communication of results, and streamlining the referral and consultation processes might prevent the delay in diagnosis and appropriate management (9).

Abdominal aortic aneurysm has been often misdiagnosed as renal colic in 10% of the cases (10, 11). The pain caused by an abdominal aortic aneurysm can radiate to the back and flank region, resembling the pain experienced in renal colic. This similarity in pain presentation can lead to initial confusion between the two conditions. It is crucial to consider abdominal aortic aneurysm in the differential diagnosis of flank pain, particularly in high-risk individuals or those with atypical features.

Abdominal CT is the gold-standard diagnostic modality to investigate the possibility of abdominal aortic aneurysm as a cause for renal colic. Abdominal CT displays good diagnostic accuracy and accurately visualizes the abdominal aorta and detects the presence of an abdominal aortic aneurysm. It provides detailed information about the size, location, and characteristics of the aneurysm, and thus helps in diagnosis and management (12). While renal colic and abdominal aortic aneurysm can present with similar flank pain, CT imaging plays a crucial role in distinguishing between the two conditions. CT scans can accurately identify the presence of an abdominal aortic aneurysm, whereas in renal colic, additional findings such as urinary stones or obstruction may be present. Often unsuspected findings unrelated to renal stone have been reported in the evaluation of flank pain (13, 14).

Prompt recognition of rare presentations of aortic aneurysms is vital to ensure timely intervention. Maintaining a high index of suspicion and considering aortic aneurysms as a potential diagnosis in patients with relevant risk factors can facilitate early recognition. Utilizing appropriate diagnostic tools such as imaging studies and considering the clinical context can aid in establishing an accurate diagnosis.

Therefore, timely recognition, accurate diagnosis, and appropriate management are crucial for optimizing patient outcomes in cases of rare presentations of aortic aneurysms (15, 16).

Conclusion

This case report highlights the importance of considering unusual presentations of aortic aneurysms and the need for a comprehensive diagnostic evaluation. Clinicians should maintain a high index of suspicion for aortic pathology, even in the absence of typical symptoms or physical examination findings.

References

1. National Heart, Lung, and Blood Institute 2021. Abdominal Aortic Aneurysm. Retrieved from https://www.nhlbi.nih.gov/health-topics/abdominal-aortic-aneurysm. Last accessed 20 June 2023.
2. Kent KC. Clinical practice. Abdominal aortic aneurysms. N Engl J Med. 2014; 371(22):2101-08.
3. Dueck AD, Kucey DS, Johnston KW, Alter D, Laupacis A. Survival after ruptured abdominal aortic aneurysm: effect of patient, surgeon, and hospital factors. J Vasc Surg. 2004; 39(6):1253-60.
4.Chaikof EL, Dalman RL, Eskandari MK, Jackson BM, Lee WA, Mansour MA, et al . The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg. 2018; 67(1): 2-77.e2.

5. Diagnosis and management of renal colic. Retrieved from https://cks.nice.org.uk/topics/renal-or-ureteric-colic-acute/diagnosis/assessment/ . Last accessed 20 June 2023.
6. Powell JT, Greenhalgh RM. Clinical practice. Small abdominal aortic aneurysms. N Engl J Med. 2003; 348 (19):1895–901.
7. Prokopowicz Z, Wroński J, Szczerbo-Trojanowska M. Obstructive nephropathy as a rare clinical presentation of abdominal aortic aneurysm. Pol J Radiol. 2007; 72(4): 63-6
8..Mukherjee D, Eagle, K. A., & Regalado, E. S. Delayed diagnosis of aortic aneurysms. Circulation. 2017; 136(8): 823–24.
9. Kessler V, Klopf J, Eilenberg W, Neumayer C, Brostjan C. AAA Revisited: A Comprehensive Review of Risk Factors, Management, and Hallmarks of Pathogenesis. Biomedicines. 2022; 10(1):94.
10. Eckford SD, Gillatt DA. Abdominal aortic aneurysms presenting as renal colic. Br J Urol. 1992; 70 (5):496–8
11. Marston WA, Ahlquist R, Johnson G Jr, Meyer AA. Misdiagnosis of ruptured abdominal aortic aneurysms. J Vasc Surg. 1992 ; 16(1):17-22.
12. Azhar B, Patel SR, Holt PJ, Hinchliffe RJ, Thompson MM, Karthikesalingam A. Misdiagnosis of ruptured abdominal aortic aneurysm: systematic review and meta-analysis. J Endovasc Ther. 2014; 21(4):568-75
13. Rucker CM, Menias CO, Bhalla S. Mimics of renal colic: alternative diagnoses at unenhanced helical CT. Radiographics. 2004;24(Suppl 1):S11–28; discussion S28–33
14. Chien DK, Chang WH, Yeh YH. Radiographic findings of a ruptured abdominal aortic aneurysm. Circulation 2010; 122(18):1880–1.
15. Akkersdijk GJ, van Bockel JH. Ruptured abdominal aortic aneurysm: initial misdiagnosis and the effect on treatment. Eur J Surg. 1998; 164(1):29-34.
16. Lech C, Swaminathan A. Abdominal aortic emergencies. Emerg Med Clin North Am. 2017; 35(4):847-67.

Physical and Emotional Domestic Violence Knowledge among Jazan University Female Students

Mona H El Mahdy[1], Sarah El-Reffaey[2], Samy S. Mahmoud[3], Amani Osman Abdelmola[4], Azhar Mohammed Alfaifi[5], Fatimah H. Dallak[6], Anwar jafar Alnass[7], Roaa Shaikhain[8], Maryam Othman Gharawi[9], Asayel Ahmad Hozaimi[10], Hoida Hadi Hadi Sahl[11], Nada Mohammed Makein[12]

(1) Professor, Family and Community Medicine Department Jazan University. Professor in Community Medicine Department, Benha University.
(2) Department of Internal Medicine & Forensic Medicine, Faculty of Medicine, Jazan University, KSA; Zagazig University, Egypt.
(3) Assistant Professor of family and community medicine department, Faculty of medicine, Jazan University, KSA; Assistant professor of Public health and Occupational medicine department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
(4) Assistant Professor of Family and Community Medicine Department Jazan University.
(5) Abuarish General Hospital, Jazan, Saudi Arabia
(6) Prince Mohammed Bin Nasser Hospital, Jazan, Saudi Arabia.
ORCID: https://orcid.org/0000-0003-1446-6007
(7) Alrazi primary health care center, Jubail, Saudi Arabia
(8) Medical student, 4th year, Faculty of Medicine, Jazan Unversity, KSA.
(9) Medical intern, City: Jazan.
(10) GP, City: Jazan
(11) Samtah Primary Healthcare Center, Jazan, Saudi Arabia
(12) Lecturer in family and Community Medicine Department Jazan university.

Corresponding author:
Mona Hussein Elmahdy
Professor Family and Community Medicine Department Jazan University,
Professor in Community Medicine Department, Benha University.
Email: dr.monaelmahdy@yahoo.com, mlmahdy@jazanu.edu.sa, dr.monaelmahdy@gmail.com

Received: July 2023. Accepted: August 2023; Published: September 1, 2023.
Citation: Mona H El Mahdy. Physical and Emotional Domestic Violence Knowledge among Jazan University Female Students .World Family Medicine. August 2023; 21(8): 74-86 DOI: 10.5742/MEWFM.2023.952561826

Abstract

Domestic violence against females is one of the most important social problems negatively affecting health psychologically and physically. This study aims to estimate the prevalence of violence against female students at Jazan University, Saudi Arabia, and identify their knowledge and response towards emotional and physical domestic violence.

Method of study: It is a descriptive cross-sectional, observational type of epidemiologic study conducted on 450 female students at 3 Faculties, female sections, Jazan University, for eight weeks. The data was collected using an Arabic questionnaire containing 35 questions and analyzed by SPSS Program.

Results: 25.6% of the female students in the studied sample were exposed to domestic violence at some point. The emotional type is the most prevalent (18.3%), followed by the physical type (16.9%). Arts faculties showed the highest rate of domestic violence (11.3%), followed by health faculties (9.3%), and the science faculties exhibited the lowest rates (4.9%). Most participants (15.78%) believed that male power in Jazan society allows them to emotionally abuse women, while 15.33% thought that physical violence against women is mainly caused by men's abuse of drugs and alcohol. 94.5% of the participants believed that violence against women has a negative impact on children and teenagers, and 86.5% supposed that the most significant psychological effects of violence against women are loss of self-confidence, frustration, and depression.

Conclusion: Domestic violence against females is prevalent in the Jazan community, with various sociodemographic and economic determinants influencing its occurrence. The most prevalent type is emotional domestic violence. Arts faculties showed the highest rating of domestic violence, then health faculties, and the least, science faculties.

Recommendations: Increase community awareness about domestic violence. Religious leaders sustain the greatest responsibility to increase awareness according to the rules of the Islamic religion.

Key words: Knowledge, physical and emotional domestic violence, Jazan University female students

Introduction

In the place where they should be safest, females are often in great danger; within their families. Intimate partner violence (also known as "domestic" violence) means that a female faces any violence by an intimate family member (father, brother, or intimate relative) or spouse; This is one of the most common and universal forms of violence experienced by females, (WHO, 2005). Violence against females poses a major threat to social and economic development (WHO, 2005). One-in-three females have experienced domestic violence (Semahegn et al., 2019). The prevalence ranges dramatically from 39% to 58%, with several types of physical and emotional abuse. However, violence is a serious problem in Arab and Islamic countries, and most abused females don't mention they were abused. Statistics show that married females are Saudi society's largest segment of victims of abuse (Halawi et al., 2017).

Violence against females takes many forms, from the overt to the subtle. It includes physical, emotional, economic, and sexual violence (WHO, 2005). Although there is no single factor to account for violence perpetrated against females, several complex and interconnected institutionalized social and cultural factors have kept females particularly vulnerable to the violence directed at them (UNICEF, 2000). Some people with very traditional beliefs may consider they have the right to control their partner and that females are not equal to men (Toby and Goldsmith, 2018). Gender inequality and lifestyle acceptance of violence are the main causes of violence against females (Mabunda et al., 2009).

In addition, severe and fatal effects on females' mental health are noted in females exposed to domestic violence. The incidence of stress-related diseases such as post-traumatic stress syndrome, panic attacks, depression, sleep and eating disorders, high blood pressure, alcohol abuse, and low self–esteem that accompany domestic violence have fatal outcomes such as homicide or suicide (UNICEF, 2000). Moreover, females may suffer from isolation, unemployment, loss of wages, lack of normal involvement in activities, and limited ability to worry about themselves and their children. Children growing up in violent families may experience a range of behavioral and emotional disturbances. These behaviors can also be associated with subsequent perpetration of violence (Mabunda et al., 2009). Children who witness or are victims of violence can learn to believe that violence is a reasonable way of resolving people's conflicts (Goldsmith, 2016).

To prevent domestic violence, developed countries provide support and counseling interventions to modulate access to services for the survivors. Home visitation program settings include: empowering females economically and socially, raising communication and relationship skills, and reducing access to harmful use of alcohol (Mabunda et al., 2009).

On the other hand, in collaboration with partners, WHO has exerted efforts to build evidence based on the size and type of violence in a different framework and supporting countries' efforts to measure violence and its effects. These efforts include strengthening research and capacity to evaluate partner violence interventions and secondly, research interventions to test and identify effective interventions in the health sector. Thirdly, is the developing of guidelines and operational tools to enhance response to partner and sexual violence and support countries and partners in implementing the Global Plan of Action on Violence (Mabunda et al., 2009).

Saudi Arabia has worked to stop domestic violence by providing social services in cooperation with charities through study, social research, and accommodation. These efforts established the Public Social Protection Administration to raise awareness among society members. Additionally, they set up the Social Guidance Unit and the toll-free number 8001245005 to provide strict confidence in social, psychological, educational, and judicial counseling (Was, 2017).

However, the problem is that there is no previous study about the prevalence of domestic violence against Jazan University female students, as well as the victims' response to domestic violence. The hypothesis is that Jazan University students are exposed to emotional and physical violence.

Objectives of the Research
This study aimed to estimate the prevalence of violence against female students at Jazan University, Saudi Arabia, and identify their knowledge and response towards emotional and physical domestic violence.

Methodology

Study area: Jazan region is the second smallest area in the southwestern corner of Saudi Arabia. The region is subdivided into 14 governorates and covers an area of 11,671 km2 with 1,567,547 inhabitants in the 2017 census. The region has the Kingdom's highest population density. Study setting: Jazan University

Study design: A descriptive, cross-sectional design of observation type of epidemiological studies.

Study population: The study target is 450 female students aged 18-30 years old enrolled in three faculties at Jazan University.

Sample size
This equation was used to calculate the sample size because the population size is unknown:

$$n = \frac{z^2_{1-\alpha} P (1 - P)}{d^2}$$

z= is determined based on confidence level.
Confidence level: 95%= z-value 1.96.
P= population proportion (assumed to be 50%=0.05).
d= absolute error, a small amount that is allowed for in case of miscalculation or change of circumstance= 5%=0.5

The formula becomes as follows:

$$n = \frac{(1.96)^2 0.5(1 - 0.5)}{0.05^2} = 384 \approx 400$$

Assuming a non-response rate of 10%:

$$\frac{(400)\,(10)}{100} = 40$$

Total sample size= 400+40+10=450

Sample techniques
It includes four stages only as follows:

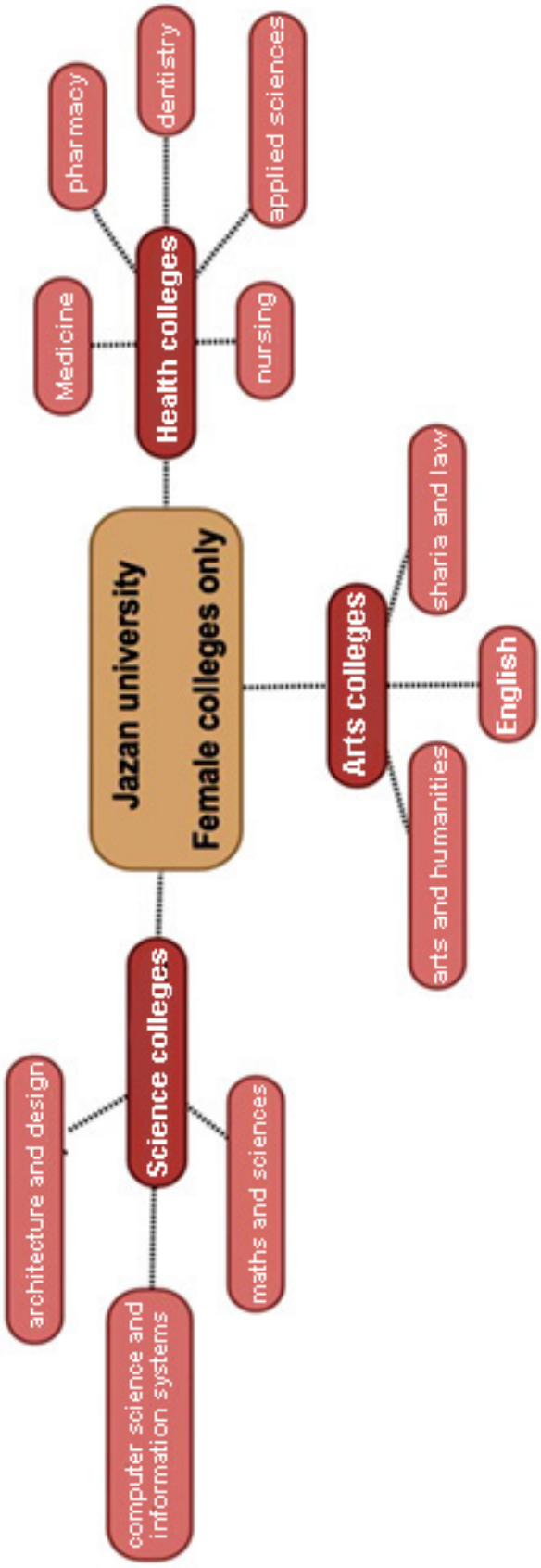
First stage: The large cluster was taken from the female students at Jazan University.

Second Stage: Participants were selected by a series of clusters from the 3 main faculties (Health, Science, and Arts). Health faculties include medicine, dentistry, pharmacy, applied sciences, and nursing. Science faculties include architecture and design, computer science and information systems, and maths and sciences. Finally, Arts faculties include Arts and Humanities, English, Sharia, and law.

Third Stage: Three Female faculties were chosen by lottery method of simple random sampling technique to be the clusters of study: Faculty of Medicine, Faculty of Maths & Sciences, and Faculty of English.

Fourth stage: Three clusters of participants were selected as a percent proportion from each Faculty

Figure 1. Distribution of the students in the study



Data collection tool
The data was collected by a semi-structured questionnaire composed of four parts and adapted to suit our culture using the Arabic language. Sociodemographic characteristics include age, educational level, and social status, secondly, the participants' background and thirdly assessment of how females respond to domestic violence.

Pilot study: A pilot study was carried-out and the questionnaire was modified, and the time was also adjusted according to its results. The results of the pilot study are not included in the final results. Cronbach's Alpha of the whole questionnaire is estimated as 0.75.

Data presentation and analysis: Data were presented and analyzed using suitable statistical methods using SPSS program version 25. Qualitative data were described using frequencies and percentages. An independent t-test was conducted to compare two continuous groups, while one-way ANOVA was conducted to compare more than two continuous groups. Values less than 0.05 were judged to be statistically significant.

Ethical consideration: Ethical approval from the Jazan University Ethical Committee was taken. Also, official approval to access the university campus was obtained from the Dean of each Faculty. Likewise, informed written consent was collected in the questionnaire, including the study background, risks, potential benefits, and declaration of voluntary participation. Besides, data collected from study participants are only used for scientific purposes. Finally, all the participants had the right to stay or withdraw at any time from the study.

Results

A total of 450 female students responded to the questionnaire. The response rate is 100%. Table 1 shows the sociodemographic characteristics of participants. Regarding age, 50.9% of participants were 22 to < 24 years old (229). For marital status, 68.9% of the female students wear single (310), married students (117, 25.9%), and divorced students (23, 5.1%) with zero widows. Regarding residence, 59% of the students (266) are from rural areas, and 41% (175) are from urban areas. As for the type of faculties, 36.0% of the students (162) were from the Arts faculties; 32.7% (147) were from the science faculties, and 31.3% (142) were from the Health faculties.

On the other hand, Table 2 shows that the overall prevalence rate of violence is 25,6% (115/450). Among the sample of the study (450 female students), the distribution of age is significantly higher in 22 to <24 years old (33.6%) than in 18 to <20 years old (20%), 20 to <22 years old (16%) and the least was the age of 24 years old and more (21.5%), P= 0.001. Regarding the distribution of female students according to the classification of Faculty, it was found that the number of students was significantly higher in the Arts faculties (31.5%) than in the Health faculties (28.6%) and Science faculties (15.5%), P= 0.004. From the side of marital status, domestic violence is significantly higher in divorced students (82.6%) compared to married students, where it is (26.4%) and in single students, it is (20.9%), P< 0.001. Lastly, regarding residence, it is higher in students from rural areas (27%) than in students from urban areas (23.3%). However, this difference is not statistically significant, P= 0.472.

Table 1: Sociodemographic characteristics of participants

	Variable	Number (450)	Percentage
Age	18 to <20	24	5.3%
	20 to <22	118	26.2%
	22 to < 24	229	50.9%
	24 and more	79	17.6%
Marital status	Single	310	68.9%
	married	117	26.0%
	divorced	23	5.1%
Residence	Village 'rural'	266	59%
	City 'urban'	184	41%
Faculty	Health	147	32.7%
	Science	141	31.3%
	Art	162	36.0%

Table 2: Prevalence of Violence according to some Variables

Characteristic	Exposed Total	Prevalence	95% CI	*P*-value
Age				
18 to <20	(3/24)	12.5%	16.3 – 23.7	.001
20 to <22	(18/118)	15.2%	12.6–19.4	
22 to <24	(77/229)	33.6%	29.2- 38	
24 and more	(17/79)	21.5%	14.2-21.2	
Faculty				
Health	(42/147)	28.6%	24.4-32.8	.004
Science	(22/141)	15.6%	27.2-35.8	
Arts	(51/162)	31.5%	12.2-19	
Marital Status				
Single	(65/310)	20.9%	17.1-24.6	<.001
Married	(31/117)	26.4%	22.3-30.4	
Divorced	(19/23)	82.6%	87.6-93.1	
Residence				
Rural	(72/266)	27%	23-31.1	.472
Urban	(43/184)	23.3%	20.05-28	
Overall prevalence	(115/450)	25.6	21.7-29.8	0.477

In addition, Table 3 shows that 15.33% of the participants (69) think that the most common cause of physical violence against women is men's abuse of drugs and alcohol. About 3% of participants (13) believe that the most likely motive for domestic violence is economic, such as poverty.

Table 4 : Participants' knowledge about emotional abuse (N=450)	No.	%
Do you think that women surrendering to violence without resistance is one of the causes of violence against women	62	13.78
Do you think that traditional thoughts are a cause of violence against women	55	12.22
Does lack of religious aspect cause violence against women	51	11.33
Is ignorance and poverty of the family causing violence against women	50	11.11
Is the disobedience of the orders of her father causing violence against women	51	11.33
Does male power in our society give the powers to bully women	71	15.78
Does men's abuse of drug and alcohol cause violence against women	38	8.44
What are the most likely motives for domestic violence (the self-motivation of a person such as the abuser being attacked in the past)	42	9.33
What are the most likely motives for domestic violence (growing up in an environment considered violence as normal behavior to dealing with problems)	55	12.22
What are the most likely motives for domestic violence (economic motives as poverty)	13	2.89
What are the most likely motives for domestic violence (customs, traditions and other social motives)	44	9.78
What are the most likely motives for domestic violence (the abuser feels the need to be dominant because of lack of self-respect)	45	10
What are the most likely motives for domestic violence (jealous)	23	5.11
What are the most likely motives for domestic violence (feeling of inferiority due to level of education or economic status)	7	6

Additionally, Table 4 shows the participants' thoughts regarding reasons for emotional violence. It was found that most participants (71, 15.78%) suppose that the male power in Jazan society gives them the power to bully women.

Table 4 : Participants' knowledge about emotional abuse (N=450)	No.	%
Do you think that women surrendering to violence without resistance is one of the causes of violence against women	62	13.78
Do you think that traditional thoughts are a cause of violence against women	55	12.22
Does lack of religious aspect cause violence against women	51	11.33
Is ignorance and poverty of the family causing violence against women	50	11.11
Is the disobedience of the orders of her father causing violence against women	51	11.33
Does male power in our society give the powers to bully women	71	15.78
Does men's abuse of drug and alcohol cause violence against women	38	8.44
What are the most likely motives for domestic violence (the self-motivation of a person such as the abuser being attacked in the past)	42	9.33
What are the most likely motives for domestic violence (growing up in an environment considered violence as normal behavior to dealing with problems)	55	12.22
What are the most likely motives for domestic violence (economic motives as poverty)	13	2.89
What are the most likely motives for domestic violence (customs, traditions and other social motives)	44	9.78
What are the most likely motives for domestic violence (the abuser feels the need to be dominant because of lack of self-respect)	45	10
What are the most likely motives for domestic violence (jealous)	23	5.11
What are the most likely motives for domestic violence (feeling of inferiority due to level of education or economic status)	7	6

Also, Figure 2 and Chart 1 show the prevalence of female students exposed to domestic violence and then the distribution according to the type of faculties.

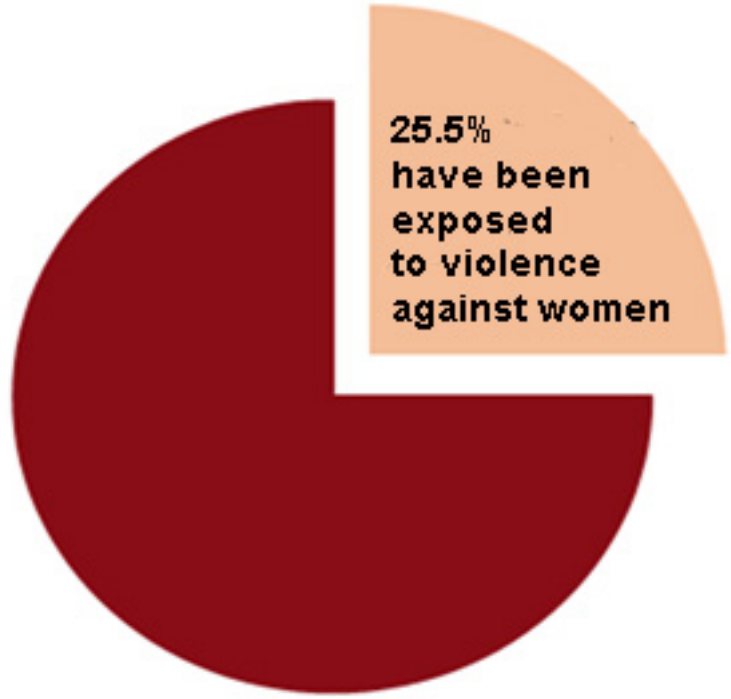
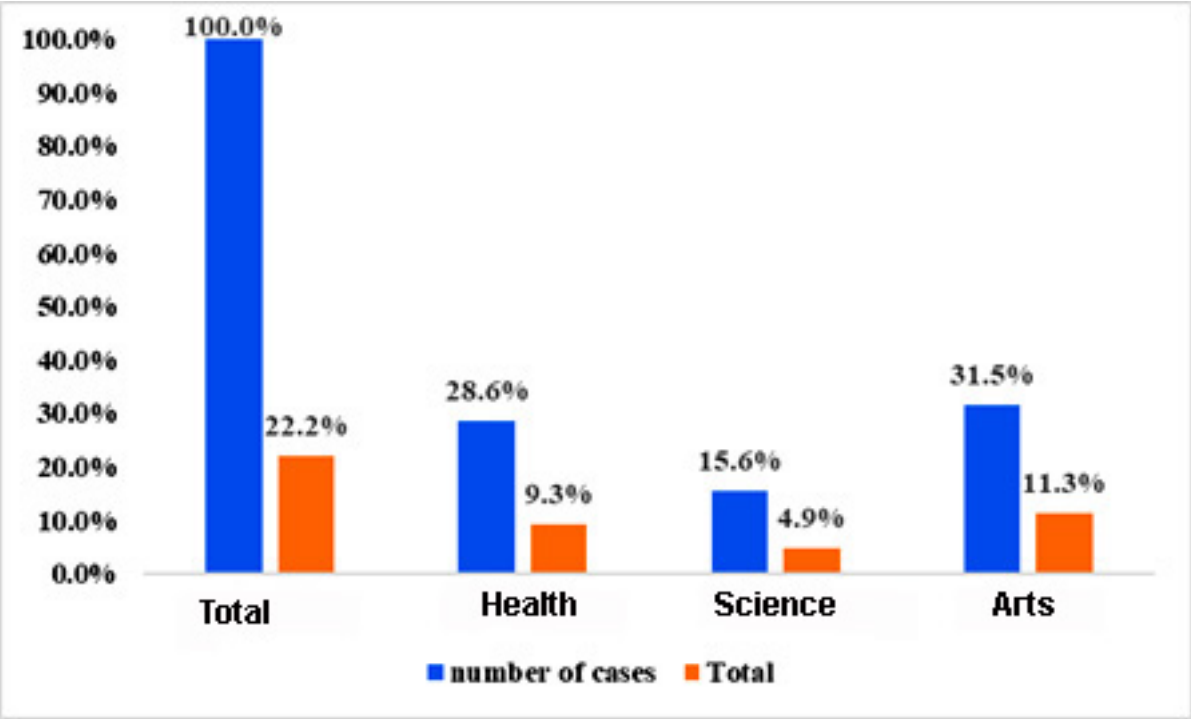


Figure 2: Prevalence of domestic violence among female students in Jizan University

Chart 1. Prevalence of Domestic Violence according to Faculty

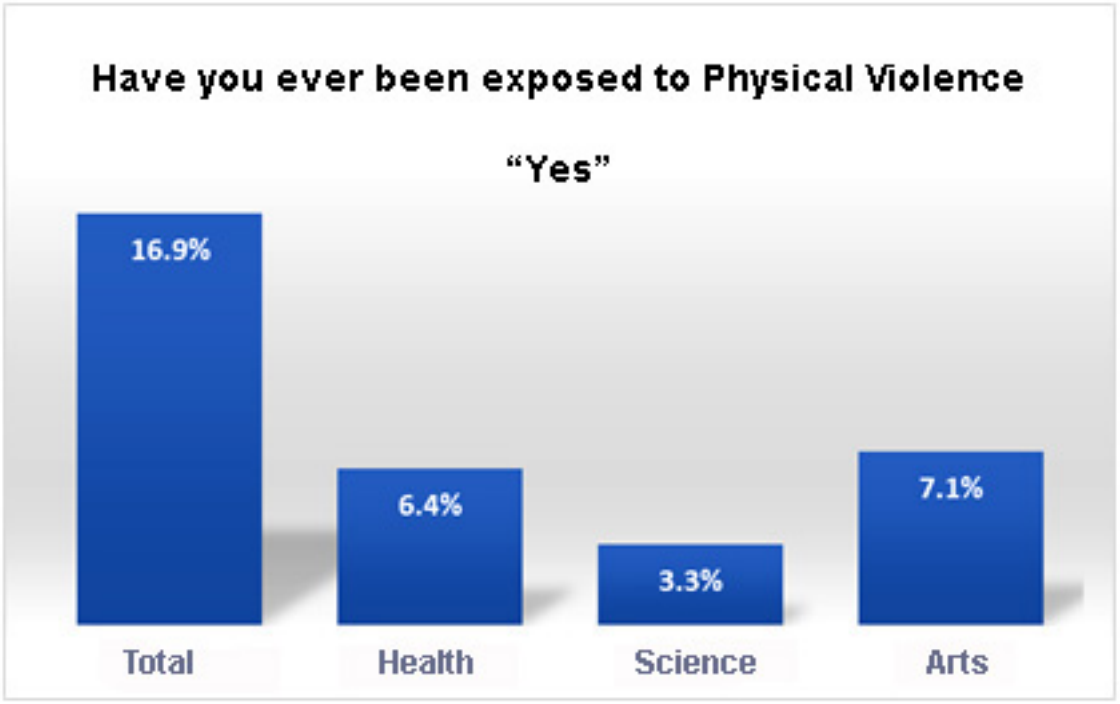


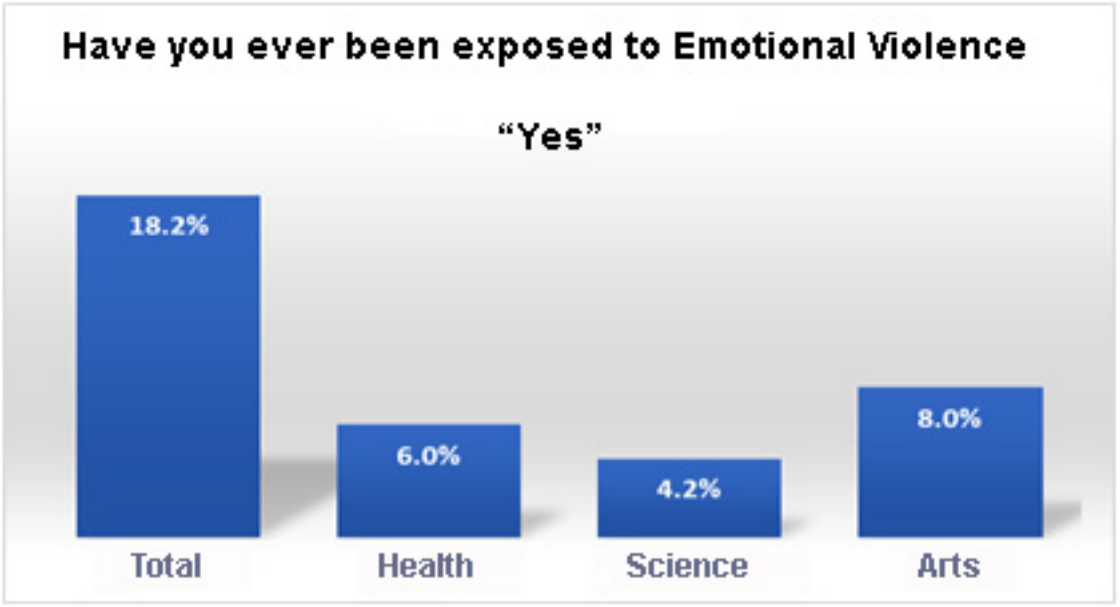
On the other hand, Table 5 and Chart 2 show that (82) of the participants who suffered from emotional violence were from the Arts faculties (36), followed by participants from the Health faculties (27), followed by participants from the Science faculties (19). Also, seventy- six of the participants who suffered from physical violence were from the Arts faculties (32), followed by participants from health faculties (29), and the least participants were from Science faculties (15).

Table 5: Distribution of physical & emotional violence among the female students according to their faculties

Type of faculties	Have suffered Violence			
	Physical Violence		Emotional Violence	
	N	% of total	n	% of total
Health (n= 147)	29	6.4	27	6.0
Science (n=141)	15	3.3	19	4.2
Arts (n=162)	32	7.1	36	8.0
Total (n=450)	76	16.9	82	18.2
P Value	.105		.168	

Chart 2. Distribution of physical and emotional violence among female students according to their faculties





Finally, Table 6 shows that 425 out of 450 female students (94.5%) think violence against women negatively impacts children and teenagers. On the other hand, 389 participants (86.5%) deduce that the most psychological effects of violence against women are loss of self-confidence, frustration, and depression. Forty-four participants (9.8%) considered that violence against women might solve arguments and marital problems, while 404 (89.8%) did not agree. The opinions for the ways to stop violence against women included restriction of patriarchy and empowering of women (45.3%) and imposition of more regulations and rules (36.2%).

Table 6: Opinions of Jazan University female students about the impact of emotional and physical domestic violence (no: 450 participants)

	Yes		No		
	Frequency	percent	Frequency	percent	Frequency (percent) of who do not know
In your opinion the most psychological effects of the violence against women are loss of self-confidence, frustration and depression	389	86.5	54	12	7(1.5)
In your opinion, violence against women has negative impact on children and teenagers	425	94.5	23	5.1	2(0.4)
In your opinion violence against women is considered as a solution for arguments and marital problems	44	9.8	404	89.8	2(04)
The best way for stoppage of violence against women in your opinion is community awareness	99	22	344	76.5	7(1.5)
The best way for stoppage violence against women in your opinion is imposition of more regulations and penalties	163	36.2	280	62.3	7(1.5)
The best way for stoppage violence against women in your opinion is to restrict patriarchy and empowering of women	204	45.3	238	53	8(1.7)

Discussion

Violence means using physical or emotional force against someone, which may result in injury, death, psychological harm, or deprivation (Rollero et al., 2019). Domestic violence is a serious problem in Arab and Islamic countries, and most abused females did not note they were abused (Halawi et al., 2017). Violence against females is everywhere, crossing cultural, class, education, income, ethnicity, and age boundaries (UNICEF, 2000). Violence against females poses a major threat to social and economic development (WHO, 2005) and is now widely recognized as a serious abuse of human rights and a major public health issue with significant consequences (Semahegn and Mengistie, 2015).

This study aimed to assess the prevalence, reasons, and perspectives of female students at Jazan University, Jazan, KSA, regarding emotional and physical domestic violence. For the socio-demographic characteristics of the study sample (Table 1), about 51% of the participants were in the age group 22 to < 24 years old (229). Regarding marital status, 68.9% of the female students were single (310), married students were 117 (25.9%), and divorced students were 23 (5.1%). Fifty-nine percent of the participants were from rural areas, and 41% from urban areas. As for the type of faculty, 35.9% of the students (162) were from Arts faculties, 32.6% (147) were from Science faculties, and 31.5% (142) were from Health faculties.

The results showed that the prevalence rate of domestic violence against women among the sample of 450 female students is 25.5% (Table 2), which is not different from the international rates of domestic violence. Many researchers and national surveys have focused on the worldwide prevalence of abuse to study its causes and impacts on females' mental and physical health status. The prevalence rates of abuse ranged from 10 - 50 percent, with different rates from developed and developing countries (Halawi et al., 2017).

Previous studies in the Kingdom of Saudi Arabia showed that domestic violence prevalence ranges dramatically from 39% to 58%, with several types of physical and emotional abuse. Statistics show that married females are Saudi society's largest segment of victims of violence (Halawi et al., 2017). Traditionally, domestic violence against females and children was not seen until 2013 as criminal in Saudi Arabia. The first major anti-domestic violence campaign, "No More Abuse," was launched in the same year. Further, the prevalence of violence has been found to increase intensively in numerous studies; however, it is still a hidden problem in the Saudi community (Halawi et al., 2017).

On the other hand, the present study found that the age group most exposed to domestic violence is female students between 22 and 24 years old (33.6%), while the least age group was 18-20 years old (Table 2). However, it was found that the higher percentage of female students exposed to domestic violence were from the faculties of Arts (31.5%) followed by those from the Health faculties (28.6%). Most female students exposed to domestic violence are divorced (82.6 %) and from urban areas (23.3%). These female students are subjected to domestic violence after divorce. It is inflicted upon them by other family members following the divorce when they returned to live with their families.

Regarding participants' knowledge about the main factors of physical abuse/violence (Table 3), it was found that 15.33% assume that the most common cause of physical violence against women is men's addiction to alcohol and drugs. In comparison, about 3% speculate that economic factors such as poverty cause physical violence. Participants' thoughts regarding reasons for emotional abuse (Table 4) showed that most participants (78%) think that the male power in Jazan society gives them the power to bully women.

Furthermore, UNICEF, 2000 stated that several complex and interconnected institutionalized social and cultural factors had kept females particularly vulnerable to the violence directed at them. The abuser feels that he needs to control the victim because of a lack of self-confidence or intense jealousy from others or when he sees himself as less than others. Some people with very traditional beliefs may think they have the right to control their partner, and females may not be equal to men. Others may have a psychological or undifferentiated personality disorder. Others have learned this behavior because they were raised in a family where domestic violence was accepted as a natural part of their family (Toby D. Goldsmith, 2018).

In addition, Mabunda et al., 2009 stated that many factors cause violence against females. These factors include a low level of education, a history of violence at home when he was young, violence as part of living, and a personality disorder. Additionally, harmful use of alcohol, social beliefs that distinguish the role of a man from females, a history of violence, discord and dissatisfaction between married individuals, male control of their partners' behavior, belief in the honor and purity of the family, low legal penalties against sexual violence, male sexual rights ideologies, gender inequality, and lifestyle acceptance of violence are identified as the main causes of violence against females.

Moreover, the current study found that out of the 450 participants, 76 suffered from physical violence, while 82 suffered from emotional violence (Table 5). By distribution according to the type of faculty, those exposed to physical and emotional violence were most in the Arts faculties (32 and 36 respectively) while the least was from the Science faculties (15 and 19 respectively). Several factors could contribute to this discrepancy and merit further discussion.

Firstly, it is crucial to explore the nature of the curricula and environments within Arts faculties compared to those in Science faculties. Arts faculties often involve extensive collaboration, critique, and communication, which may

inadvertently create an environment where disagreements or conflicts can escalate to violence. Artistic expression is more personal than science, where objectivity is valued; hence comments or encounters may be more emotionally charged.

Secondly, the faculties' cultural values and social dynamics may also affect exposure rates. For instance, Arts faculties may attract people with personality traits or emotional sensitivity, making them more vulnerable to violence. Science students may be more logical and have more stress and conflict management skills, which may lessen violence rates. Furthermore, considering faculty support systems and resources, scientific institutions may have better grievance and conflict resolution processes than Arts schools. Arts schools may not have such tools, or students may not trust them. The demographics of the faculties, external stressors, and institutional changes may have influenced these conclusions. For instance, a higher concentration of varied students in Art faculties may increase the probability of misunderstandings and disputes. An alternative conjecture could revolve around the temperamental predispositions of individuals electing to pursue these fields of study. To illustrate, it is conceivable that science-oriented students commonly exhibit traits characterized by a pragmatic and down-to-earth disposition.

Limitation

Several limitations should be taken into account concerning the present study. Initially, this study utilized a cross-sectional design, which inherently limits the ability to establish causal relationships between variables. Although this study observed associations and correlations between various factors, the directionality or causality of these relationships cannot be definitively determined. Future research employing longitudinal or experimental designs would be beneficial in elucidating the causal effects more accurately.

In addition, this study was self-funded by the authors, which may have constrained the available resources and influenced the scope and scale of the research. The absence of external funding might have limited the sample size, data collection methods, and access to specialized equipment or expertise. Consequently, the generalizability and depth of our findings could be impacted.

Additionally, to comprehensively evaluate the impact of the 2020-2030 vision implementation on female wellness and expectations, it is recommended to conduct a longitudinal study. Such a study could span several years, tracking changes over time and capturing the evolving dynamics of female empowerment and rights gained during this period. Long-term studies would provide valuable insights into the sustained effects of policy changes on women's lives.

Future research endeavors should focus on assessing the multifaceted impact of policy implementations on various aspects of female wellness and expectations. These processes could employ mixed-method approaches to capture quantitative data on health indicators, socio-economic factors, and subjective measures such as well-being and empowerment. Additionally, qualitative research methods, such as interviews and focus groups, could provide a deeper understanding of women's lived experiences and their evolving expectations.

Finally, the authors affirm that there are no conflicts of interest between themselves and any external agencies or organizations that could potentially bias the results or interpretation of this study. The research was conducted independently, and the authors declare no financial, personal, or professional associations that may have influenced the findings' design, analysis, or reporting. Transparency and impartiality were maintained throughout the research process to ensure the integrity of the study.

Conclusion

The results of the study comply with the research hypothesis. Domestic violence against females is not just highly prevalent in the Jazan community, it occurs in the entire world, with various socio-demographic and economic determinants influencing its occurrence. Emotional type of domestic violence against females is the most prevalent type. Female students in the Faculty of Arts expressed domestic violence more than others.

Recommendations

This study recommends implementing strategies to enhance community awareness concerning domestic violence, specifically focusing on violence against females. It emphasizes the significance of safeguarding women at risk and proposes stricter regulations and penalties for perpetrators of abuse, particularly in cases involving females. Additionally, it advocates for the restriction of patriarchal authority in order to empower women. The dissemination of religious awareness and the application of Islamic principles to the treatment of women and wives should be undertaken by religious leaders. Furthermore, it suggests conducting further studies incorporating in-depth interviews to discern the specific factors contributing to domestic violence and promote prevention awareness. Also, it could be used as a base to prepare awareness programs for females about Emotional and Physical domestic violence

References

Africa, S., Report, T. A., African, S., Service, P., Vos, D., Work, S., & Werk, M. (2013). Types of Domestic Violence Experienced by Women in Ilze Slabbert , Sulina Green, 49(2), 234–247.

Department of Gender, Women and Health Family and Community Health World Health Organization, 51.

Goldsmith, T. (2016). What Causes Domestic Violence? Psych Central, 1–6.

Halawi, A. A. A., Almalki, Z. A. A., & Alsadah, A. (2017). Prevalence and Risk Factors for Abuse among Saudi Females, KSA. The Egyptian Journal of Hospital Medicine, 68(1), 1082–1087. https://doi.org/10.12816/0038213

Mabunda, L., Action, S., & Mulher, F. (2009). Violence Against Women, (November 2007).
Rollero, C., Bergagna, E., & Tartaglia, S. (2019). What is Violence? The Role of Sexism and Social Dominance Orientation in Recognizing Violence Against Women. Journal of Interpersonal Violence, 36, NP11349 - NP11366.
Semahegn, A., & Mengistie, B. (2015). Domestic violence against women and associated factors in Ethiopia; Systematic review. Reproductive Health, 12(1). https://doi.org/10.1186/s12978-015- 0072-1
Semahegn, A., Ankomah, A., Assefa, N., Torpey, K., & Manu, A. (2019). Adapted tool for the assessment of domestic violence against women in a low-income country setting: a reliability analysis . International Journal of Women's Health, Volume 11, 65–73. https://doi.org/10.2147/ijwh.s181385
Toby D. Goldsmith, M. (2018). psychcentral. Retrieved from https://psychcentral.com/lib/what-causes- domestic-violence/
Types of Domestic Violence. (2019). Retrieved from https://www.acesdv.org/domestic-violence- graphics/types-of-abuse/
UNICEF. (2000). Combating Domestic Violence : Domestic Violence Against Women And Girls Editorial Overview Scope Of The Problem. Children, (6).
Was. (2017). spq newspaper. Retrieved from https://mobile.sabq.org/fZw62K
WHO. (2005). Addressing violence against women and achieving the Millennium Development Goals.
Wikipedia. (2019a). Domestic violence in Saudi Arabia. Retrieved from https://en.wikipedia.org/wiki/Domestic_violence_in_Saudi_Arabia
Wikipedia. (2019b). Violence. Retrieved from https://en.wikipedia.org/wiki/Violence

Non-Urgent Pediatric Presentations to the Emergency Department, Khamis Mushayt Maternity and Children Hospital, Saudi Arabia

Waleed Al Jabir[1]; Badr Ayed Al-alfard[2]; Abdullatef Ali Muhaya[3]; Abdullah Al Farhan[4]

(1) Pediatric senior registrar, Khamis Mushayt Maternity & Children Hospital, Saudi Arabia
(2) Pediatric Emergency Fellow, Abha Maternity & Children Hospital, Saudi Arabia
(3) Pediatric Emergency Fellow, Khamis Mushayt Maternity & Children Hospital, Saudi Arabia
(4) Pediatric, specialist, Khamis Mushayt Maternity & Children Hospital, Saudi Arabia

Corresponding author
Dr. Waleed Al Jabir
Email: wma1407@hotmail.com

Received: July 2023. Accepted: August 2023; Published: September 1, 2023.
Citation: Waleed Al Jabir et al. Non-Urgent Pediatric Presentations to the Emergency Department, Khamis Mushayt Maternity and Children Hospital, Saudi Arabia. World Family Medicine. August 2023; 21(8): 87-97 DOI: 10.5742/MEWFM.2023.95256183

Abstract

Aim of Study: To explore parents' perspectives regarding why parents (caregivers) prefer to escort their less urgent, or non-urgent sick children to the emergency departments (EDs) instead of using other more appropriate healthcare services.

Methods: This study followed a quantitative cross-sectional design at Khamis Mushayt Maternity and Children's Hospital (KMMCH). A study questionnaire was designed by the researchers to interview parents of 400 children who inappropriately attended the ED to identify the reasons for their inappropriate attendance at the ED. Data collection was performed during the period of January 2023 to explore the proportions of different attendances that were deemed inappropriate according to the hospital's followed triage system. The interviews were conducted with parents/caregivers of non-urgent and less urgent children during their waiting times.

Results: The age of 18.3% of parents was <30 years, while 28.5% were 30-39 years old. More than half of the parents' visits were non-urgent, while 43.25% were less-urgent, 55.3% of patients visited the ED before due to similar complaints, while 46% visited a primary health care center before their ED visits. The main reasons for visiting the ED instead of the primary healthcare centers (PHCCs) were to save time (49.3%) and to get an earlier appointment (48%). Patients' triage levels differed significantly according to parents' age groups ($p<0.001$), nationality ($p=0.022$), educational level ($p=0.022$), ED visits for similar complaints ($p<0.001$), and previously visiting the PHCC for the current health problem ($p=0.002$). Triage levels also differed significantly according to some reasons for choosing to go to the ED instead of the PHCC, especially to get an earlier appointment ($p=0.044$), preferring the healthcare services provided by the ED ($p=0.005$), having a nearby ED ($p=0.001$), or being at the hospital at that time ($p=0.002$).

Conclusions: There is a clear relationship between inappropriate ED visits and certain associated factors, indicating that prevention would be best targeted to certain categories, such as Saudi, younger, and educated parents. The main reasons for inappropriate ED visits are to save time and to avoid getting a late appointment.

Recommendations: This study emphasized the importance of implementing proper health education and redirection of patients with inappropriate ED visits. Conducting a detailed analysis of the shortages in the utilization of primary healthcare resources is a pressing necessity. Further nationwide research on patients' perspective for non-urgent ED presentations is largely needed.

Key Words: Emergency Department, Triage, Children, Non-urgent level, Less urgent level.

Introduction

Emergency departments (EDs) constitute an integral service for healthcare systems worldwide. They provide immediate point-of-access care for urgent medical conditions and injuries. However, overcrowding at EDs may result in increasingly stressed staff and ineffectively provided emergency services. This often leads to increased patient waiting times, treatment delays, impaired access, economic losses, and unethical consequences (1).

Emergency Department crowding is an important patient safety concern and a global public health problem. Many countries report significant and unsustainable increases in emergency presentations. A growing number of studies have found that these increases cannot be explained by population growth alone (2).

The use of emergency departments by non-urgent patients has become an important public health problem. Several studies showed that more than half of emergency visits are not urgent. This undesirably affects the quality of the provided patient care and lowers the satisfaction of both the patients and the staff in the emergency department (3).

Patients' conditions become classified according to standard triage categories. The main purpose of triage is to distinguish non-urgent patients and increase the quality of care for actual urgent patients, and allow urgent cases to become immediately managed. On the other hand, non-urgent patients become evaluated in fast-track units and are taken to the waiting room to be examined in their turn. In the EDs, emergency physicians have to work as if in polyclinics (4).

In Saudi Arabia, ED services are increasingly needed. It is provided at all governmental healthcare institutions completely free of charge to all patients. However, triage practice is not fully standardized, and in some MOH EDs, formal triage is not applied, while others have individually followed several Western systems of triage. Some of these triage systems include the Australian Triage Scale, the Emergency Severity Index, and the Canadian Emergency Department Triage and Acuity Scale (CTAS), which is widely implemented at tertiary centers (5).

In Saudi Arabia, the lack of a standardized triage system in EDs constitutes many problems, from the confusion regarding who should be seen first to how resources should be distributed. Moreover, there is a growing demand for emergency services, mainly due to the steady population growth, and the inappropriate use of its services. Previous reports estimated that over half of the patients attending EDs in Saudi Arabia are patients with primary care or non-urgent problems. Therefore, the identification of the reasons why some patients unjustifiably attend emergency departments instead of using more appropriate healthcare services is expected to improve patient safety and promote better and more efficient access to ED services (6).

Aim of study

To explore parents' perspectives regarding why they prefer to escort their less urgent, or non-urgent sick children to the emergency departments (EDs) instead of using other more appropriate healthcare services.

Methodology

This study followed an exploratory cross-sectional design. The research obtained and analyzed emergency attendance data from one large hospital in Khamis Mushayt City for a period of one month (January 2023), identifying the proportions of different pediatric attendances that were deemed appropriate (i.e., resuscitation, emergent, or urgent) or inappropriate (less urgent or non-urgent) according to the hospital's followed triage system (CTAS).

Study setting

The researchers purposively selected a pediatric tertiary care hospital (i.e., KMMCH), which receives the largest number of pediatric ED patients in Khamis Mushayt City.

Data collection tool

Based on the review of relevant literature, the researchers designed a study questionnaire for data collection (3; 7). It included the following:

A) Sociodemographic characteristics of parents: Age, gender, nationality, educational status, current employment status.

B) Characteristics of children: Age, gender, main presenting symptom(s).

C) ED visit characteristics: Urgency level, time of visit, primary complaint, previous visit(s) to the ED or a primary health care center.

The developed study questionnaire was validated by two consultants in Emergency and Pediatrics. The researcher conducted a pilot study on 20 parents of children attending the ED to test the data collection tool. The time needed to fill in the questionnaire and its wording was assessed to be about 5 minutes. Based on the findings of the pilot study, the final version of the questionnaire was reached. Data from the pilot study were excluded from the main study.

Sampling

The present study included 400 parents/caregivers of children who attended the ED for non-urgent or less urgent causes. The researchers consecutively interviewed 400 parents of children (aged less than 18 years) who had been triaged as less urgent or non-urgent, during all three shifts (morning, evening, and night) to identify the reasons for their inappropriate attendance (levels V or IV) to the ED. Parents of children with emergency levels (resuscitation, emergent and urgent cases) were not included.

Data collection

During January (2023), the researchers paid daily visits to the study hospital to conduct face-to-face interviews with parents of children attending the ED, using the study questionnaire. Parents were included consecutively until

the required sample size was fulfilled (n=400). All interviews were conducted with parents of children at the ED during their waiting times.

Data analysis

Collected data were coded and then entered and analyzed using the Statistical Package for Social Sciences (IBM, SPSS, version 28). Descriptive statistics (frequency and percentage for qualitative variables in addition to mean and standard deviation for quantitative variables) were calculated. Cross-tabulation using X^2 test was used to measure the association between variables.

Ethics and Human Subjects Issues

Before conducting the interviews, all eligible participants were clearly informed about the study objectives and were asked to provide their written consent to participate in the current study. Confidentiality and privacy were completely assured to all participants. Collected data were secured by restricting unauthorized access.

Results

Table (1) shows that the age of 18.3% of parents/caregivers was less than 30 years, while 28.5% were 30-39 years old, 33.3% were 40-49 years old and 20% were 50 years old or more. The majority of parents/caregivers were Saudi (83.5%), and more than two-thirds were university-educated (68.8%). Most parents were governmentally or privately employed (33.8% and 40%, respectively), while 20.3% were unemployed/housewives. Regarding the age of children presenting at the ED, 29% were infants, 32.5% were 1-5 years old, and 38.5% were more than 5 years old. Boys had more ED visits than girls (53% and 47%, respectively).

Figure (1) shows that 56.75% of recorded ED visits were non-urgent (Level V), while 43.25% were less-urgent visits (Level IV).

Table (2) and Figure (2) show that fever, cough, and minor trauma were the main causes for children with IV/V triage levels being escorted to the ED (27.5%, 18.8%, and 17.5%, respectively).

Table (3) shows that 55.3% of parents/caregivers had visited the same ED before due to similar complaints, while 46% visited a primary health care center before their visit to the ED.

Table (4) shows that the main reasons for parents' visits to the ED instead of the PHCC were to save time (49.3%), to get an earlier appointment for healthcare (48%), prefer to receive healthcare services at the ED (15.8%), living nearby an ED (14.2%) and visiting the hospital for any reason at that time (12.3%).

Table (5) shows that children's triage levels differed significantly according to their parents' age groups ($p<0.001$), with the highest non-urgent prevalence among younger parents (aged <30 years). Saudi sick children visited the ED for non-urgent reasons significantly more than non-Saudi sick children ($p=0.022$). Moreover, university-educated parents/caregivers visited the ED for non-urgent reasons significantly more than less-educated parents/caregivers ($p=0.022$). However, triage levels did not differ significantly according to parents' gender or employment status. Moreover, triage levels did not differ significantly according to the child's gender or age group.

Table (6) shows that children's triage levels differed significantly according to previously visiting the ED due to similar complaints ($p<0.001$), with non-urgent visits being higher among those who did not visit the ED before. Moreover, patients' triage levels differed significantly according to previously visiting the PHCC for the current health problem ($p=0.002$), with non-urgent visits being higher among those who had not previously visited the PHCC.

Table (7) shows that children's triage levels differed significantly according to some reasons for choosing to go to the ED instead of the PHCC, especially to get an earlier appointment ($p=0.044$), preferring the healthcare services provided by the ED ($p=0.005$), having a nearby ED ($p=0.001$), or being at the hospital at that time ($p=0.002$). However, triage levels did not differ significantly according to parents' choice to save time.

Table 1: Personal characteristics of participant parents/caregivers

Personal Characteristics	No.	%
A) Parents/Caregivers:		
Age (in years)		
• <30	73	18.3
• 30-39	114	28.5
• 40-49	133	33.3
• 50+	80	20.0
Gender		
• Male	227	56.8
• Female	173	43.3
Nationality		
• Saudi	334	83.5
• Non-Saudi	66	16.5
Educational level		
• Illiterate	31	7.8
• School (Primary/Intermediate/Secondary)	94	23.5
• University	275	68.8
Employment		
• Private	160	40.0
• Government	135	33.8
• Unemployed/Housewife	81	20.3
• Student	17	4.3
• Retired	7	1.8
B) Child		
Age groups		
• Infancy	116	29.0
• 1-5 years	130	32.5
• >5 years	154	38.5
Gender		
• Male	212	53.0
• Female	188	47.0

Table 2: Children's main reasons/symptoms for non-urgent or less urgent visits to the ED

Reasons/Symptoms	No.	%
Fever	110	27.5
Cough	75	18.8
Minor trauma	70	17.5
Dysuria	54	13.5
Constipation	42	10.5
Rhinorrhea	20	5.0
Diarrhea	17	4.3
Others	12	3.0

Table 3: Previous visits of parents/caregivers to emergency departments or PHC centers for their sick children

Parents' previous visits	No.	%
A previous visit to the same ED due to child's similar complaints		
• Yes	221	55.3
• No	179	44.8
A previous visit to a PHCC for the current health problem		
• Yes	184	46.0
• No	216	54.0

Table 4: Parents' perspectives regarding the reasons for visiting the Emergency Department with their sick children instead of going to the primary healthcare center

Parents' Perspectives †	No.	%
To save time	197	49.3
To get an earlier appointment	192	48.0
I prefer ED healthcare services	63	15.8
ED is nearby to me	57	14.2
Being at the hospital at that time	49	12.3

† More than one choice is possible

Table 5: Children's triage levels according to their parents' personal characteristics

Personal Characteristics	Less urgent		Non-urgent		P Value
	No.	%	No.	%	
A) Parents/Caregivers					
Age (in years)					
• <30	15	20.5	58	79.5	
• 30-39	47	41.2	67	58.8	
• 40-49	64	48.1	69	51.9	<0.001
• 50+	47	58.8	33	41.3	
Gender					
• Males	98	43.2	129	56.8	
• Females	75	43.4	98	56.6	0.971
Nationality					
• Saudi	136	40.7	198	59.3	
• Non-Saudi	37	56.1	29	43.9	0.022
Educational level					
• Illiterate	20	64.5	11	35.5	
• School	51	54.3	43	45.7	0.001
• University	102	37.1	173	62.9	
Employment					
• Student	4	23.5	13	76.5	
• Retired	4	57.1	3	42.9	
• Private	66	41.3	94	58.8	0.394
• Government	62	45.9	73	54.1	
• Unemployed/Housewife	37	45.7	44	54.3	
B) Child					
Age groups					
• Infancy	46	39.7	70	60.3	
• 1-5 years	55	42.3	75	57.7	
• >5 years	72	46.8	82	53.2	0.490
Gender					
• Male	94	44.3	118	55.7	
• Female	79	42.0	109	58.0	0.641

Table 6: Patients' triage levels according to their previous visits to emergency departments or primary healthcare centers

Previous visits	Less urgent		Non-urgent		P Value
	No.	%	No.	%	
To ED due to similar complaints					
• Yes	119	53.8	102	46.2	
• No	54	30.2	125	69.8	<0.001
To a PHCC for the same health problem					
• Yes	95	51.6	89	48.4	
• No	78	36.1	138	63.9	0.002

Table 7: Children's triage levels according to their parents' perspectives regarding the reasons for visiting the ED instead of the PHC center

Parents' Perspectives	Less urgent		Non-urgent		P Value
	No.	%	No.	%	
To save time					
• Yes	81	41.1	116	58.9	
• No	92	45.3	111	54.7	0.396
To get an earlier appointment					
• Yes	93	48.4	99	51.6	
• No	80	38.5	128	61.5	0.044
I prefer ED healthcare services					
• Yes	17	27.0	46	73.0	
• No	156	46.3	181	53.7	0.005
ED is nearby to me					
• Yes	36	63.2	21	36.8	
• No	137	39.9	206	60.1	0.001
Being at the hospital at that time					
• Yes	11	22.4	38	77.6	
• No	162	46.2	189	53.8	0.002

Figure 1: Recorded emergency levels

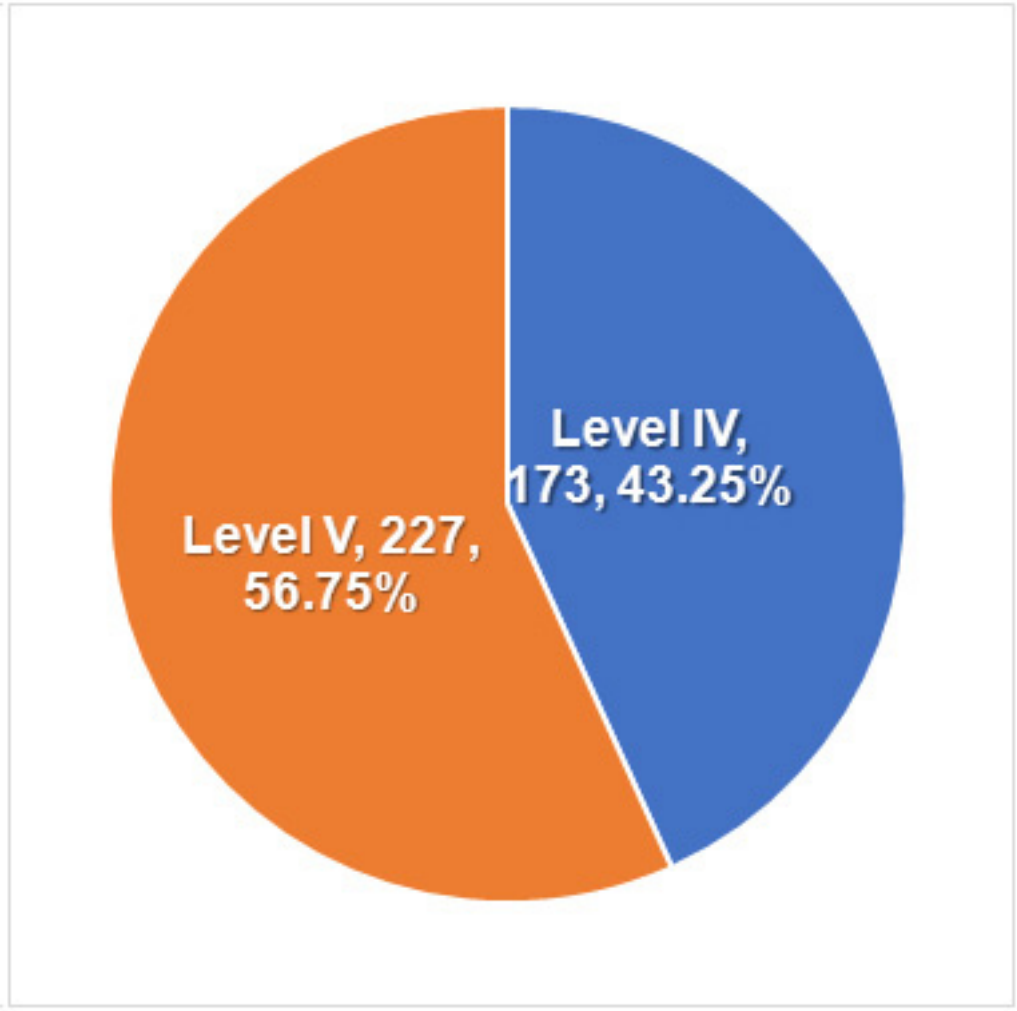
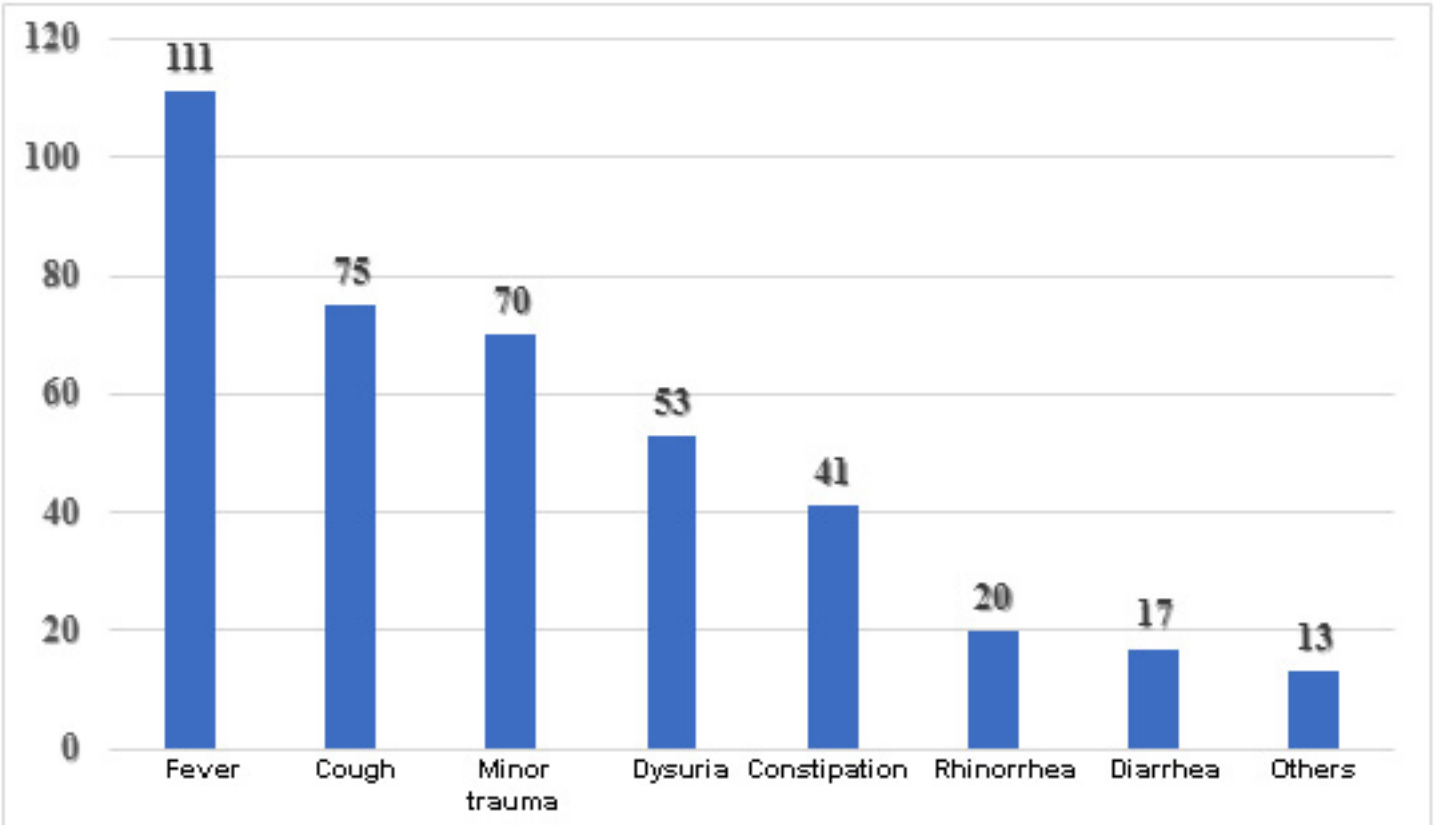


Figure 2: Main causes for children attending the Emergency Department for non-urgent or less urgent causes



Discussion

This study included 400 children who were escorted by their parents/caregivers to the ED in KMMCH. Fever, cough, and minor trauma were the main causes of being escorted to the ED (27.5%, 18.8%, and 17.5%, respectively).

Read et al. (8) noted that it has been realized that more than half of the requests for healthcare services at EDs were completely non-urgent. Such inappropriate ED visits can impede the ability of ED healthcare personnel to timely and safely treat emergency cases. Therefore, non-urgent patients may hinder access for urgent cases and have a negative impact on staff attitudes (9). In the UK, Harris et al. (10) found that 78% of ED attendances were unnecessary. Moreover, in the USA, several studies have shown that 30% to 50% of non-urgent conditions visit the ED (11-12).

In Jeddah City, Saudi Arabia, Alabbasi et al. (13) found that among ED patients visiting King Abdullah Medical Complex, 65% were less urgent, while 9.9% were non-urgent. In Riyadh City, Alnasser et al. (14) found that 56.4% of ED patients in King Abdullah Bin Abdul-Aziz University Hospital were classified as less-urgent, and 5% were non-urgent.

Guckert et al. (15) noted that there is wide variability in the magnitude of non-urgent visits to the ED, mainly due to the varying definitions and the subjective nature of measuring the ED visit inappropriateness. Internationally, 24-40% of all ED visits are inappropriate.

Agusala et al. (16) noted that overcrowding due to non-urgent visits is an increasing challenge for pediatric EDs despite several attempts to reduce the number of non-urgent visits through educational measures. Moreover, prolonged waiting times, decreased quality of received patients' care, increased risk of medication errors, increased morbidity, excess deaths, and increased patient dissatisfaction are indirect results of unnecessary visits to the ED (9; 17).

Morley et al. (2) warned that the negative consequences of ED crowding include poorer patient outcomes and the inability of staff to adhere to guideline-recommended treatment. Moreover, overcrowding may compromise patient care and is one of the most challenging problems facing EDs every day. Bezzina et al. (18) noted that an avoidable part of the increased overcrowding in EDs is induced by patients with non-urgent problems who refer themselves, are unlikely to require admission and are more suitable for other services, at primary healthcare centers. Moreover, Khattab et al. (5) emphasized that in modern healthcare systems, overcrowding and poor hospital flow are intolerable. Therefore, data-driven, evidence-based policies are needed.

Al-Nozha et al. (19) reported that half of the medical directors in Riyadh City, Saudi Arabia, complained that ED overcrowding is a major problem due to inappropriate ED visits. The current healthcare system in Saudi Arabia has identified a considerable rise in the number of ED visits, leading to a considerable increase in lengths of waiting times for ED patients, which ultimately leads to ED overcrowding (5).

Alabbasi et al. (13) warned that emergency services at Saudi governmental hospitals are frequently over-utilized for non-emergency cases. Therefore, the present study aimed to explore patients' perspectives regarding why some less urgent, or non-urgent patients prefer to attend emergency departments instead of using other more appropriate healthcare services. Moreover, primary care services are frequently insufficient to manage the demand for health treatment and require modification to reduce the burden on ED. Uscher-Pines et al. (11) stressed that, ideally, need should be the major determinant of healthcare utilization; however, a non-urgent ED visit occurs when care is sought at an ED that could have been handled in a primary care setting.

The study of Baker et al. (20) compared two groups of parents to assess the impact of a short educational video, shown to them during an ED visit for minor complaints. Nevertheless, ED visits for minor children's complaints did not decrease. Guckert et al. (15) argued that even though the results of educational measures remain ambiguous, improving knowledge and ability could have reassuring effects on parents, thus enabling them to handle non-urgent complaints at home.

Taype-Huamaní et al. (21) emphasized that the demands for attention in EDs have been rapidly progressive. However, the group that is growing the most is that of the less urgent patients (Level IV), i.e., those who make inappropriate use of the EDs. For several decades, healthcare providers in developed countries have claimed that up to 55% of the visits to EDs are for non-urgent complaints, which are more suitable for primary healthcare (22).

The majority of our parents/caregivers were Saudi (83.5%), males (56.8%), aged 30-49 years (61.8%), university-educated (68.8%), and employed (73.7%). Moreover, the comparison between non-urgent and less-urgent patients revealed that non-urgent patients were significantly more than less-urgent among younger patients (aged <30 years), significantly more among Saudi than non-Saudi patients, and among university-educated than less-educated patients. Almost one-third of the children were infants, and more than half of the children were males. However, the child's age or gender did not differ significantly according to triage levels.

Guckert et al. (15) explained that it is likely that parents are often alarmed faster during their child's first years of life, due to many different reasons (difficulties of communication with a baby/toddler, and misinterpretation of their symptoms, needs, or problems). Guckert et al. (15) also reported that males were more likely to attend inappropriately than females.

In Jeddah City, Alabbasi et al. (13) reported that males constituted 62.5% of the ED patients, while in Riyadh City, Alnasser et al. (14) found that most of the non-urgent patients were females. Moreover, in Peru, Taype-Huamaní et al. (21) reported that non-urgent ED patients were mainly females, with high school or university qualifications.

This variation may reflect differences in the definition of inappropriate ED presentation or differences in the structure and use of healthcare services among countries.

The present study revealed that more than half of the participant children had been escorted to the ED before due to similar complaints, while 46% visited a primary health care center before visiting the ED. Parents' main perspectives regarding the reasons for escorting their sick children to the ED instead of the governmental PHCCs, which provide free healthcare service to all patients, were to save time, to get an earlier appointment for healthcare, prefer going to the EDs than PHCCs to receive healthcare, live nearby to an ED, and taking the chance to visit the ED while being at the hospital for any other reason. Non-urgent visits were significantly higher among those who has not visited the ED before, and among those who came directly to the ED without a previous visit to the PHCC. Moreover, patients' triage levels differed significantly according to parents' perspectives regarding visiting the ED or the PHCC, especially to obtain an earlier appointment, preferring the healthcare services provided by the ED, having a nearby ED, or being at the hospital at that time.

In Italy, Valent and Busolin (23) reported that a short distance from home to the hospital is a predictor for non-urgent ED visits. Similarly, in Australia, Alele et al. (24) found that although visiting the PHCCs would provide superior healthcare service to the sick child than that expected to be provided at the always overcrowded EDs, living close to the pediatric ED is associated with increased parents' non-urgent pediatric ED presentations.

Guckert et al. (15) added that presentation to the pediatric ED within the morning office hours was a predictor for non-urgent visits. They attributed this finding to the fact that some parents who recognize the non-urgent nature of their children's complaints refrain from visiting the pediatric ED at night, but prefer the ED to a general practitioner at a primary healthcare center for possibly different reasons, such as the difficulty to obtain an appointment at the PHCC as soon as needed, parents expect a longer waiting time at the PHCCs and the assumption they will get faster treatment and high-quality diagnostics at the pediatric ED.

Morley et al. (2) suggested that, for the management of inappropriate ED visits, the solutions should be directed at the introduction of whole-of-system initiatives to meet timed patient disposition targets, as well as extended hours of primary care, with system-wide solutions tailored to address identified patients' perspectives. Developing and targeting interventions to reduce or manage levels of these inappropriate presentations should be a pressing necessity. As a first step, it is necessary to gain a good understanding of the perspectives of patients who are most likely to present inappropriately, and why such attendances are most likely to occur (McHale et al., 2013).

Although there have been several attempts to reduce the occurrence of non-urgent visits (e.g., by providing a primary care service in EDs), inappropriate visits to EDs remain a burden on ED services (25). An effective method of addressing inappropriate ED presentation included the provision of primary healthcare physicians either alongside emergency physicians in the ED itself or attached to the ED in a general surgery practice. This was intended to provide alternative options for what is considered inappropriate ED attendance (26).

It is to be noted that both the Saudi "National Transformation Program 2020" and the "Saudi Vision 2030" plans have identified problems with the current healthcare system, including the heavy burden faced by the EDs, and have proposed targets for improving access to, and quality of healthcare in the Kingdom of Saudi Arabia, especially primary and preventive care. These plans have identified problems with the current healthcare system, including the burden faced by EDs (5).

Study Strengths and Limitations

This study contributes to evidence-based decisions to minimize inappropriate emergency attendance and to reduce costs. The results of the present study are expected to help policymakers and administrators in the Saudi Ministry of Health to improve provided emergency healthcare services. Our study provides insight into the magnitude of the ED inappropriate attendance problem and its solution. Moreover, patients' identified perspectives will provide healthcare administration with a clear identification of problems in the primary healthcare system that encourages patients to follow inappropriate short-cut ED visits.

However, a few study limitations are to be considered. First, this study followed a cross-sectional research design, which is good for hypothesis generation, rather than hypothesis testing (Wang and Cheng, 2020). Moreover, data collection regarding parents' perspectives was completely subjective. In addition, the study included a single site, i.e., KMMCH.

Conclusion

There is a clear relationship between inappropriate pediatric ED visits and certain associated factors, e.g., parents' age, nationality, and education indicating that prevention would be best targeted to certain categories, such as Saudi, younger, educated patients. The main reasons for inappropriate pediatric ED visits are to save time and to avoid getting a late appointment. Therefore, it is important to implement proper health education programs. A 24-hour phone healthcare service that is available to the entire population to get medical advice and/or direction to an appropriate service is expected to limit non-urgent visits to ED. Moreover, conducting further research on visits to ED. Moreover, conducting further research on detailed analysis

of the shortages in the utilization of primary healthcare resources is a pressing necessity. Administrative and policy organization of the healthcare system is necessary to provide easy access to PHCCs and avoid delayed appointments and minimize patients' waiting times.

References

1. Mohr, N.M.; Wessman, B.T.; Bassin, B.; Elie-Turenne, M.C.; Ellender T, Emlet, L.L.; et al. (2020). Boarding of Critically Ill Patients in the Emergency Department. Crit Care Med. 2020; 48(8): 1180–1187. doi: 10.1097/CCM.0000000000004385.
2. Morley C, Unwin M, Peterson GM, Stankovich J, Kinsman L. Emergency department crowding: A systematic review of causes, consequences and solutions. PLoS ONE 2018; 13(8): e0203316. https://doi.org/10.1371/journal.pone.0203316.
3. Idil H, Kilic, T.Y, Toker, I, Turan, K.D, & Yesilaras, M. (2018). Non-urgent adult patients in the emergency department: Causes and patient characteristics. Turkish Journal of Emergency Medicine 18:71-74.
4. Yancey, C.C.; & O'Rourke, M.C. (2021). Emergency Department Triage. StatPearls [Internet]. Website: Emergency Department Triage - StatPearls - NCBI Bookshelf (nih.gov). Accessed on May 1st, 2022.
5. Khattab E, Sabbagh A, Aljerian N, Binsalleeh H, Almulhim M, Alqahtani A et al. Emergency medicine in Saudi Arabia: a century of progress and a bright vision for the future. International Journal of Emergency Medicine 2019;12:16.
6. Aljohani, M.S. (2017). Emergency department triage in Saudi Arabia: towards a standardised national triage system. Medicine. DOI:10.4225/03/5894008D94B97. Corpus ID: 201151173. Website: [PDF] Emergency department triage in Saudi Arabia: towards a standardised national triage system | Semantic Scholar. Accessed on 2/3/2022.
7. Arafat, A, Al-Farhan, A, Abu Khalil, H. Implementation of the Canadian Emergency Department Triage and Acuity Scale (CTAS) in an Urgent Care Center in Saudi Arabia. International Journal of Emergency Medicine 2016; 9:17.
8. Read JG, Varughese S, Cameron PA. Determinants of non-urgent Emergency Department attendance among females in Qatar. Qatar Med J. 2014; 16:98e105.
9. Durand AC, Palazzolo S, Tanti-Hardouin N, Gerbeaux P, Sambuc R, Gentile S. Non-urgent patients in emergency departments: rational or irresponsible consumers? Perceptions of professionals and patients. BMC Res Notes 2012; 5:525-533.
10. Harris MJ, Patel B, Bowen S: Primary care access and its relationship with emergency department utilisation: an observational, cross-sectional, ecological study. Br J Gen Pract 2011, 61:e787–e793
11. Uscher-Pines L, Pines J, Kellermann A, Gillen E, Mehrotra A. Emergency department visits for nonurgent conditions: systematic literature review. Am J Manag Care. 2013; 19(1):47–59.
12. McCormack LA, Jones SG, Coulter SL. Demographic factors influencing nonurgent emergency department utilization among a Medicaid population. Health Care Manag Sci. 2017; 20: 395–402.
13. Alabbasi K, Kruger E, Tennant M. Evaluation of Emergency Health-Care Initiatives to Reduce Overcrowding in a Referral Medical Complex, Jeddah, Saudi Arabia. Saudi J Health Syst Res 2021; 1:134–139. DOI: 10.1159/000517487.
14. Alnasser S, Alharbi M, Alibrahim AA, Al Ibrahim AA, Kentab O, Alassaf W, et al. Analysis of Emergency Department Use by Non-Urgent Patients and Their Visit Characteristics at an Academic Center. International Journal of General Medicine 2023:16 221–232.
15. Guckert L, Reutter H, Saleh N, Ganschow R, Muller A, Fabian E. Nonurgent visits to pediatric emergency department before and during the first peak of the COVID-19 pandemic. International Journal of Pediatrics, 2022; Article ID 7580546. DOI: 10.1155/2022/7580546.
16. Agusala V, Vij P, Agusala V, Dasari V, Kola B. Can interactive parental education impact health care utilization in pediatric asthma: a study in rural Texas. The Journal of International Medical Research 2018; 46(8): 3172 –3182.
17. Di Somma S, Paladino L, Vaughan L, Lalle I, Magrini L, Magnanti M. Overcrowding in emergency department: an international issue. Intern Emerg Med. 2015; 10(2): 171–5.
18. Bezzina AJ, Smith PB, Cromwell D, Eagar K: Primary care patients in the emergency department: Who are they? A review of the definition of the 'primary care patient' in the emergency department. Emerg Med Australas 2005, 17:472–479.
19. Al-Nozha MM, Abdullah M, Arafah MR, Khalil MZ, Khan NB, Al-Mazrou YY, et al. Hypertension in Saudi Arabia. Saudi Med J. 2007;28(1):77–84.
20. Baker MD, Monroe KW, King WD, Sorrentino A, Glaeser PW. Effectiveness of fever education in a pediatric emergency department. Pediatric Emergency Care, 2009; 25(9): 565 –568.
21. Taype-Huamaní W, De la Cruz-Rojas L, Miranda-Soler D, Amado-Tineo J. Characteristics of the non-urgent demand in the emergency service of a social security hospital in Peru. Rev. Fac. Med. Hum. January 2020; 20(1):20-26. DOI 10.25176/RFMH.v20i1.2544.
22. Backman A-S, Blomqvist P, Lagerlund M, Carlsson-Holm E, Adami J. Characteristics of non-urgent patients Cross-sectional study of emergency department and primary care patients. Scandinavian Journal of Primary Health Care, 2008; 26: 181-187.
23. Valent F, Busolin A. Distance to the pediatric emergency department and nonurgent visits in Friuli Venezia Giulia, Italy. Pediatric Emergency Care 2018; 34:193– 197.
24. Alele FO, Emeto TI, Callander EJ, Watt K. Non-urgent paediatric emergency department presentation: a systematic review. Journal of Paediatrics and Child Health 2019; 55(3): 271–277.
25. McHale P, Wood S, Hughes K, Bellis MA, Demnitz U, Wyke S. Who uses emergency departments inappropriately and when - a national cross-sectional study using a monitoring data system. BMC Medicine 2013, 11:258.
26. Bosmans JE, Boeke AJ, van Randwijck-Jacobze ME, Grol SM, Kramer MH, van der Horst HE, van Tulder MW: Addition of a general practitioner to the accident and emergency department: a cost-effective innovation in emergency care. Emerg Med J 2012, 29:192–196.
27. Wang X, Cheng Z. Cross-Sectional Studies: Strengths, Weaknesses, and Recommendations. Chest, 2020; 158(1): S65-S71.

A Patient with Crohn's Disease Presenting with a Picture Mimicking a Strangulated Incisional Hernia: A Case Report

Saad Dhafer Hussain Alshahrani

MD, Lecturer, Surgery Department, College of Medicine, Bisha University, Bisha, Saudi Arabia

Corresponding Author:
Dr. Saad Dhafer H. Alshahrani
Email: Saadoo.oo54@gmail.com

Received: July 2023. Accepted: August 2023; Published: September 1, 2023.
Citation: Saad Dhafer Hussain Alshahrani. A Patient with Crohn's Disease Presenting with a Picture Mimicking a Strangulated Incisional Hernia: A Case Report. World Family Medicine. August 2023; 21(8): 98-104 DOI: 10.5742/MEWFM.2023.95256184

Abstract

Objective: To report a case of Crohn's disease that presented with a clinical picture mimicking a strangulated incisional hernia.

Case Report: A 33-year-old Saudi male patient presented to the Emergency Department (ED) with vomiting, pain, and swelling at the right iliac fossa after lifting heavyweight objects two days earlier. The patient had a past history of appendectomy through a transverse incision nine years earlier. Clinically, the patient was vitally stable. He had tenderness at the right iliac fossa, and rebound tenderness. A tender swelling (6 x 8 cm) was observed underneath the previous scar. It was firm, not expansile on cough, and not reducible, with no redness or skin changes. The laboratory report showed normal results for complete blood count, apart from slight leukocytosis. Blood electrolyte levels, renal and liver function tests were normal. Plain CT abdomen showed a defect in the transversus abdominis muscle with the presence of swelling beneath the oblique muscles associated with air, which were connected to the bowel. The preliminary diagnosis was a "strangulated incisional hernia". After laparotomy, the swelling showed pus within the external oblique aponeurosis, with a fistula tract connected to the ileum. After abdominal exploration, the inflammation was observed to be limited to the ileum and cecum with no other abnormality noted. Ileocecectomy was done with side-to-side anastomosis between the ileum and ascending colon. The resected part was sent for histopathology, which confirmed the characteristics of Crohn's disease.

Conclusions: The diagnosis of Crohn's disease remains challenging. Its management is multi-disciplinary. Surgical management is dependent on disease location and severity. It seems that early surgery is gradually going to play a more important role in the multidisciplinary management of Crohn's disease, rather than being a last-resort therapy.

Key Words: Crohn's disease, Diagnosis, Surgical management, Case Report.

Introduction

Crohn's disease is a chronic, granulomatous, transmural patchy inflammatory bowel disease, which can affect the entire gastrointestinal tract and also extra-intestinal organs. It is associated with local and systemic complications. Crohn's disease has the highest incidence and prevalence rates in Western countries, with a peak incidence in young adulthood (1).

By the end of 2017, the highest prevalence rates of Crohn's disease were in Europe (322 per 100,000 in Germany) and North America (319 per 100,000 in Canada). Despite the fact that the incidence in developed Western countries is stabilizing, the burden of costs associated with solving emerging problems remains high. By the end of 2019, its prevalence exceeded 0.3% of the total population in many other regions of the world(2).

In Saudi Arabia, the disease is yet not well-documented. However, the drastic changes in diet and lifestyle, as well as increasing smoking among younger generations may partially be responsible for an increasing trend of Crohn's disease (3).

Over the past decades, incidence and prevalence rates of Crohn's disease have been increasing most in newly industrialized countries. This suggests that the still unclear etiology may be related to industrialization and westernization of lifestyle (4-6).

According to the Montreal classification, Crohn's disease can be divided into ileal (L1), colonic (L2), ileocolonic (L3) and isolated (L4) upper disease (which can also be added to the first three when concomitant), and behavior can be divided into non-stricturing and non-penetrating (B1), stricturing (B2) and penetrating (B3) types with or without the perianal disease (7).

van Praag et al. (8) noted that, patients with Crohn's disease typically present with transmural, penetrating disease of the terminal ileum or colon. Since Crohn's disease is known for its intermittent and relapsing courses, many different therapies have been studied. Usually, medical therapy is started as the first line of treatment, whereas surgery is considered a last treatment resort when medical therapy fails.

This study aims to report a case of Crohn's disease that presented with a clinical picture mimicking a strangulated incisional hernia.

Case Report

On April, 2nd, 2022, a 33 year old Saudi male patient presented to the Emergency Department (ED) in King Abdullah Hospital, Bisha City, Saudi Arabia, complaining of pain in the right iliac fossa associated with a swelling in the same area, that came to his attention after lifting heavyweight objects two days earlier, followed by frequent vomiting.

The patient had a past history of acute appendicitis nine years earlier. The patient's hospital record indicated that he underwent appendectomy through a transverse incision. The appendix was removed, pus was controlled, and a drain was left during the patient's hospital stay for four days. The histopathology report of the removed appendix showed acute appendicitis on top of a chronic picture.

Clinically, the patient was vitally stable. He had tenderness at the right iliac fossa, and rebound tenderness. A tender swelling (6 x 8 cm) was observed underneath the previous scar. It was firm, not expansile on cough, and not reducible, with no redness or skin changes.

The laboratory report showed normal results for complete blood count, apart from slight leukocytosis. Blood electrolyte levels, renal and liver function tests were normal. Findings of X-ray chest and abdomen were also normal. CT abdomen with double contrast was advised for the patient, but this was denied due to a previous history of hypersensitivity to the used contrast medium. Therefore, a plain CT abdomen was performed and showed a defect in the transversus abdominis muscle with the presence of swelling beneath the oblique muscles associated with air, which were connected to the bowel (Photos 1-4).

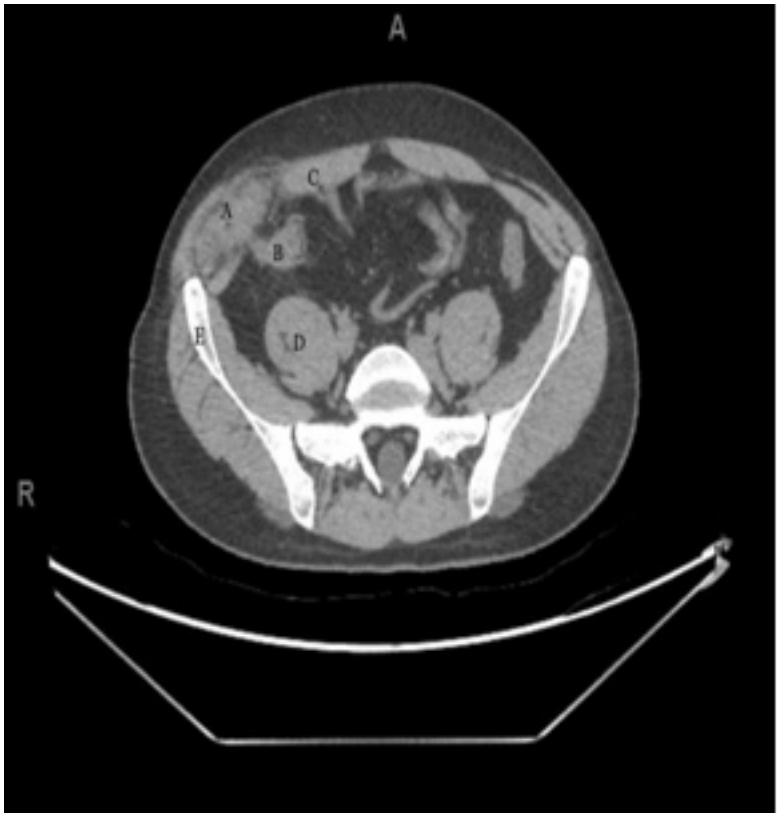


Photo (1): Plain abdominal CT showing A) The swelling; B) the small bowel; C) Rectus abdominis muscle; D) Psoas major muscle; E) iliac bone

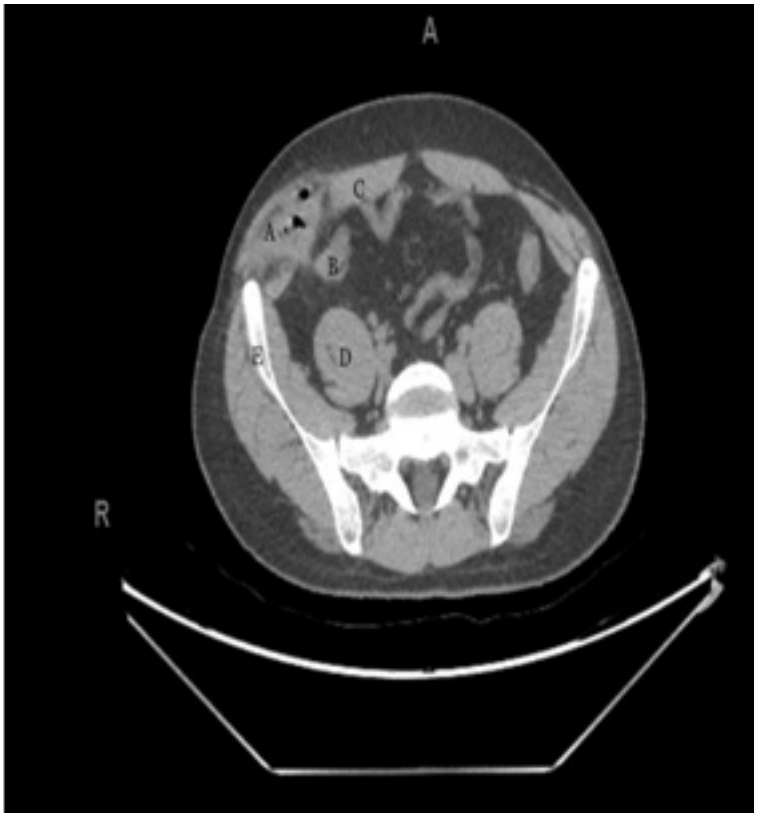


Photo (2): Plain abdominal CT showing the small bowel (B) connected to the swelling (A) with the swelling having air inside, C) Rectus abdominis muscle; D) Psoas major muscle; E) iliac bone

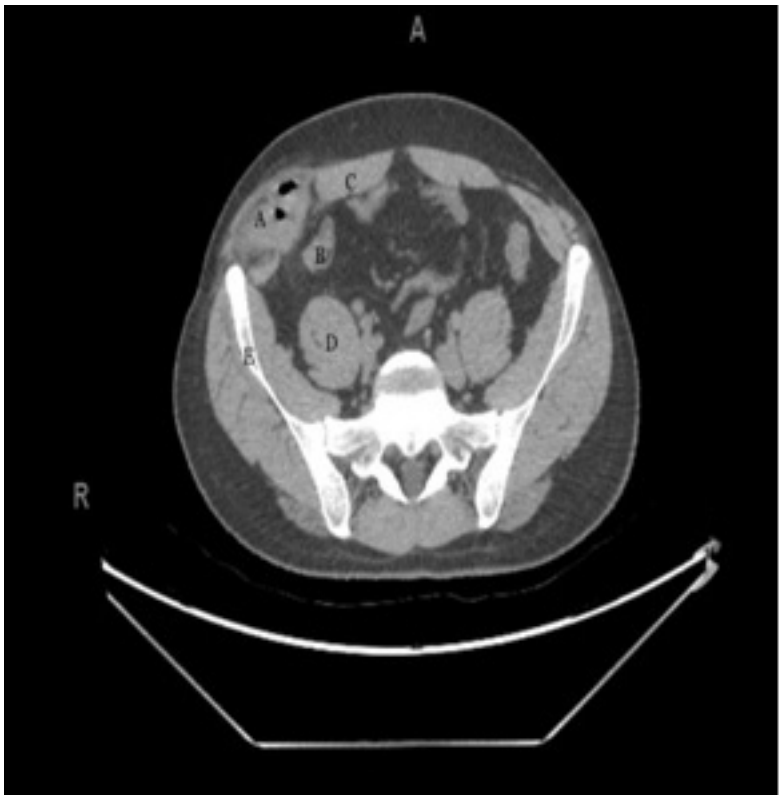


Photo (3): Plain abdominal CT showing the small bowel (B) is separate from the swelling (A); the swelling lies between the rectus abdominis muscle (C) and the iliac bone (E).

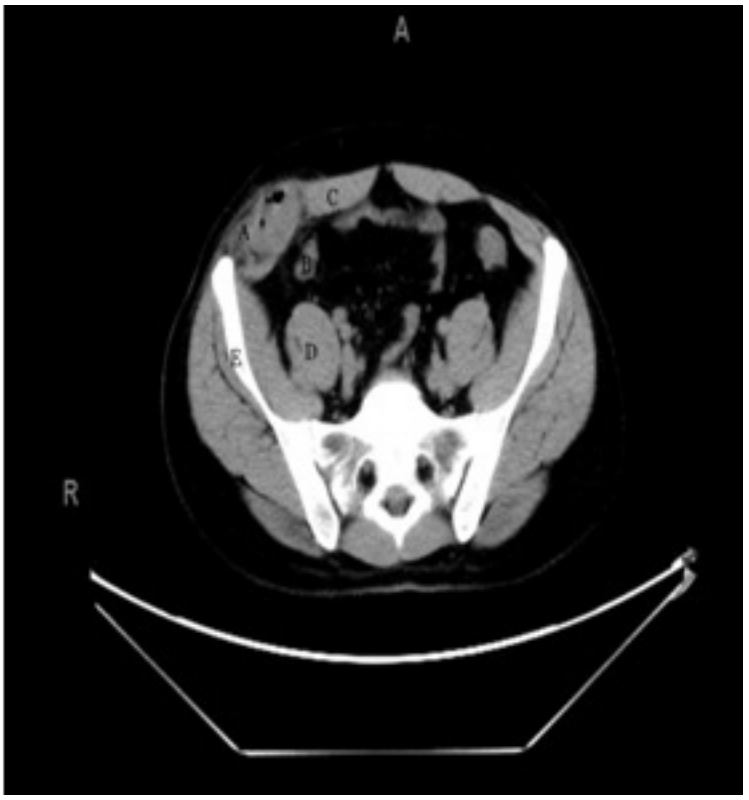
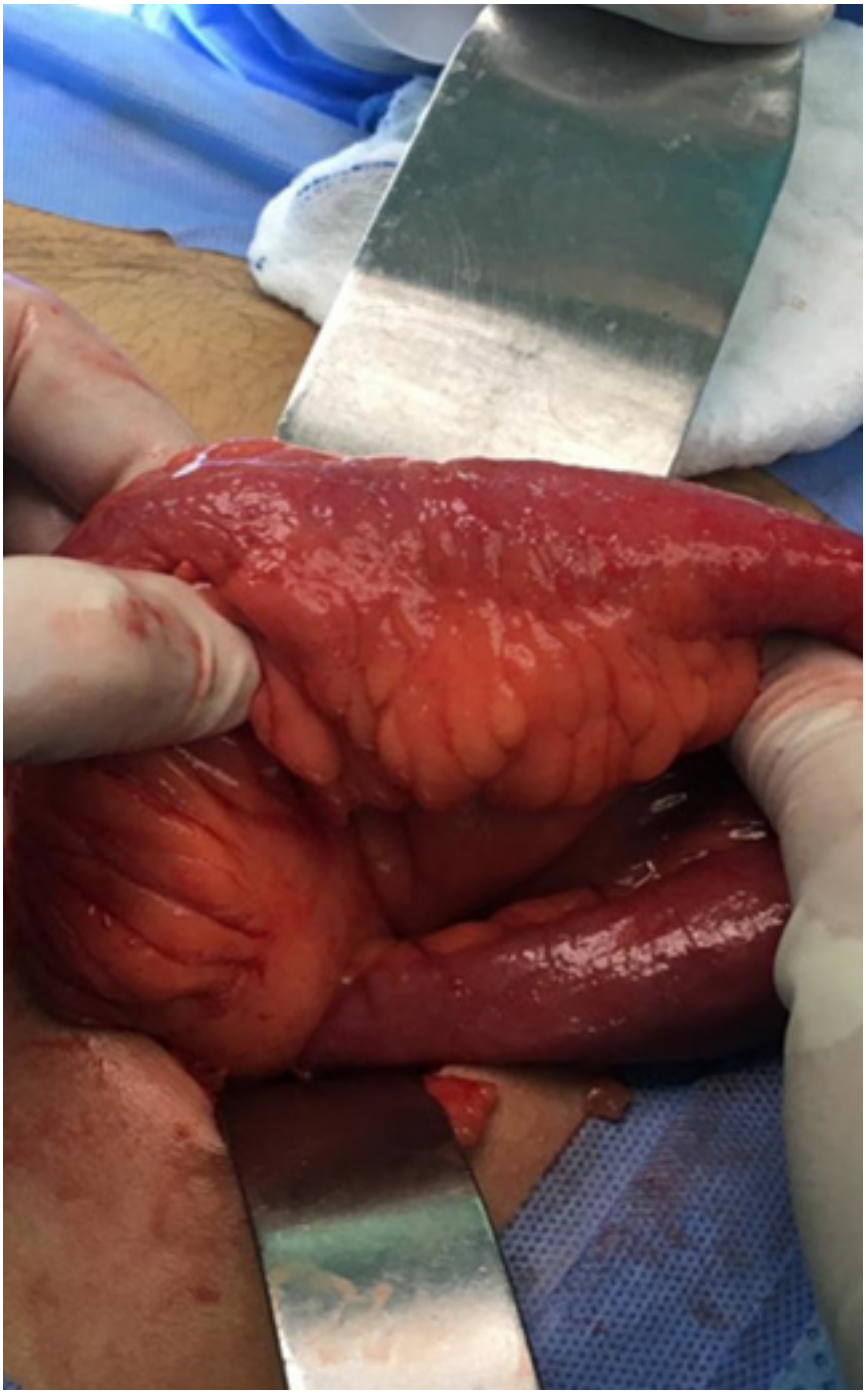


Photo (4): Plain abdominal CT showing the swelling (A) is outpouching a defect in the transversalis abdominis muscle

**Photo (5): The terminal ileum delivered through the incision.
There is evidence of mesenteric fat creeping on the bowel wall (Crohn's disease sign)**



The preliminary diagnosis was a "strangulated incisional hernia". Our patient was led to the operative theater for exploration. We started with a McBurney incision, but with subsequent dissection, it was decided to convert to laparotomy, because we thought that the swelling was post-appendectomy incisional hernia. However, the swelling showed pus within the external oblique aponeurosis, with a fistula tract connected to the ileum. The ileum and cecum were delivered through the incision. Both the ileum and the cecum were severely inflamed, with dusky walls, mesenteric creeping fat on the ileal wall, and very fragile mesentery (Photo 5). Therefore, the definite diagnosis was settled as: "Crohn's Disease".

After exploration of the whole abdomen, the inflammation was observed to be limited to the ileum and cecum with no other abnormality noted. Ileocecectomy was done with side-to-side anastomosis between the ileum and ascending colon. The resected part was sent for histopathology, which revealed transmural intestinal wall inflammation, marked edema, extensive hemorrhagic areas, mixed inflammatory cell infiltrate, lymphoid aggregate, and many congested blood vessels extending throughout all layers of the intestinal wall with the presence of non-caseating granuloma. The mesentery showed multiple lymph nodes with features of reactive hyperplasia. No neoplastic pathology was noted. The whole abdomen was explored for other abnormalities of Crohn's disease.

A drain was left in the pelvis and the abdomen was closed. The histopathology report confirmed the characteristics of Crohn's disease for the resected part.

In the postoperative period, the patient was kept fasting for two days, then a clear liquid diet was allowed. A drain was left in place for four days and then was removed. The patient was started on broad-spectrum antibiotics till the results of the culture and sensitivity testing revealed E. coli, and he was started on I.V. Ceftriaxone 1 gm BID, and I.V. Metronidazole 500 mg TID was commenced initially for two days, then he continued receiving Ceftriaxone alone for five days. Finally, the patient was discharged home in good general condition and with a clean wound.

At follow-up, one week later, the patient was referred to the Medical Department within the hospital for further management of his condition.

Discussion

The preliminary diagnosis of our case was a "strangulated incisional hernia". This preliminary diagnosis was based on full history taking and clinical examination of our case. Moreover, laboratory findings were inconclusive apart from the slight leukocytosis; blood electrolytes, renal and liver function tests were all normal. Therefore, the diagnosis was mainly based on his presenting symptoms suggestive of intestinal obstruction, the observed swelling at the right iliac fossa, and his past history of appendectomy through a transverse incision.

This case presentation supports the notion that Crohn's disease can be tricky to diagnose because its symptoms can mimic various other conditions (9). Babayeva et al. (2) added that only a detailed collection of the patient's history and a precisely adjusted examination plan can provide enough material to establish the correct diagnosis. Lack of physician awareness of immune-inflammatory diseases, and, in certain cases, limited availability or accessibility of some diagnostic methods, can lead to diagnostic errors.

Wei et al. (10) reported that many Crohn's disease cases were misdiagnosed. Most of these misdiagnosed Crohn's disease cases had normal abdominal physical examinations. The definitive diagnosis of Crohn's disease was especially difficult because their clinical presentations were equivocal and nonspecific. Their laboratory features were also non-specific, with anemia (11-15), raised erythrocyte sedimentation rate (11-12; 16), or raised C-reactive protein (12; 16-17). Other laboratory features were normal or not described.

Although a CT abdomen with double contrast was advised for the patient, a plain CT abdomen was performed instead because of the patient's known history of hypersensitivity to the used contrast medium. The definitive diagnosis could be reached after laparotomy with observation of severely inflamed ileum and the cecum, and mesenteric creeping fat on the ileal wall.

Panés et al. (18) stressed that cross-sectional imaging techniques, including computed tomography (CT), and magnetic resonance imaging, have come to the forefront in the management of Crohn's disease. These techniques are all useful and provide similar accuracy for making the initial diagnosis, monitoring disease activity, and identifying complications (e.g., fistulas, and abscesses). They complement endoscopy because they can identify extraluminal pathology and examine the gastrointestinal tract not accessible to endoscopic procedures. If the patient can tolerate the contrast load, CT and magnetic resonance enterography are preferred to standard CT and magnetic resonance imaging protocols.

CT diagnosis is needed to tell Crohn's disease apart from other conditions, for its inflammatory process determination and reference effect on involved bowel wall, extraluminal, and mesentery complications (19-20). Morphology of the bowel wall is key for the diagnosis. In Crohn's disease, the bowel wall circumferential thickening is usually symmetric and concentric. Other features of Crohn's disease include intestinal stenosis, fistula formation, multiple levels, or segmental involvement (21-22).

CT studies provide the most consistent results but have the downside of radiation exposure. Magnetic resonance studies have no radiation exposure, but are expensive, may have limited availability, and are more difficult for patients to tolerate. Ultrasonography is readily available and has no radiation exposure, but it is highly operator-dependent and can be limited by body habitus. Choosing which modality to pursue depends on the patient's age, pregnancy status, current clinical condition, local expertise, and availability (18; 23-24). Wei et al. (10) added that although a CT scan to determine the morphology of the bowel wall is a key to correct diagnosis, each case of Crohn's disease still had challenges for diagnosis and administrating the appropriate treatment.

Yin et al. (25) emphasized that creeping fat (fat wrapping) is a significant characteristic of Crohn's disease. They added that the creeping fat is a rich source of pro-inflammatory and pro-fibrotic cytokines with a complex immune microenvironment. The inflamed and stricturing intestine is often wrapped by the creeping fact, which is associated with greater severity of Crohn's disease. The large amount of innate and adaptive immune cells as well as adipocytes in the creeping fat promote fibrosis in the affected intestine by secreting large amounts of pro-fibrotic cytokines, adipokines, growth factors, and fatty acids. Moreover, the creeping fact is a potential therapeutic target for Crohn's disease treatment and a promising biomarker for predicting response to drug therapy.

Matsui et al. (26) argued that, although the diagnosis of Crohn's disease is relatively easy when classical morphological findings are present, it is quite difficult to differentiate from other diseases when only early findings or non-classical findings are present. Hisabe et al. (27) added that no diagnosis can be made based on some nonspecific findings because a substantial number of

Crohn's disease cases do not satisfy the diagnostic criteria, whose definitive diagnosis requires repeated observations.

Shepherd (28) stated that the most characteristic microscopic features of Crohn's disease are its multifocal involvement and the triad of histological features: focal ulceration, and transmural inflammation in the form of lymphoid aggregates and granulomas. Pulimood et al. (29) emphasized that it is important to take multiple biopsies from all segments of the bowel, including both endoscopically normal and abnormal areas when the diagnosis is not clear.

Therefore, the final diagnosis of Crohn's disease results from clinical findings coupled with endoscopic, histologic, radiologic, and/or biochemical testing. History, physical examination, and basic laboratory findings drive the decision to pursue the diagnosis. If the patient has a toxic presentation, standard CT should be the first test. If the patient does not have a fulminant presentation, ileocolonoscopy with biopsy should be the first test, and esophagogastroduodenoscopy should be considered for children. Cross-sectional imaging should follow so that the full extent of disease seen by endoscopy can be determined or to identify disease not visualized by endoscopy. Identifying the complete extent of the disease is important for developing a treatment plan. When ileocolonoscopy and cross-sectional imaging are negative and concern for Crohn's disease is still high, capsule endoscopy would be the next step. If this study is negative, it is moderately certain that the disease is not present (30-31).

Our case was managed surgically. Ileocecoctomy was done with side-to-side anastomosis between the ileum and ascending colon. One week after discharge, the patient was referred to the Medical Department for further management of his Crohn's disease.

van Praag et al. (8) noted that both disease location and behavior are most important to evaluate when determining appropriate treatment strategies. Fistulas for example often arise from abscesses caused by perforating disease activity, although abscesses can also arise from an existing fistula if the drainage is blocked. Ileal and ileocolonic Crohn's disease Consensus guidelines recognize the importance of surgery in complex ileocolonic disease with, e.g., abscesses, obstruction, or sepsis. Around 3 out of 4 Crohn's patients will undergo surgery during the course of their lives. However, over the past decades, it became apparent that earlier surgery could be applied for specific disease variants and in patients with severe disease. Extensive small bowel resections resulting in short bowel syndrome, and permanent stomata should be avoided (32).

Predominantly inflammatory ileal Crohn's strictures can be treated with medical therapy and surgery. Since the patients are primarily diagnosed and treated by physicians, medical therapy is usually started and surgery is traditionally reserved for the patients not properly responding to the medical therapy (33-35). Ileocaecal resection can be performed with both single- and multiport laparoscopy. In single-port laparoscopy, the entire procedure can be facilitated through one extraction site, which not only improves cosmetic outcomes but is also associated with less need for postoperative pain medication (Gardenbroek et al., 2013).

In conclusion, the diagnosis of Crohn's disease remains challenging. Its management is multi-disciplinary. Surgical management is dependent on disease location and severity. It seems that early surgery is gradually going to play a more important role in the multidisciplinary management of Crohn's disease, rather than being a last-resort therapy.

References

1. Gasparetto M, Guariso G. Highlights in IBD epidemiology and its natural history in the paediatric age. Gastroenterol Res Pract 2013; 829040–829012. Doi: 10.1155/2013/829040.
2. Babayeva GH, Asadova GV, Musayev JS, Mahmudov UR, Quliyev FV, Hasanova AI. Difficulties in the Differential Diagnosis of Crohn's Disease [Internet]. Crohn's Disease - The Current State of the Art [Working Title]. IntechOpen; 2023. Available from: http://dx.doi.org/10.5772/intechopen.110699.
3. Al-Mofleh IA, Azzam NA. Crohn's disease Increasing trend in Saudi Arabia. Saudi Med J 2013; Vol. 34 (11): 1105-1113.
4. Prideaux L, Kamm MA, De Cruz PP, Chan FK, Ng SC. Inflammatory bowel disease in Asia: a systematic review. J Gastroenterol Hepatol 2012; 27(8):1266–1280. Doi: 10.1111/j.1440-1746.2012.07150.x.
5. Su HY, Gupta V, Day AS, Gearry RB: Rising incidence of inflammatory bowel disease in Canterbury, New Zealand. Inflamm Bowel Dis 2016; 220 (9):2238–2244. doi: 10.1097/mib.0000000000000829.
6. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2017; 390(10114):2769–2778. Doi: 10.1016/S0140-6736(17)32448-0.
7. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006; 55(6):749–753. Doi: 10.1136/gut.2005.082909.
8. van Praag EMM, Buskens CJ, Hompes R, Bemelman WA. Surgical management of Crohn's disease: a state of the art review. International Journal of Colorectal Disease 2021; 36:1133–1145. Doi: 10.1007/s00384-021-03857-2
9. Ramirez W, Pinto-Garcia P. Misdiagnosis Is Common With Crohn's. It Happened to Me. GoodRx 2023 [Internet]. Website: Can Crohn's be a Misdiagnosis? Yes, It Happened to Me - GoodRx. Accessed on July 31st, 2023.
10. Wei J-P, Wu X-Y, Gao S-Y, Chen Q-Y, Liu T, Liu G. Misdiagnosis and Mistherapy of Crohn's Disease as Intestinal Tuberculosis Case Report and Literature Review. Medicine 2016; 95(1):1-5. DOI: 10.1097/MD.0000000000002436.

11. Basar O, Koklu S, Koksal D, et al. Intracranial tuberculomas in a nonimmuncompromised patient with abdominal tuberculosis misdiagnosed as Crohn's disease. Dig Dis Sci. 2005;50:1279–1282.
12. Wong WM, Lai KC, Yiu WC, et al. Intestinal tuberculosis mimicking fistulizing Crohn's disease. J Gastroenterol Hepatol. 2007;22:137–139.
13. Foster BD, Buchberg B, Parekh NK, et al. Case of intestinal tuberculosis mimicking Crohn's disease. Am J Case Rep. 2012;13:58–61.
14. Shojaei E, Abdi LZ, Faraji HS, et al. Intestinal tuberculosis sometimes mimics Crohn's disease. Acta Med Iran. 2013;51:814–815.
15. Gonzalez-Puga C, Palomeque-Jimenez A, Garcia-Saura PL, et al. Colonic tuberculosis mimicking Crohn's disease: an exceptional cause of massive surgical rectal bleeding. Med Mal Infect. 2015;45:44–46.
16. Loh KW, Bassily R, Torresi J. Crohn's disease or tuberculosis? J Travel Med. 2011;18:221–223
17. Papis D, Branchi V, Gomez L, et al. Abdominal tuberculosis mimicking Crohn's disease's exacerbation: a clinical, diagnostic and surgical dilemma. A case report. Int J Surg Case Rep. 2015;6C: 122–125.
18. Panés J, Bouzas R, Chaparro M, et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Aliment Pharmacol Ther. 2011;34(2):125-145.
19. Zhao XS, Wang ZT, Wu ZY, et al. Differentiation of Crohn's disease from intestinal tuberculosis by clinical and CT enterographic models. Inflamm Bowel Dis. 2014;20:916–925.
20. Weng MT, Wei SC, Lin CC, et al. Seminar Report From the 2014 Taiwan Society of Inflammatory Bowel Disease (TSIBD) Spring Forum (May 24th, 2014): Crohn's disease versus intestinal tuberculosis infection. Intest Res. 2015;13:6–10.
21. Park YH, Chung WS, Lim JS, et al. Diagnostic role of computed tomographic enterography differentiating Crohn disease from intestinal tuberculosis. J Comput Assist Tomogr. 2013;37:834–839.
22. Park MJ, Lim JS. Computed tomography enterography for evaluation of inflammatory bowel disease. Clin Endosc. 2013;46:327–366.
23. Gionchetti P, Dignass A, Danese S, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 2: surgical management and special situations. J Crohns Colitis. 2017;11(2):135-149.
24. Gomollón F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. J Crohns Colitis. 2017;11(1):3-25.
25. Yin Y, Xie Y, Ge W, Li Y. Creeping fat formation and interaction with intestinal disease in Crohn's disease. United European Gastroenterol J. 2022; 10(10): 1077–1084. Doi: 10.1002/ueg2.12349.
26. Matsui T, Yao T, Sakurai T, et al. Clinical features and pattern of indeterminate colitis: Crohn's disease with ulcerative colitis-like clinical presentation. J Gastroenterol. 2003;38:647–655.
27. Hisabe T, Hirai F, Matsui T, et al. Evaluation of diagnostic criteria for Crohn's disease in Japan. J Gastroenterol. 2014;49:93–99.
28. Shepherd NA. Granulomas in the diagnosis of intestinal Crohn's disease: a myth exploded? Histopathology. 2002;41:166–168.
29. Pulimood AB, Peter S, Ramakrishna B, et al. Segmental colonoscopic biopsies in the differentiation of ileocolic tuberculosis from Crohn's disease. J Gastroenterol Hepatol. 2005; 20:688–696
30. Pennazio M, Spada C, Eliakim R, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. Endoscopy 2015; 47(4):352-376.
31. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults [published correction appears in Am J Gastroenterol. 2018;113(7):1101]. Am J Gastroenterol. 2018; 113(4):481-517.
32. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. Ann Surg 2000; 231(1):38– 45. Doi: 10.1097/00000658-200001000-00006.
33. Ponsioen CY, de Groof EJ, Eshuis EJ, et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. The Lancet Gastroenterology & Hepatology 2017; 2(11):785–792. Doi: 10. 1016/s2468-1253(17)30248-0.
34. de Groof EJ, Stevens TW, Eshuis EJ, et al. Cost-effectiveness of laparoscopic ileocaecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: the LIR!C trial. Gut 2019; 68(10):1774–1780. Doi: 10.1136/gutjnl-2018-317539.
35. Stevens TW, Haasnoot ML, D'Haens GR, et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: retrospective longterm follow-up of the LIR!C trial. The Lancet Gastroenterology & Hepatology 2020; 5(10):900–907. Doi: 10.1016/s2468-1253(20)30117-5.
36. Gardenbroek TJ, Verlaan T, Tanis PJ, et al. Single-port versus multiport laparoscopic ileocecal resection for Crohn's disease. Journal of Crohn's & Colitis 2013; 7(10): e443–e448. Doi: 10.1016/j. crohns.2013.02.015.

Hypertonic Saline Solution Compared to Mannitol for the Management of Elevated Intracranial Pressure in Children: A Systematic Review

Abdullah Saleh A. Alfarhan[1]; Khalid Mohammed S. Alsleem[2]; Sultan Abdulwahab M. Asiri[1]; Ahmed Mohammed Hadi Hadadi[3]; Talal Mohammed Saeed Alshahrani [3]

(1) Pediatric Registrar at Khamis Mushait Children and Maternity Hospital, Saudi Arabia
(2) Pediatric Senior Registrar, Ahad Rufidah Hospital, Ministry of Health, Saudi Arabia
(3)Pediatric Resident, Khamis Mushait Children and Maternity Hospital, Saudi Arabia

Corresponding author:
Dr. Abdullah Saleh A. Alfarhan
Pediatric Registrar at Khamis Mushait Children and Maternity Hospital,
Saudi Arabia
Email: asalfrhan@gmail.com

Received: July 2023. Accepted: August 2023; Published: September 1, 2023.
Citation: Abdullah Saleh A. Alfarhan et al. Hypertonic Saline Solution Compared to Mannitol for the Management of Elevated Intracranial Pressure in Children: A Systematic Review. World Family Medicine. August 2023; 21(8): 105-111
DOI: 10.5742/MEWFM.2023.95256187

Abstract

Objective: To explore the effectiveness of commonly used dosing for mannitol (MN) compared with hypertonic saline solution (HSS) in children with elevated intracranial pressure (ICP) due to diabetic ketoacidosis (DKA), head trauma, or acute central nervous system (CNS) infections.

Methods: We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A structured literature review was carried out using the component of the PICO framework. The literature search was conducted in Medline, Ovid, Embase, Google Scholar, and PubMed. A combination of relevant search terms was used. Electronic searches were supplemented by manual searches of references of included studies and review articles. The duplicate citations were identified and removed.

Results: A total of 169 articles were identified through the searches, while 8 articles met the inclusion criteria. The characteristics and results of included studies were discussed, regarding the study design, sample size, and outcome.

Conclusions: Osmotic agents, such as HSS and MN are commonly used in the management of high ICP. HSS (3% or 7.5%) has superior therapeutic effects over MN (20%) in lowering increased ICP in children with cerebral edema.

Key Words: Cerebral edema, Increased intracranial pressure, Children, Osmotic agents, Mannitol, hypertonic saline solution, systematic review, PRISMA.

Introduction

Increased intracranial pressure (ICP) is a common health problem, which is frequently triggered by brain edema. As high ICP is related to increased death and impaired functional results, its control is quite important (1-2). Osmotic agents are commonly used to reduce elevated ICP, improve cerebral perfusion pressure, and presumably improve cerebral blood flow. Yet, osmotic agents have other physiological effects that can influence cerebral blood flow (3).

Elevated ICP pressure has a major impact on the worsening of the patient's neurologic status, through the impairment of brain perfusion. To reduce the intensity and the time spent with increased ICP, the infusion of MN has been recommended as a first-line agent. However, the side effects of MN are significant. In traumatic brain injury, 3% hypertonic saline solution (HSS) shows varied results in comparison with 20% MN (4). The growing interest in the use of 3% HSS has challenged the use of MN (5).

Hypertonic saline solution (HSS) and MN are osmotic agents that are commonly used in the management of high ICP. However, the clinical advantage of one over the other has not been confirmed (6). The effectiveness of MN in the management of elevated ICP, and its complications are still unclear (7). There are limited randomized controlled trials (RCTs) that have compared mannitol and 3% HSS regarding their ability to reduce ICP (8-10). However, since the magnitude of brain shrinkage depends mostly on the depth of the osmotic gradient established between plasma and brain tissue compartments, such comparisons about the respective effectiveness of MN and 3% HSS in reducing ICP are difficult to interpret (4).

Although osmotic agents have been utilized to reduce cerebral edema for nearly 5 decades, significant controversy regarding the choice of agent and dosing exists (11). Since mannitol and HSS may differ regarding their clinically relevant mechanisms of action, there is a need to determine which osmotic compound could be the most appropriate for patients with elevated ICP (4).

The available studies comparing mannitol with HSS in the management of children with raised ICP are quite scarce (12). Therefore, we undertook this systematic review to explore the effectiveness of commonly used dosing for mannitol compared with HSS in children with raised ICP due to diabetic ketoacidosis, head trauma, or acute CNS infections.

Materials and Methods

Research question

In children with increased ICP (or cerebral edema), is it better to administer MN or 3% HSS?

The PICO framework was followed to develop the review questions, as follows:

- P (Population): Children with increased ICP (or cerebral edema)
- I (Intervention): 3% Hypertonic saline solution.
- C (Comparator): Mannitol.
- O (Outcome): Lowering ICP.

Literature search

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A structured literature review was carried out using the component of the PICO framework. The literature search was conducted in Medline, Ovid, Embase, Google Scholar, and PubMed.

Combinations of the following search terms were used: intracranial pressure, type 1 diabetes, diabetic ketoacidosis, head trauma, cerebral edema, cerebral hypertension, mannitol, hypertonic saline. No search for grey literature or unpublished literature was performed.

Electronic searches were supplemented by manual searches of references of included studies and review articles. The duplicate citations were identified and removed.

Two reviewers (ASAA and SAMA) independently assessed the quality of studies using the Newcastle–Ottawa Scale quality assessment tool for observational studies. To reach a consensus, all different opinions about quality assessment were discussed with a third senior reviewer (KMSA).

Inclusion and exclusion criteria

We included studies that met the following criteria:

- Free full-text articles published in the English language in the last 10 years (2003-2022).
- Articles reporting on comparative management of increased ICP among children by both MN and 3% HSS.

The exclusion criteria were:

- Single case reports or case series, abstracts, review articles, and commentaries to articles.
- Articles reporting exclusively on adult cases.
- Articles reporting on the management of increased ICP either by MN only or by HSS only.

Data extraction

The following data were extracted from retrieved articles: publication year, study characteristics, sample size, research design, assessment points, measures used, number of assessments during pregnancy, onset, course, and prevalence rates.

Results and Discussion

Study characteristics

Figure (1) presents the PRISMA flow chart, showing that of 169 articles identified through the searches;, eight articles met the inclusion criteria of comparing the outcome of treatment of increased ICP/cerebral edema among children by MN or HSS. The characteristics and results of the included studies are summarized in Table (1).

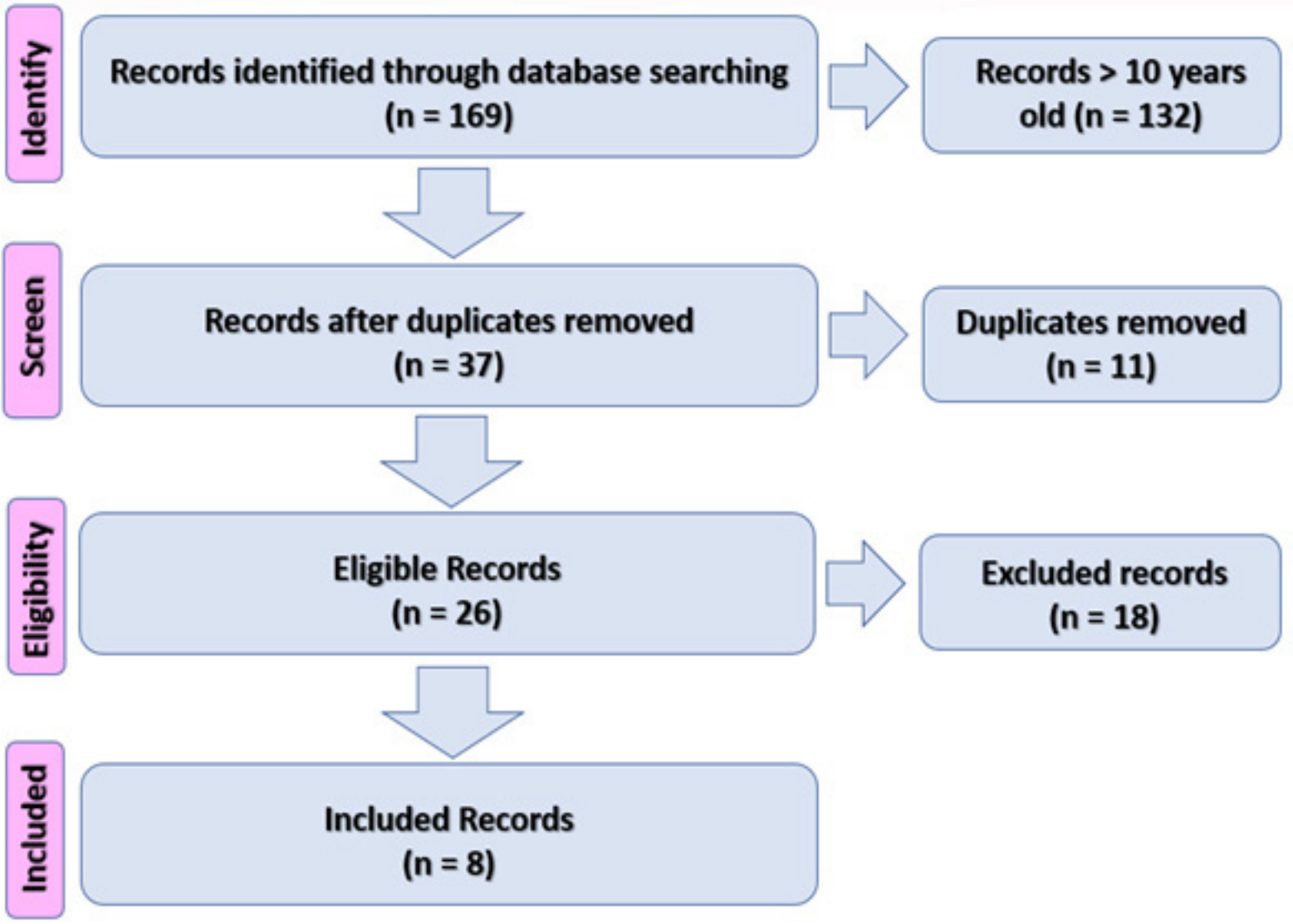


Table 1: Summary of the main results

Authors	Year	Study design	Sample size	Diagnosis	Dose	Outcome
Vialet et al. [8]	2003	RCT	7.5% HSS: 10 20% MN: 10	Raised ICP due to head trauma	HSS: 2 mL/kg bw of 2400 mOsm/kg/H_2O MN: 2 mL/kg bw of 1160 mOsm/kg/H_2O	HSS > MN
Battison et al. [13]	2005	Cross-over RCT	9 patients	ICP >20 mmHg due to head trauma or subarachnoid hemorrhage	100 mL of 7.5% HSS + 6% dextran-70 solution over 5 mins MN: Rapid IV infusions of 200 mL	HSS > MN
Yildizdas et al. [15]	2006	Retrospective	3% HSS: 25 MN: 22 Both: 20	Cerebral edema due to intracranial hemorrhage, encephalopathy, meningitis	HSS: 0.5-2 mL/kg/h infusion rate. Each bolus was applied as 1 mL/kg for 15 min. MN: 0.5 g/kg for the first 2 doses. Maintenance: 0.25 g/kg/dose	HSS > MN
Kumaraguru et al. [14]	2012	RCT	3% HSS: 40 20% MN: 40	Cerebral edema due to DKA	HSS: 5ml/kg IV, over 20 min/8 hrs MN: 1.5ml/kg IV, over 20 min/8 hrs	HSS = MN
DeCourcey et al. [16]	2013	Retrospective	3% HSS: 299 20% MN: 1202 Both: 131	Cerebral edema due to DKA	---	HSS > MN
Rameshkumar et al.[12]	2020	RCT	3% HSS: 29; 20% MN: 28	Raised ICP due to CNS infection	HSS: 10 mL/kg loading, followed by 0.5–1 mL/kg/hr infusion MN: 0.5 gram/kg/dose	HSS > MN
Wellard et al. [17]	2021	Retrospective	3% HSS: 17 20% MN: 5 HSS + MN: 8	Raised ICP due to head trauma	---	HSS > MN
Kochanek et al. [18]	2022	Retrospective	HSS: 192; MN: 159	Traumatic brain injury	---	HSS > MN

ICP: Intracranial pressure HSS: Hypertonic saline solution MN: Mannitol
RCT: Randomized controlled trial DKA: Diabetic ketoacidosis CNS: Central nervous system

This systematic review included four RCTs (8; 13-14); and Rameshkumar et al. (12), in addition to four retrospective studies (15-18).

The included eight studies had variable sample sizes, ranging from nine children in the cross-over RCT (13) and 10 children receiving HSS compared with 10 children receiving MN in the RCT of Vialet et al. (8) to 1632 (299 received HSS; 1202 received MN: 1202; and 131 received both HSS and MN).

The studies included in the present systematic review comprised children with cerebral edema as a result of different causes, mainly diabetic ketoacidosis (14; 16), central nervous system infections (12; 15), or head trauma (8; 13; 17-18).

Nehring et al. (19) described different causes of cerebral edema. For example, "cellular or cytotoxic" edema often results within minutes of the insult and affects glial, neuronal, and endothelial cells within the brain. In cytotoxic edema, the cells lack hemostatic mechanisms, and primarily sodium enters the cell freely, with the failure of the export mechanism. Traumatic brain injury causes this form of edema.

Nehring et al. (19) added that "interstitial" cerebral edema results from the outflow of cerebrospinal fluid from the intraventricular space to the interstitial areas of the brain. Patients with meningitis are examples of those affected by this etiology. Moreover, "osmotic" edema generally stems from derangements affecting osmolarity, such as hyponatremia, diabetic ketoacidosis (DKA), or similar metabolic pathologies.

Murad et al. (20) noted that various versions describing the hierarchy (i.e., pyramid) of evidence focused on showing weaker study designs at the bottom (e.g., basic science and case series), followed by case–control, and cohort (prospective and retrospective) studies in the middle, then at the very top the RCTs, and systematic reviews. The quality of obtained evidence drives the strength of recommendations, which is one of the last translational steps of research.

The present systematic review compared the outcome of children with cerebral edema after being treated with MN and/or HSS. The commonly prescribed concentration of MN was 20%, while that for HSS was mainly 3%, but the HSS concentrations used in the studies of Vialet et al. (8) and Battison et al. (13) were 7.5%.

It is to be noted that children with cerebral edema should be promptly controlled to prevent further injury, and complications, such as increased ICP. Avoidance of hypotonic fluids is a strong recommendation in instances of cerebral edema as they can worsen the condition and cause elevations in ICP. Various methods are available to help control ICP, such as positioning, and hyperosmolar therapy (19).

Desai and Damani (21) stressed that hyperosmolar therapy is the cornerstone for the management of patients with increased ICP. It is used in various pathologies and has become a valuable therapy in modern neurological critical care worldwide, which has stood the test of time. The discovery of hyperosmolar therapy has not only provided a wealth of data for the management of increased ICP, but has also allowed us to develop new treatment strategies by improving our understanding of the molecular mechanisms of cerebral inflammation, blood-brain permeability, and cerebral edema in all modes of neuronal injury.

Hypertonic saline solution (HSS) and MN are examples of osmotic agents used in the management of high ICP. Their ICP-decreasing properties are well known (6). Rameshkumar et al. (12) noted that the side effects of mannitol, like osmotic diuresis and hypotension, are significant and can lead to increased morbidity. Due to this, HSS has been compared with 20%-mannitol in patients with cerebral edema but with variable results.

Findings of the present systematic review indicate the superiority of HSS (3% or 7.5%) over 20% mannitol for the management of increased ICP.

This finding is in accordance with those reported by several RCTs, showing higher effectiveness on ICP after an infusion of 3% HSS than after an equimolar infusion of MN (4). Moreover, a longer duration of ICP reduction was observed after the use of 3% HSS, due to the combination of HSS with 6% hydroxyethyl starch solution or with 6% dextran solution (13), which are known to prolong the effects of HSS.

Adelson et al. (22) argued that although MN continues to be the most commonly used hyperosmotic agent for the management of cerebral edema, there is increasing evidence of the superior benefits of HSS. Although much of the research on HSS use in pediatrics is retrospective, there is sufficient evidence present for HS to be included as a better option for hyperosmolar therapy.

Brenkert et al. (23) found that about one-third of their DKA patients with a concern for cerebral edema received HSS. However, a consensus statement on the treatment of DKA in children and adolescents recommends prompt treatment of suspected cerebral edema with MN. Nevertheless, the diuresis potentially seen with MN may lead to unwanted adverse effects, such as intravascular dehydration, hypotension, prerenal azotemia, and even decreased cerebral blood flow (24).

Based on case reports and expert consensus, Dunger et al. (25) reported that there are no definite beneficial effects with the use of MN over HSS, which is a better alternative to MN use. Similarly, Curtis et al. (26) described a 13-year-old in DKA with a declining Glasgow Coma Scale score despite receiving a total of 0.7 g/kg of MN. A 5-mL/kg dose of 3% HSS was rapidly infused with the return of the patient's Glasgow Coma Scale score to 15 within five minutes. There were no signs of neurological damage at the time of discharge.

Kamat et al. (24) also described the use of 3% HSS in 4 patients with altered mental status and DKA. Each patient received at least one bolus at a dose of 10 mL/kg over 30 minutes. All patients showed improvement in neurological status, and no adverse effects of therapy were described.

Yildizdas et al. (15) stated that HSS has also been shown to be effective in the management of cerebral edema of infectious, anoxic, hemorrhagic, and metabolic origin. In children with cerebral edema secondary to non-traumatic causes, 3% HSS use was associated with significantly lower mortality rates and shorter duration of a comatose state when compared with MN.

Study Limitations

This study included free full-text articles published in the English language and the focus was on the last 10 years. There were only 9 eligible studies fulfilling the inclusion criteria. Despite the inclusion of four RCTs, which occupy the top of the hierarchy of evidence, five retrospective studies were included, which lie in the middle of the hierarchy of evidence and are usually associated with the risk of recall bias (24).

Conclusion

Osmotic agents, such as HSS and MN are commonly used in the management of high ICP. HSS (3% or 7.5%) has superior therapeutic effects over MN (20%) in lowering increased ICP in children with cerebral edema.

References

1. Badri S, Chen J, Barber J, Temkin NR, Dikmen SS, Chesnut RM, et al. Mortality and long-term functional outcome associated with intracranial pressure after traumatic brain injury. Intensive Care Med. 2012; 38:1800–9. doi: 10.1007/s00134-012-2655-4.
2. Melhem S, Shutter L, Kaynar AM. A trial of intracranial pressure monitoring in traumatic brain injury. BioMed Central 2014; 14:13713. doi: 10.1186/cc13713.
3. Scalfani MT, Dhar R, Zazulia AR, Videen TO, Diringer MN. Effect of osmotic agents on regional cerebral blood flow in traumatic brain injury. J Critic Care 2012; 27:526. Doi: 10.1016/j.jcrc.2011.10.008.
4. Francony G, Fauvage B, Falcon D, Canet C, Dilou H, Lavagne P, et al. Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure. Crit Care Med 2008; 36(3): 795-800.
5. White H, Cook D, Venkatesh B: The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury. Anesth Analg 2006; 102:1836–1846.
6. Zhang W, Neal J, Lin L, Dai F, Hersey DP, McDonagh DL, et al. Mannitol in critical care and surgery over 50+ years: a systematic review of randomized controlled trials and complications with meta-analysis. J Neurosurg Anesthesiol 2019; 31:273–84. doi: 10.1097/ANA.0000000000000520.
7. Wakai A, Roberts I, Schierhout G: Mannitol for acute traumatic brain injury. Cochrane Database Syst Rev 2007: CD001049.
8. Vialet R, Albanese J, Thomachot L, et al: Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. Crit Care Med 2003; 31:1683–1687.
9. Harutjunyan L, Holz C, Rieger A, et al: Efficiency of 7.2% hypertonic saline hydroxyethyl starch 200/0.5 versus mannitol 15% in the treatment of increased intracranial pressure in neurosurgical patients: A randomized clinical trial. Crit Care 2005; 9:R530–R540.
10. Bentsen G, Breivik H, Lundar T, et al: Hypertonic saline (7.2%) in 6% hydroxyethyl starch reduces intracranial pressure and improves hemodynamics in a placebo-controlled study involving stable patients with subarachnoid hemorrhage. Crit Care Med 2006; 34:2912–2917.
11. Hinson HE, Stein D, Sheth KN. Hypertonic Saline and Mannitol Therapy in Critical Care Neurology. Journal of Intensive Care Medicine 2013; 28(1):3-11.
12. Rameshkumar R, Bansal A, Singhi S, Singhi P, Jayashree M. Randomized Clinical Trial of 20% Mannitol Versus 3% Hypertonic Saline in Children With Raised Intracranial Pressure Due to Acute CNS Infections. Pediatric Critical Care Medicine 2020; 21 (12):1071-1080. DOI: 10.1097/PCC.0000000000002557.
13. Battison C, Andrews PJ, Graham C, Petty T. Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. Crit Care Med 2005; 33:196–202.
14. Kumaraguru D, Poovazhagi V, Sangareddi S, Padmanabhan R, Jeyachndran P. Effectiveness of 3% saline versus mannitol in children with cerebral oedema of non-traumatic etiology. Journal of Pediatric Sciences. 2012;4(3):e143.
15. Yildizdas D, Altunbasak S, Celik U, et al. Hypertonic Saline Treatment in Children with Cerebral Edema. Indian Pediatr. 2006;43:771-779.
16. DeCourcey DD, Steil GM, Wypij D, Agus MSD. Increasing Use of Hypertonic Saline Over Mannitol in the Treatment of Symptomatic Cerebral Edema in Pediatric Diabetic Ketoacidosis. Pediatric Critical Care Medicine, 2013; 14(7): 694–700. doi:10.1097/pcc.0b013e3182975cab.
17. Wellard J, Kuwabara M, Adelson PD and Appavu B. Physiologic Characteristics of Hyperosmolar Therapy After Pediatric Traumatic Brain Injury. Front. Neurol. 2021; 12:662089. doi: 10.3389/fneur.2021.662089.
18. Kochanek PM, Adelson D, Rosario BL, Hutchison J, Ferguson NM, Ferrazzano P, et al. JAMA Netw Open. 2022; 5(3): e220891. doi: 10.1001/jamanetworkopen.2022.0891.
19. Nehring SM, Tadi P, Tenny S. Cerebral Edema StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Website: Cerebral Edema - StatPearls - NCBI Bookshelf (nih.gov). Accessed on July 20th, 2023.
20. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. Evid Based Med 2016; 21 (4): 125-127. DOI: 10.1136/ebmed-2016-110401.

21. Desai A, Damani R. Hyperosmolar therapy: A century of treating cerebral edema. Clinical Neurology and Neurosurgery, 2021; 206: 106704. Doi: 10.1016/j.clineuro.2021.106704.
22. Adelson PD, Bratton SL, Carney NA, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents: use of hyperosmolar therapy in the management of severe pediatric traumatic brain injury. Pediatr Crit Care Med. 2003;4(suppl 3):S40-S44.
23. Brenkert TE, Estrada CM, McMorrow SP, Abramo TJ. Intravenous Hypertonic Saline Use in the Pediatric Emergency Department. Pediatr Emer Care 2013;29: 71-73
24. Kamat P, Vats A, Gross M, et al. Use of hypertonic saline for the treatment of altered mental status associated with diabetic ketoacidosis. Pediatr Crit Care Med. 2003; 4:239-242.
25. Dunger DB, Sperling MA, Acerini CL, et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child. 2004; 89:188-194.
26. Curtis JR, Bohn D, Daneman D. Use of hypertonic saline in the treatment of cerebral edema in diabetic ketoacidosis (DKA). Pediatr Diabetes. 2001; 2:191-194.