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Our planet - our health

A time for humanity to unite and end all wars and together rescue our planetary home

Editorial

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In this issue a number of papers discussed important topic for the region and family medicine including a review on the use of artificial intelligence in Family Medicine.

Saquib Irfan et al provide a Comparative Analysis of Oral and parenteral routes of Administration of Vitamin B2. The focus of the review was to investigate whether one route of administration is superior to the other. Only randomized trials were included and studies about B12 administration for purposes other than pure deficiency, were excluded. Three studies were included. In conclusion, the published data suggested that oral and parenteral both are equally efficient with little controversy. Further research with better study design and larger sample size is mandatory.

Helvaci et al., looked at the Terminal endpoints of systemic atherosclerotic processes in sickle cell diseases. The authors stressed that Sickle cell diseases (SCD) are severe inflammatory processes in the vasculature mainly on capillary endothelium since they are the main distributors of hardened red blood cells into the tissues. On the other hand, aging and male gender alone may be the most significant underlying risk factors of the systemic atherosclerosis since male gender lives about seven years shorter than female gender worldwide. All patients with the SCD were included into the study. The study included 222 males and 212 females with similar mean ages (30.8 versus 30.3 years, $p>0.05$). Smoking ($p<0.001$), alcohol ($p<0.001$), disseminated teeth losses ($p<0.001$), ileus ($p<0.001$), cirrhosis ($p<0.001$), leg ulcers ($p<0.001$), digital clubbing ($p<0.001$), coronary heart disease (CHD) ($p<0.05$), chronic renal disease (CRD) ($p<0.05$), chronic obstructive pulmonary disease (COPD) ($p<0.001$), and stroke ($p<0.05$) were all higher in male gender. Interestingly, mean ages of stroke (33.5 years), COPD (33.6 years), clubbing (35.4 years), CHD (35.7 years), cirrhosis (37.0 years), and CRD (39.4 years) were the highest among the other atherosclerotic consequences. The authors concluded that Smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, COPD, and stroke-like atherosclerotic risk factors or terminal endpoints were all higher in male gender with the SCD. Since aging alone may be the major associated factor of the systemic atherosclerosis, stroke, COPD, digital clubbing, CHD, cirrhosis, and CRD may be the terminal endpoints of systemic atherosclerotic processes in human body since the mean ages of the above pathologies were the highest among the other atherosclerotic consequences in the SCD.

Lesley, reviewed “AI and FM – a cautionary tale”. She stressed that Education and Medicine are two of the greatest achievements of humankind and this knowledge has been faithfully passed down by generations for millennia. Each generation builds on the knowledge of previous generations.

High technological advances have also brought many advantages to humans but because they tend to be 'owned' by the very few, they have increasingly become commercialised and indeed weaponised. In a world of identity theft, cybercrime, scams, fraud, war and genocide, humanity needs to be very careful about trusting in the integrity of AI. Particularly, Family Medicine should always be based on the individuality of every patient within their unique circumstances. The Covid era saw a great change in the delivery of medicine and particularly in remote consultations. Telemedicine has now become entrenched in most countries, despite some limitations and has added to the growing use of ICT in medicine. With a computer on most doctors' desks globally, family doctors are able to take advantage of so many online facilities and sources of information. ICT has made the job easier but has also added levels of complexity and the need for added security. We already have 'software' as the 'AI' supporting many diagnostic choices. This software is a tool, however, not a decision maker and the educated physician can access that tool for speed of diagnosis and recommended care. Asking a machine to make that diagnosis is a totally different matter.Certainly national health authorities need to provide guidance and oversight of the resources doctors are using to ensure ongoing accuracy and safety. In the bigger picture should we be entrusting the world's most valuable knowledge to competing tech platforms when the cyber world is already riddled with divisions and crime. Should not human health always be in the hands of humans, our well educated, trusted doctors who have insight into the intricacies of each individual patient's life.

Dr Elghblawi, reviewed the topic of sleep paralysis from a personal experience.

"I had for some years I can't count, a daily terrible night experience, and the scariest moment that I feared was the night when it fell and released its curtain down. I knew that sleeping time would visit me and would horrify me the most causing extreme distress. It's like witnessing death, I can't talk, I can't shout for help or scream or cry out, I can't move, I can't open my eyes, struggling hard but cannot. I just feel impending doom on my chest squeezing me very hard, where I can't breathe in fully, along with hearing buzzing and hissing sounds loudly for a few seconds, maybe minutes and then it releases as brought you back to life, to reality to reborn again as a spell let go and passes away after a great struggle".

Comparative Analysis of Oral and Parenteral Routes of Vitamin B12 Administration

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Abstract

Vitamin B12 is essential for the neurological system, and erythropoiesis among other important functions. Malnutrition, malabsorption such as in a case of atrophic gastritis and certain drugs like Metformin, can cause B12 deficiency. B12 can be administered both orally and parenterally. The rout of administration of B12 has been subject to extensive research regarding efficacy.

The focus of this review was to investigate whether one route of administration is superior to the other. Only randomized trials were included and studies about B12 administration for purposes other than pure deficiency, were excluded. Three studies were included. In conclusion, the published data suggested that oral and parenteral both are equally efficient with little controversy. Further research with better study design and larger sample size is mandatory.

Keywords: Vitamin B12 administration, Oral, parenteral

Introduction

A collection of nutrients called vitamins are necessary for a healthy human metabolism. Human growth, the maintenance of the neurological system, and synthesis of RBCs all require vitamin B12 also known as cobalamin. Items including eggs, seafood and meats are the only natural providers of vitamin B12. Age-related daily needs dictate the recommended dietary allowances. RDA for adults is 2.4 µg /day of vitamin B12 as stated by Doets EL, in 't Veld PH, Szczecińska A (1). Age-related increases in vitamin B12 insufficiency are likely brought on by the increased likelihood of food-cobalamin malabsorption in this population. In addition to chronic H. Pylori infection, chronic metformin, proton pump inhibitor usage, and gastric atrophy is known to be the main cause of this malabsorption (2).

Individuals in a lower strata of society, females, and non-Hispanic Blacks are more prone to have poor vitamin B12 consumption, according to an examination of NHANES data from 2015–2016 (3). In the USA and the United Kingdom, the frequency of vitamin B12 insufficiency is approximately 20% in persons over 60 compared to roughly 6% in adults under 60. Additionally, during pregnancy, blood vitamin B12 levels frequently decrease, occasionally to subnormal levels, although they typically rebound to normal following delivery (4). Historically, intramuscular injections have been used to deliver vitamin B12 supplementation. However, a number of case-control and case series research have recently shown that oral intake after delivery has an equivalent level of effectiveness and safety (5). Although vitamin B12 is widely accessible and has a proven safety record, oral prescriptions for it are uncommon. But in Sweden in 2000, 73% of the entire amount of vitamin B12 prescription was taken orally (6). A single-center, randomized control trial was carried out recently, which concluded that parenteral vitamin B12 increased hemoglobin values and serum levels better than the oral intake, however, both groups revealed increased levels (7).

There was a systematic review conducted in 2015 and then updated in 2018. Vitamin B12 therapy by oral versus intramuscular injection was contrasted in two randomized control studies. B12 was administered orally at doses of 1,000 and 2,000 mcg. Both trials used a 1,000 mcg intramuscular vitamin B12 dosage, which was given by nurses. According to the scant evidence found in this systematic analysis, daily high dosages of 2000 mcg of vitamin B12 taken orally are just as beneficial as injections into the muscles (8). The trials that were examined also provided scant evidence for certain individuals with disorders linked to malabsorption receiving sufficient hematological, biochemical, and clinical effects of per oral B12 supplementation.

Objectives

To determine the efficacy of oral vitamin B12 compared to parenteral vitamin B12 for vitamin B12 deficiency.

What makes this review significant?

There was a review conducted by Vidall J, Butler CC, Cannings R et al in 2005 (8), where they concluded that in persons who are vitamin B12 deficient, large oral dosages of the vitamin may be just as effective as parenteral vitamin B12 delivery in achieving brief hematological and nervous system outcomes. In 2018, there was an update of this review by Wang H et al, where it was demonstrated that oral therapy is cost effective and IM and oral vitamin B12 have similar effects for restoring normal blood vitamin B12 levels(9). They signified that vitamin B12 taken orally has lower risks than parenteral Vitamin B12. Better randomization along with effective blinding procedures and a larger participant pool along with proper reporting should all be used in subsequent research studies.

Methods and Material

Study selection criteria for the current systematic review:

- The inclusion criteria for our systematic review were randomized trials assessing the efficacy of oral versus parenteral routes of Vit B12 administration.
- Exclusion criteria included patients with any confounding diseases like end-stage renal failure and research with the objectives of Vit B12 administration for cardiovascular diseases.

Population type

Vitamin B12 deficient participants who satisfied the requirements for vitamin B12 replacement treatment because they are vitamin B12 deficient.

Criteria for diagnosing vitamin B12 insufficiency

Vitamin B12 insufficiency levels were defined as serum levels below 200 pg/mL (below 148 pmol/L).

Intervention used:

Oral administration of Vit B12 to 1 group and parenteral to other.

Outcome measurements:

Comparison of efficacy of both routes of administration, with other considerations such as future direction and socioeconomic effects. The following results were examined in the review, but they were not used to select which research to include or retain.

Data collection and analysis

We looked through all possibly relevant publications' complete texts. We retrieved important participant and intervention variables as well as trial results for those studies that met the inclusion criteria. We incorporated important trial features such as trial design, site, and sample size population. In order to reduce the chance of bias, we explained the procedure used to create the selection sequence for each included experiment. When studies' inclusion criteria, settings, treatments, and follow up protocols were sufficiently comparable, random effects meta-analyses was conducted taking into account the impacts of the whole distribution (10).

Description of Studies

Characteristics of included studies:

Rahul Tandon 2022

Methods	Single-centered, open-label randomized control trial (March 2015 - June 2016)
Participants	**Inclusion criteria:** • Age less than 18, • Mean corpuscular volume (MCV) above 110 fL, hyper-segmented neutrophils present, thrombocytopenia • Vitamin B12 levels below 150 pg/ml. **Exclusion criteria:** Blood transfusions or Vit B12 therapy prior
Interventions	Study centers: 1 Prior treatment: No
Aim of study	To compare oral vitamin B12 therapy with parenteral therapy in children with macrocytic-megaloblastic anemia. **Copied from research paper**

Random sequence generation (selection bias)	WINPEPI software
Blinding of participants and personnel	Open-label study

Zahit Bolaman 2003

Zahit Bolaman 2003

Methods	A ninety day, single-centered, prospective, randomized, open-label study,
Participants	**Inclusion criteria:** aged ≥16 years • serum vitamin B12 concentration <160 pg/ml • megaloblastic anemia MCV >94 fL (normal value, 80–94 fL). **Exclusion criteria:** Cancer history, lack of folate, inability to take oral medicine, and medication use
Interventions	Number of study centers: 1 Treatment before study: No
Aim of study	To assess the effects and financial cost of oral versus intramuscular vitamin B12 treatment in patients with megaloblastic anemia due to cobalamin deficiency
Random sequence generation (selection bias)	Block randomization method
Blinding of participants and personnel	The open-label study, single center

Rabia Gönül Sezer 2018

Methods	Jan to Dec 2016, prospective, randomized, single-center
Participants	**Inclusion criteria:** Children aged 1 month to 18 years with serum vitamin b12 levels below 300 pg/ml, focusing on symptoms like failure to thrive, anemia, and tingling sensation. **Exclusion criteria:** It excluded newborns with no signs of failure to thrive or anemia and patients with chronic diseases, those allergic to vitamin B12, and individuals receiving micronutrients supplementation or lacking consent.
Interventions	Number of study centers: 1 Treatment prior to study: No
Aim of study	To compare the efficacy of oral vitamin B12 formulations and intramuscular vitamin B12 in restoring serum B12 levels in children with nutritional vitamin B12 deficiency.
Random sequence generation (selection bias)	Not mentioned in research article

Interventions

All of the trials included in this group compared oral Vit B12 with the parenteral administrations.

Regarding Study, no 1 of included research; All individuals who entered the trial received a single 1000 g intramuscular or intravenous dosage; afterwards they were randomly allocated to receive the following doses parenterally (group A) or orally (group B).

In the parenteral group, children under the age of ten received 03 doses of 1000 g of vitamin B12 administered intramuscularly (IM), whereas children aged ten to eighteen received a total of 05 doses. Afterwards, two further doses of a comparable potency were administered again in the end of the first and second follow-up months.

In group B, daily doses of 1500 g for children under two and one pill for those between two and 18 years old were administered for a total of 12 weeks.

Regarding Study, no 2 Cobalamin 1000-g was given intravenously to the parenteral group once a day for 10 days. After 10 days, both treatments were given once a week for 4 weeks, and subsequently once per month for the rest of their life.

The 1000-g ampule of Vit B12 was combined with 20 milliliter of fruit juice and supplied orally once daily for 10 days to the per oral group. Because cobalamin pills weren't accessible in Turkey at the time of this trial, they weren't used. At trial days 0, 10, and 30 of therapy, the same doctor spoke with and evaluated each patient.

Regarding the Study, no 3, parenteral treatment protocol included one week at 100 mcg per day, followed by one week at 1000 mcg on alternate days, one week at 1000 mcg twice per week, and one week at 1000 mcg. The oral dose comprised a mixture of a multivitamin complex including 50 mg thiamin, 250 mg pyridoxin, and 1000 vitamin B12 as part of their treatment. Patients were given one pill daily for a month, at least an hour before a meal when they were fasting.

Outcomes

Endpoints quoted in the abstract of publications

Study No. 1	Outcome measures written in the abstract: Three months after therapy, changes in blood vitamin B12 levels and total hemoglobin levels were compared.
Study No. 2	Not mentioned in the abstract
Study No. 3	Not mentioned in the abstract

Trials reporting our primary outcomes:
All of the trials included in this review reported the serum levels of Vit B12 and other hematological parameters before and after the administration of treatment doses.

Study No 1 reported that when compared to children who received vitamin B12 orally, those who received parenteral vitamin B12 saw a substantial increase in hemoglobin and blood vitamin B12 levels.

Study No. 2 in this systematic review, therapy with oral vitamin B12 was just as efficient as therapy with IM cobalamin. In addition, oral vitamin B12 had lower cost and was more tolerated compared to intramuscular therapy. To ascertain the efficacy of oral vitamin B12, longer term investigations are required due to the smaller sample size and short duration of this study.

As per study no. 3 values for vitamin B12 after therapy were substantially higher than those before treatment. Vitamin B12 levels rose in the parenteral administration arm from 183.5 ± 47 pg/mL to 482 ± 318.9 pg/mL in the oral and from 175.5 ± 42.5 pg/mL to 838 ± 547 pg/mL in the parenteral treatment arm.

Regarding future directions, they suggested that as a first-line therapy for vitamin B12 insufficiency in children, oral preparations may be deemed safe.

Primary outcome:
Serum Vit B12 values were significantly increased in all three studies but were different for oral and parenteral groups.

The study conducted by Rahul Tandon et al revealed that there was a considerably higher increase in vitamin B12 level in the parenteral group [600 (389,775) vs 399 (313,606) pg/ml. Eighty participants (63.7%) were girls, 55 (68.7%) were between the ages of 10 and 18, and eight (10%) were young children. **So the Vit b12 level increased in the parenteral group more than oral.**

In research performed by Zahit Bolaman et al 10 of the 70 patients who were included in the trial were eliminated because they did not show up for the follow-up visit after the first 10 days of therapy. On day 0 (zero) serum levels of Vit B12 were 72.9 in the oral group with SD (54.8), while 70. 2 in the parenteral group with SD (59.1). After 90 days of treatment a rise in serum levels was noticed, 213.8 in the oral group while 225.5 in the parenteral group. **They concluded that both routes of dosage application were equally effective.**

In Rabia Gönül Sezer et al's prospective research, 142 children (66 girls and 76 boys) were included. Of those, 60 received intramuscular treatment and 82 received per oral vitamin B12 therapy. Vitamin B12 levels rose in the oral intervention group from 183.5 47 pg/mL to 482 318.9 pg/mL and in the injectable medication arm from 175.5 42.5 pg/mL to 838 547 pg/mL. **They concluded that both routes are effective but the parenteral group showed a slight extra rise in serum Vit B12 levels than the other group.**

Discussion

Doctors frequently believe that taking oral supplements would lead to an increase in the well-being and quality of life of vitamin B12 deficient patients. But their protocols are not evidence-based (11). Over time, doctors have grown more confident in oral vitamin B12.

There was a study conducted in Sweden; its objective was to assess the patterns of VitB12 sales in the market. They experienced that oral doses were registered not only for short-term outcomes but also for maintenance purposes (12). Researchers also revealed that oral dose was better for some patients. After many of these cases, researchers started comparing the efficacy of oral and parenteral routes relating to their normalizing serum level effects.

In this systematic review, we included three randomized controlled trials directly related to the study objective. The follow-up duration ranged from 90 days to 12 months. We had 292 patients having vitamin B12 deficiency, participating in this research. After consideration of study participants, management, outcome measures, and follow-up, we established that meta-analysis was not appropriate. A major consideration was the variations of oral treatment regimens and varied eligibility for study inclusion.

All three studies included in this review possess the same dose of 1000mcg, with no issue with higher oral doses. Two studies concluded that with parenteral administration there was more increase in Vit B12 serum levels, while one of them concluded that both routes of administration have equal effects. Furthermore, there were also no substantial differences in Haemoglobin MCV levels and total homocysteine across the treatment groups. The expenses of management delivered in the per oral form of vitamin B12 costs were far less than in the parenteral vitamin B12 therapy group.

The majority of dietary vitamin B12 passes through the body actively through intrinsic factors, with passive diffusion accounting for around 1% of vitamin B12 absorption. As a result, an oral administration of 1000 g daily should be enough to achieve the necessary dietary daily requirement (12). All three studies were not blinded. Nevertheless, the results were determined by both the hematological and neurological outcomes of both therapies, but laboratory tests were most likely blinded.

Due to the small population size and low quality of data, we could not assess whether the lack of intrinsic factors which are crucial for absorption can affect the normalization function of oral and parenteral routes. There was a review conducted by Emmanuel Andrès et al in 2010 to evaluate oral and nasal methods other than traditional parenteral ones focusing on patients with VitB12 malabsorption. There were three prospective randomized trials and five prospective cohort studies that revealed confirmation that oral cobalamin therapy may properly address cobalamin deficiency (13).

All three studies were undertaken in primary care settings, where most persons with vitamin B12 deficiency are managed, making generalization of the results easier. Another element influencing generality is that the three studies included extensive exclusion criteria.

The research included in this review employed both methylcobalamin and cyanocobalamin. It must be mentioned that the bioavailability of cyanocobalamin in aqueous solution formulations is significantly decreased. Additionally, normalizing blood levels of vitamin B12 and its metabolites indicates therapy response is insufficient. There is the possibility of no direct relationship between blood vitamin B12 adjustments and clinical symptom relief (14). Evidence given in the current 3 studies is also insufficient because only one of them has documented the post-treatment neurological responses.

Conclusion

This debate on the efficacy of different routes of administration has a history of almost 50 years. But still, there is a gap of evidence in the literature. The published data suggests that oral and parenteral routes are equally efficient with little controversy.

References used for Current Research

1. Tandon R, Thacker J, Pandya U, Patel M, Tandon K. Parenteral vs Oral Vitamin B12 in Children With Nutritional Macrocytic Anemia: A Randomized Controlled Trial. Indian Pediatrics [Internet]. 2022 Sep 15;59(9):683–7. Available from: https://pubmed.ncbi.nlm.nih.gov/35642923/
2. Sezer RG, Akoğlu HA, Bozaykut A, Özdemir GN. Comparison of the efficacy of parenteral and oral treatment for nutritional vitamin B12 deficiency in children. Hematology. 2018 Mar 24;23(9):653–7.
3. Bolaman Z, Kadikoylu G, Yukselen V, Yavasoglu I, Barutca S, Senturk T. Oral versus intramuscular cobalamin treatment in megaloblastic anemia: A single-center, prospective, randomized, open-label study. Clinical Therapeutics. 2003 Dec;25(12):3124–34.

Additional References - Bibliography

1. Doets EL, in 't Veld PH, Szczecińska A, Dhonukshe-Rutten RAM, Cavelaars AEJM, van 't Veer P, et al. Systematic Review on Daily Vitamin B12 Losses and Bioavailability for Deriving Recommendations on Vitamin B12 Intake with the Factorial Approach. Annals of Nutrition and Metabolism. 2013;62(4):311–22.
2. Andrès E, Kaltenbach G, Noel E, Noblet-Dick M, Perrin AE ., Vogel T, et al. Efficacy of short-term oral cobalamin therapy for the treatment of cobalamin deficiencies related to food-cobalamin malabsorption: A study of 30 patients. Clinical & Laboratory Haematology. 2003 May 20;25(3):161–6.
3. Han S, Wu L, Wang W, Li N, Wu X. Trends in Dietary Nutrients by Demographic Characteristics and BMI among US Adults, 2003–2016. Nutrients. 2019 Nov 1;11(11):2617.
4. Obeid R, Murphy M, Solé-Navais P, Yajnik C. Cobalamin Status from Pregnancy to Early Childhood: Lessons from Global Experience. Advances in Nutrition [Internet]. 2017 Nov 7;8(6):971–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5683008/
5. Sezer RG, Akoğlu HA, Bozaykut A, Özdemir GN. Comparison of the efficacy of parenteral and oral treatment for nutritional vitamin B12 deficiency in children. Hematology. 2018 Mar 24;23(9):653–7.
6. Nilsson M. Medical intelligence in Sweden. Vitamin B12: oral compared with parenteral? Postgraduate Medical Journal. 2005 Mar 1;81(953):191–3.
7. Tandon R, Thacker J, Pandya U, Patel M, Tandon K. Parenteral vs Oral Vitamin B12 in Children With Nutritional Macrocytic Anemia: A Randomized Controlled Trial. Indian Pediatrics. 2022 May 31;59(9):683–7.
8. J VA, Cc B, R CJ, A G, K H, A M, et al. Oral Vitamin B12 Versus Intramuscular Vitamin B12 for Vitamin B12 Deficiency [Internet]. The Cochrane database of systematic reviews. 2005. Available from: https://pubmed.ncbi.nlm.nih.gov/16034940/
9. Wang H, Li L, Qin LL, Song Y, Vidal-Alaball J, Liu TH. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database of Systematic Reviews. 2018 Mar 15;
10. Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. Journal of the Royal Statistical Society: Series A (Statistics in Society) [Internet]. 2009 Jan;172(1):137–59. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1467-985X.2008.00552.x/full
11. Hvas AM ., Juul S, Nexo E, Ellegaard J. Vitamin B-12 treatment has limited effect on health-related quality of life among individuals with elevated plasma methylmalonic acid: a randomized placebo-controlled study. Journal of Internal Medicine. 2003 Feb;253(2):146–52.
12. Kolber MR, Houle SKD. Oral vitamin B12: a cost-effective alternative. Canadian Family Physician [Internet]. 2014 Feb 1 [cited 2020 Jul 27];60(2):111–2. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3922551/
13. Andrès E, Fothergill H, Mecili M. Efficacy of oral cobalamin (vitamin B12) therapy. Expert Opinion on Pharmacotherapy. 2010 Jan 21;11(2):249–56.

AI and FM – a cautionary tale

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Abstract

Education and Medicine are two of the greatest achievements of humankind and this knowledge has been faithfully passed down by generations for millennia. Each generation builds on the knowledge of previous generations.

High technological advances have also brought many advantages to humans but because they tend to be 'owned' by the very few, they have increasingly become commercialised and indeed weaponised.

In a world of identity theft, cybercrime, scams, fraud, war and genocide, humanity needs to be very careful about trusting in the integrity of AI. Particularly, Family Medicine should always be based on the individuality of every patient within their unique circumstances.

The Covid era saw a great change in the delivery of medicine and particularly in remote consultations. Telemedicine has now become entrenched in most countries, despite some limitations, and has added to the growing use of ICT in medicine.

With a computer on most doctors' desks globally, family doctors are able to take advantage of so many online facilities and sources of information. ICT has made the job easier but has also added levels of complexity and the need for added security.

We already have 'software' as the 'AI' supporting many diagnostic choices. This software is a tool however, not a decision maker and the educated physician can access that tool for speed of diagnosis and recommended care. Asking a machine to make that diagnosis however is a totally different matter.

Certainly national health authorities need to provide guidance and oversight of the resources doctors are using to ensure ongoing accuracy and safety. In the bigger picture should we be entrusting the world's most valuable knowledge to competing tech platforms when the cyber world is already riddled with divisions and crime. Should not human health always be in the hands of humans, our well educated, trusted doctors who have insight into the intricacies of each individual patient's life.

Keywords: Artificial intelligence, family medicine

Introduction

While birds and some animals train their young in the art of survival the outstanding feature of humans has always been tool making and the passing down of knowledge through the generations. Today up to a third of our lives can be spent in formal education.

Each generation builds on the knowledge and skills of the past and we have made stunning advances in architecture, design, technology, medical care, art, literature and music.

In hand with these advancements however, we have also been plagued, by wars, genocide, political dictatorships, and crime. These blots on the landscape of human existence are generated by humanity's baser side. Arguably the disease and plagues we have also endured over the millennia have also been spread, if not caused, by humanity's worst habits. Many have been caused by the disrespect and cruelty we show toward the other creatures on earth as well as our fellow humans. To date however, we have avoided global monopoly and coercion. That time has ended.

70% of people of the world now live in cruel, autocratic dictatorships and those who don't, live under threat of the same.

On the other side of the scale, we are under attack by fake news, wars and cybercrime and greed and monopoly. The digital age has lessened that divide and the tentacles of evil and division can now reach into most homes and businesses on the planet. The purveyors of fake news and prejudice already use this web of deception.

AI is general knowledge already within the public domain. This knowledge is in ICT format however and is gleaned from multiple sources online. Not all sources are necessarily accurate or true however and AI is 'literal'. It does not necessarily question the veracity or nuances of such knowledge.

Proper AI has the power to overcome the dilemma of often deliberately false or misleading (marketed or malicious) information and to contribute to and universalise it. The success or failure of AI is tied strictly to the protocols and the integrity of the purveyors (technology companies) and the messages within their offerings. I suggest it will be an endless cycle of excellence and corruption as it has always been with humans. For that reason it is imperative that the use of "AI" is strictly governed, particularly in vital areas such as medicine. The purveyors should never 'own' the Intellectual Property they distribute as it is not theirs. They can own the software and algorithms which they use to deliver it and be judged in that.

AI has become the seeding ground for some of the big techs to flex their muscles and to pretend they are offering great services to humanity. They are not. 99% of AI currently and arguably is just software and algorithms – in some cases inglorious search engines. This is also the opinion of most of the purveyors of technology. We all need to watch very carefully and to constantly evaluate what is being served up to us as ingenuity and ensure it is not a complex trap.

Family medicine is primary healthcare that provides continuing and comprehensive medical and sociological care for the individual and family across all ages, genders, diseases, and parts of the body.

It should treat each patient as an individual in the context of family, locations/geography, socioeconomic condition and affordability of care prescribed.

Equally the rapport between doctor and patient greatly affects compliance with proper use of therapeutics and lifestyle modifications like diet, rest and exercise.

Psychological aspects of patient care also rely specifically on a range of personal issues of each individual patient's life. Often these considerations are also pertinent to individual family structures e.g in cases of domestic violence.

While there are many practical shortcuts that can be provided by AI across the sciences and humanities is it wise to rely on AI for the diagnosis and care provided in family medicine. Rapport between doctor and patient is built on trust developed over years. AI cannot pick up visual or verbal clues.

Doctors are making huge decisions every day based on physical, emotional, practical, financial, and familial aspects of a patient's life. Family medicine encourages the patient to divulge their concerns within an atmosphere of trust.

Who is going to protect the integrity of family medicine in the age of Artificial Intelligence: humans? machines? AI itself?

AI is general knowledge not patient specific knowledge or borrowed knowledge. It is not Applied knowledge. Commercialism and marketing and fake news are rife in the entire business world, particularly the big tech world is becoming a haven for commercial monopolies and increasingly taken over by dictators trying to re-write history to their own story and platform, and reap money from national coffers.

Nearly half of the world's entire wealth is in the hands of millionaires (Credit Suisse Global Wealth Report).

Add to that cybercrime for fraudulent and malicious purposes and sadly what was once the promise of global parity and equity for all humans now actively works against them. Scams, identity theft, revenge content, propaganda, harassment, the child sexual assault trade, human trafficking, targeted bullying etc are now some of the biggest players.

Many of the big techs are focused on money and are difficult to bring into line when it comes to social issues and values and norms and anything that affects their profits.

Shelf life of medical education, Language, dialects and terminology.
As a global medical educator and ICT publisher I find the 'shelf life' of medical education and information is 3 months to 3 years depending on the topic .Technical and medical advances happen all the time and more than often an old practice or recommendation becomes debunked due to a new study finding a better approach.

An obvious example is the recent Global Covid pandemic. It would not have got a mention in AI initially and in the ensuing months when little was known about it; information changed often. Also many details were withheld for political and medical reasons. Even today scientists do not have the full picture.

Currently AI seems to be English centric. Additionally there are different medical terms for the same condition globally e.g. oedema (also spelt edema) vs anasarca. Oedema is still used in some countries to represent all severities of oedema.

Even in the same country terms like FBC and CBC are used for the same tests in different states.

On a highly successful global medical education project I produced for several NGOs we had to have the education suitable for every doctor in the world. This meant we could not assume ethnicity, geography, any level of undergraduate medical or general education, gender, age, culture, religion, or standard medical terminology, availability of affordable tests etc. The learning was in the doing and we worked with 26 countries to get to our final international tertiary program. It was the first ever internationally accredited tertiary course. There were hundreds of thousands of anomalies and cross-meanings and considerations required.

I also found up to 30% missing medical education in later global work – mostly due to poverty (what is best practice when doctors cannot afford expensive diagnostic equipment and patients cannot afford prescribed medicines or tests) but also cultural, religious, geographical and climatological issues.

In one such project I then re-delivered/customised with an NGO my QA&CPD produced for Australian doctors to make it suitable for low income nations' doctors. We had successful national trials in Nepal validating our 'localisation' approach. And it was not just a patient issue. We were also aware of the poverty of doctors who did not have modern diagnostic equipment in their office and the psychological impact of that.

What is AI?
"AI" currently is general knowledge already within the public domain. This knowledge is mostly in ICT format however and is gleaned from multiple sources online. Not all sources are necessarily accurate or true however and AI is 'literal'. It does not necessarily question the veracity of such knowledge.

Most technology experts see AI as another name for software/a software application/an algorithm which is applied to so many useful tools for modern living. "True AI" which should draw logical conclusions on data in the domain is rare.

The "AI functions on the various browsers seem to just elevate their own searches above the usual search functions in a browser. They provide summaries of information from the regular searches below the "AI response". Most of these summaries are quite facile. Fine for the homework assignments but not scientists. They are essentially search engines, an electronic encyclopaedia, a research tool. As such it is more refined than a search engine which does not VALIDATE the data it presents but there are already some glaring problems with it.

It may be useful for completing school assignments but is it a safe substitute for the knowledge and empathy of a family doctor who uses all his/her senses; sight, sound, (insight?) knowledge, and memory.

So who pays?
We used to pay a heavy sum for Encyclopaedias before ICT put most of this data online. The pay principle then became advertising driven revenue based on targeted advertisements on the topics users researched or viewed online.

While most pharmaceutical companies and device manufacturers are reputable they are highly profitable commercial entities and currently have their representatives visit doctor surgeries globally to push their own products. This commercial aspect hopefully will not enter the AI decision making systems. But where there are choices of competing therapeutics there will be attempts to influence prescribing.

How and when is AI updated?
Users should be given a time scale of original information source and the various updates to be able to verify the written material. The world keeps turning ....

Oppression dictatorships and fake news
With cybercrime abounding, all forms or business and health activity need to be carefully guarded. Hospitals around the world have been targeted by cybercrime, and for 2 reasons:
1. The corruption and destruction of systems of other countries by subversive governments
2. Identity theft to allow international crime to access bank accounts and other capital

Measurements show that closed autocracies have increased from 25 to 30 countries globally. Dictatorships are on the rise around the world. Today, 5.4 billion people, 70 per cent, live in dictatorships.

Dictators have 2 weapons – violent repression and fake news/propaganda from taking over the media outlets in 'their' countries. There have already been many such global examples of democracies being attacked by rogue governments.
https://worldpopulationreview.com/country-rankings/dictatorship-countries

In non-dictatorships the big media tech companies have their own commercial agendas and can involve monopolistic activities. There have been attempts to break their monopolies but they are still all pervading.

Malevolence – and the era of Cyber Warfare and Fake News
These electronic advances could have been like Bill Gates Microsoft Word. As a Publisher I blessed him and my main activity as a postgraduate medical educator using ICT/multimedia has not only seen ICT a great time and work saver it also had the potential to bring parity and equity to the world. Sadly that world is bedevilled by cybercrime, identity theft, fraud and exclusion. The 'dark web' has set itself up and befouled the global system to such a degree many globally feel it is not safe to use ICT at all. Children are urged not to go online. My dream of parity and equity of healthcare for the world is now a lonely and unprofitable road. Education is the way of human advancement and we need to be very careful in whom we put our trust.

Who pays?
Currently the tech giants are saying 'they won't charge us for AI' (our own collective knowledge garnered over millennia). I would be very wary of any such statements. Okay, we pay for education and have paid for encyclopaedia sets in our analog past but the re-housing of data does not mean the storage unit owns the data. Indeed my own and other's evaluation of the AI purveyors agree it may speed up the search for data but its offerings do not go far past the 'search engine' fare. And to a degree the element of trust has diminished. I suggest for a flawless and honourable system, all data should come free for all the world. Only in that way came we be sure of its non-malevolence. That data also needs to be highly protected.

This includes free availability of education systems in all countries. Why cannot we have a good dream every once in a while. Once it was a scandal if there were errata in a published document. Now there are deliberate attempts to obfuscate. About a third of the world (me included) misspelled dilemma as dilemna due to an error in a text book. There was a typo from 1842 in the book 'The Mirza' by British diplomat James Justinian Morrie. We can tell that it is a typo because he spells the same word 'dilemma' in six other places within the same book. The misspelling seems to have then gained currency and been transmitted within theological papers for the rest of the century, and half way into the next. During this time the same misspelling also found its way into the German language. The earliest example of this was from 1843, just one year after Morier's typo. It is suggested th reason 'dilemna' came into mainstream English usage and the core curriculum, was its appearance in Twain's Huckleberry Finn in 1884.

Will we just faithfully believe anything we are told online?
With big countries like the US and China in particular spilling out filth that is destroying land, sea and air and ICT being used to track and spy on law abiding citizens who speak up on these issues, to control and repress them, can we ever trust these systems again. These are the real challenges. The system needs to be fixed and flawless before we can put human lives in the hands of potential malfeasants. Corrupt governments have come and gone in most countries ad nauseum.

Am I the only person astonished that humans are blithely totally aware that we are destroying the planet's air, water and land and causing growing ecosystem damage which is already causing floods, fires and mass famines and lack of drinking water and nobody is genuinely fighting this? That we have primitive dictators still playing their games of wars and genocide happening across the world and the global population is not standing united against the psychopaths? Is this a time we should be just listening to what machines tell us is correct? Machines do not have morals, or intellect, or decency or loyalty or sacrifice. It is great that we can use them to save so much time in doing repetitive tasks or searching for elusive data but remember who and what we are.

Rather we are being occupied with baubles and AI and 'likes' and video games. The most serious game of life and death is happening on the planet as I write and it is real and those who dare mention it are called 'catastrophists' by the malevolent and greedy few. These are often the same people bringing us the 'miracles of AI'.

AI – does one size fit all?
In my work on global medical education on the Applied Sciences of Oncology some interesting observations came out of the project developed over many years to meet conditions in all countries.

We had to 'educate without teaching'. We could not assume (any common language, medical terminology, undergraduate general or medical education.) There was no ethnicity, no geography, no climate, no religion or culture that we could refer to. Using AI also needs to look at these issues but currently what has been churned out seems to focus on first world culture. Maybe just those with some money still left in their pockets.

From all the data in the ASO project we noticed a course of antibiotics in a lifetime of a person in a developing nation with an untreated chronic condition could have saved longterm cancer and we found that the mind did indeed play a part in the efficacy of cancer treatment. I think these observations were made with love - a caring concern for WHY these patterns emerged.

This is just one small illustration of no matter how much AI is 'out there to be tapped into' the situation in populations around the world are all different and language/dialects are different even within countries. My philanthropic work has found up to 30% missing medical education globally. Much of this has to do with poverty e.g. what is the education for where a doctor cannot afford modern diagnostic equipment and the patient cannot afford the medicines or tests prescribed. Indeed we had to re-write (localise) my first world produced postgrad medical education (QA&CPD) for doctors in each country we worked in and not only cater to medical issues pragmatically but local customs, religions, endemic issues etc. .

Primary care is linked to these differences and is very much a practical consideration in a wide range of human conditions.

Looking at the even bigger picture …
We already have many people globally self-diagnosing from details online – this may be both a good and bad thing. Some advice is often better than no advice but there are obvious concerns of misdiagnosis and or trauma from advice delivered without any form of counselling of patients.

Good family doctors are also proactive looking out for potential harm on an individual basis and screening for disease in cases of local outbreaks. They are aware that each patient is in a family dynamic, that some patients are altruistic and unselfish and may turn down expensive treatment or prolonged life for the economic considerations for families. In family medicine every patient is an individual and should be treated as such.

AI for evil
Even more disturbingly citizens of dictatorships are being tracked and face recognised by universal surveillance – not for their benefit but for their dictators to keep an eye on them so they can stop subversion.

Human DNA is being collected by rogue states as a means of oppression and limiting of movement of populations 'earmarked' for genocide.

These practices are people's worst nightmares already. They always have been and there have been many books and films on these 'dystopian futures'. The reality we are currently facing as a global people is far worse than the literary mind can project as many so called movements are anti-human (apart from those in their dictatorship clique – and even they have to continually watch their backs).

What is next? – your DNA shows you have no right to live. Where and how can you hide when your biochemistry condemns you to death? Is this histrionics? Just a worse nightmare?, look at the current world where genocide is happening before our eyes.

And it is not just the topic of a Compassion Circuit in John Wyndham's short story where an 'over-caring' AI robot decided a frail woman needed a full body transplant, to be cut off at the head. Compassion is not listed in the real problems facing the relegation of care of humans. (The Seeds of Time/The Compassion Circuit John Wyndham)

Will we 'hand over' to machines? After all humans and computers are much the same; we are run by electricity – all atomic matter is electric; indeed we are not much more than electric circuitry ourselves, with a few photons thrown in and a magnetic field.

These days it is argued (How the Universe Works) by theoretical astrophysicists and quantum physicists– that all atomic matter is consciousness – we in the known universe are all made of the same stuff – and we are also all electricity which should have made 'true AI' really interesting, but again what is churned out just deals with the same old topics out there that we already know about. We are holograms that have made holograms. We are intelligence that has made some clever technology. Sadly it is still mostly primitive technology. We are AI (with a sprinkling of EI) using 'AI'.

I suggest that EI (Emotional Intelligence) is the crux of the matter
EI is our biggest human asset in our brutal and unjust world and lack of EI is our greatest danger.

With the current geopolitical state of the world it is far too dangerous to put any vital information online in ICT or 'AI' format - it will just provide temptation for degenerate actors to attack populations.

While I have never come across another life form, plant or animal, that was evil, there is a huge variety of 'human nature' – some are peaceful, gentle and caring, but some are evil and brutal and cruel, war mongers and mass murderers. Indeed there seems to be no end to the way humans can cause harm. The two greatest forces working against a cohesive society are lust for money and lust for power.

All electronic information sources which can be used by the malfeasant are already being exploited.

Of all life in the known universe, humans are the only ones known to be greedy (take more than they need) or deliberately malicious. Yes, most of us are vacuous creatures and need good advice but I suggest we need to work out who and what we are and our standards along with our limitations before we get to the ridiculous stage of putting all we have learned over the millennia in the hands of a few.

The ego and ethical shallowness of some humans shows no bound along with greed and lust for power. They in effect already 'rule the world'.

We all 'know better' but we don't 'do better' – that will never change.
Ai is already being used politically to create fake news and fake images - as with many aspects of IT, organised crime is making it difficult to trust any communication online and its costs ordinary people $1.026 trillion globally, equating to 1.05% of the global GDP, per year. This amount reflects the impact of scams and identity theft on individuals and economies around the world.

I would have thought that finding a totally safe environment for the world's knowledge to be housed and dispensed from, would be the first and most important aspect to be considered before looking at its distribution.

As the world becomes more corrupt and overtaken by misers and dictators, medicine too will be devalued - music artists and actors are currently losing work to AI. You don't have to pay a machine and you can make it do whatever you want. AI may be the final knife in the back of civilised humanity, NOT because AI it is in itself corrupt but because of human greed and lust for power.

What a great market human health is - we already have gross national players in certain nations harvesting people's organs for sale, convincing vacuous people to change their look with very questionable and health destroying and disfiguring plastic surgery techniques while children in other countries need basic healthcare to survive. And this is being condoned by governments in the most autocratic states and in democracies. The 'victims of plastic surgery' are victims of AI already – wanting to look like images that are already faked.

And take pity on the animals that are being slaughtered worldwide for fakery and profit.

How long before AI consulting rooms online?
You think you are talking to a doctor and getting personal advice but the 'creature' before you does not have a heart and mind, does not have sympathy and empathy, does not 'think out of the box' – literally!

Certainly AI will be the buzz word and the basis of marketing in the next decades and we will see a multitude of re-naming of old products that never thought for themselves in the first place. AI is already becoming boring in its self-labelling and self–aggrandising. What was once a clever algorithm or software will now have a trendy name.

Various technology company leaders also question what is being served up as "AI":

AI according to the technology experts:
Open AI calls Elon Musk's lawsuit 'frivolous' and 'incoherent' in legal filing.

The Tesla CEO's suit says the company abandoned the founding mission of openly sharing its technology to better humanity.

What to make, then, of the explosion of supposed-AI in media, industry, and technology? In some cases, the AI designation might be warranted, even if with some aspiration. Autonomous vehicles, for example, don't quite measure up to R2D2 (or Hal), but they do deploy a combination of sensors, data, and computation to perform the complex work of driving. But in most cases, the systems making claims to artificial intelligence aren't sentient, self-aware, volitional, or even surprising. They're just software. (Hauser, Larry, Alma College, U. S. A.)

Artificial intelligence is cited as a barrier to strengthen an American border wall, but the "barrier" turns out to be little more than sensor networks and automated kiosks with potentially-dubious built-in profiling. ((Hauser, Larry, Alma College, U. S. A.)

Isbell suggests two features necessary before a system deserves the name AI. First, it must learn over time in response to changes in its environment.

For Isbell, "true" AI requires that the computer program or machine exhibit self-governance, surprise, and novelty.

"Whenever someone says 'AI' what they're really talking about is 'a computer program someone wrote.'" bot author Allison Parrish

Stanford computer scientist Jerry Kaplan makes a similar argument: AI is a fable "cobbled together from a grab bag of disparate tools and techniques."

Microsoft's Kate Crawford: 'AI is neither artificial nor intelligent'

Alan Turing asked, "Can a machine think?".

Only rational individuals have standing as moral agents and status as moral patients subject to certain harms, such as being betrayed. Only sentient individuals are subject to certain other harms, such as pain and suffering.

If that is the case then have they thought of the moral issues involved, and in the case of Family Medicine including patient safety and human rights implications of what they 'say'. If used for medical advice do they operate in accordance with the Hippocratic Oath. Can they make medical decisions in palliative care, can they do 'small harm today to lessen longer term harm'. I.e., therapeutic surgery. Have they considered the welfare of that patient in terms if his/her age, family position, religion, social norms, the patient's hopes and dreams or that patient's wish to no longer face every day in pain? Any family doctor will know that these considerations are unique to every single patent. Mostly they come down to individual patient's wishes. Every patient has the right to make their own decisions even if they go against the norm. Palliative Care is the basis of John Wyndham's "AI story" The Compassion Circuit. It was written in 1954. We still have not learned.

Descartes says our intelligence is amply manifest in our speech. Alan Turing suggested that if computers showed human level conversational abilities to a level of other humans we could be assured of their intelligence.

Yes computers can perform extremely complex calculations, but is this intelligent? If it is then a hand calculator is also AI.

MYCIN applies rules culled from interviews with expert human diagnosticians to descriptions of patients' presenting symptoms to diagnose blood-borne bacterial infections. MYCIN displays diagnostic skills approaching the expert human level, albeit strictly limited to this specific domain.

But I suggest MYCIN would be at a loss when it comes to presenting the patient with the diagnosis in relation to the patient's temperament, family situation, economic situation, etc. My company developed the first BMI calculator using ICT as part of an educational package decades ago but I did not call it a GP/FP or doctor. It was and is a tool.

Can AI tell when a human lies, for good or bad reason, not for their own sake, but for the sake of others to save them pain, to save the family from expensive outlay for a medical procedure, to retain their dignify because they put dignity and decency before the value of their own life. That is what makes them intelligent humans - applying reason, not logic. An astute human/doctor may 'know the nature of a man/patient and know family dynamics, an astute family doctor may recognise that dignity can take precedence over the purely practical. We all have a lot to learn.

Human Intelligence (HI) and Emotional Intelligence (EI)

Humans are more than eating and defecating and pill popping and self-hygiene entities – they have memories and tastes and preferences and non-metabolic pain and sad memories and love and hate, heartbreak and fear, and soul and inspiration and duty and loyalty and devotion – those human qualities cannot be quantified and do not necessarily follow any logic.

We need to have faith in the future, stop wars and usury and greed and violence, and save our world – these are all real terms as is the very nature of human intelligence. Leave me with my worries and pains lying with my back on the grass on a sunny day watching fluffy clouds pass by and pondering on the true nature of life and the complexities of the universe.

Of course AI should have been a gift to us all – to help us manage the endless data and knowledge we have discovered and developed over the many millennia we have lived. Putting it all into the hands of the greedy and the malfeasant does not seen a good idea.

The "Hero factor- when an action goes beyond all reason or caution, but a human does it anyway out of kindness and even with a fatal end is NOT good machine logic but would be classified Emotional Intelligence. Perhaps this is the crux of intelligence. A machine needs to qualify its actions and suggestions with Emotional Intelligence before it can lay claim to Intelligence. Without such intelligence it remains as barbarous as the humans who lack the same EI.

References and Bibliography

Credit Suisse Global Wealth Report

Descartes, René. 1637. Discourse on Method. Trans. Robert Stoothoff. In The Philosophical Writings of Descartes, Vol. I, 109-151. New York: Cambridge University Press, 1985
Fodor, Jerry A. 1975. The Language of Thought. New York: Thomas Y. Crowell.

Fodor, J. A. and Z. Pylyshyn. 1988. "Connectionism and Cognitive Architecture: A Critical Analysis."Cognition 28: 3-71.

Gödel, K. 1931. "On Formally Undecidable Propositions of Principa Mathematica and Related Systems." In On Formally Undecidable Propositions, New York: Dover, 1992.

Hauser, Larry, Alma College, U. S. A.

How the Universe Works (Television series). Discovery Channel · Pioneer Productions · Science Channel. 2010

Lovelace, Augusta, Ada. 1842. "Translator's notes to L. F. Menabrea's `Sketch of the analytical engine invented by Charles Babbage, Esq.'." In Bowden (ed.) 1953: 362-408.

Turing, Alan M. 1936-7. "On Computable Numbers with an Application to the Entscheidungsproblem." In The Undecidable, ed. Martin Davis, 116-154. New York: Raven Press, 1965. Originally published inProceedings of the London Mathematical Society, ser. 2, vol. 42 (1936-7): 230-265; corrections Ibid, vol. 43 (1937): 544-546.

Turing, Alan M. 1950. Computing machinery and intelligence. Mind LIX:433-460.

Wyndham John, The Compassion Circuit, The Seeds of Time. 1954

Terminal endpoints of systemic atherosclerotic processes in sickle cell diseases

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Abstract

Background: Sickle cell diseases (SCD) are severe inflammatory processes in the vasculature mainly on capillary endothelium since they are the main distributors of hardened red blood cells into the tissues. On the other hand, aging and male gender alone may be the most significant underlying risk factors of the systemic atherosclerosis since male gender lives about seven years shorter than female gender worldwide.

Methods: All patients with the SCD were included into the study.

Results: The study included 222 males and 212 females with similar mean ages (30.8 versus 30.3 years, p>0.05). Smoking (p<0.001), alcohol (p<0.001), disseminated teeth losses (p<0.001), ileus (p<0.001), cirrhosis (p<0.001), leg ulcers (p<0.001), digital clubbing (p<0.001), coronary heart disease (CHD) (p<0.05), chronic renal disease (CRD) (p<0.05), chronic obstructive pulmonary disease (COPD) (p<0.001), and stroke (p<0.05) were all higher in male gender. Interestingly, mean ages of stroke (33.5 years), COPD (33.6 years), clubbing (35.4 years), CHD (35.7 years), cirrhosis (37.0 years), and CRD (39.4 years) were the highest among the other atherosclerotic consequences.

Conclusion: Smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, COPD, and stroke-like atherosclerotic risk factors or terminal endpoints were all higher in male gender with the SCD. Since aging alone may be the major associated factor of the systemic atherosclerosis, stroke, COPD, digital clubbing, CHD, cirrhosis, and CRD may be the terminal endpoints of systemic atherosclerotic processes in human body since the mean ages of the above pathologies were the highest among the other atherosclerotic consequences in the SCD.

Key words: Sickle cell diseases, atherosclerosis, stroke, chronic obstructive pulmonary disease, digital clubbing, coronary heart disease, cirrhosis, chronic renal disease

Introduction

Chronic endothelial damage may be the major cause of aging by causing end-organ insufficiencies in human body (1). Much higher blood pressures (BP) of the afferent vasculature may be the main accelerating factor by causing recurrent injuries on vascular endothelium. Probably, all afferent vasculature including capillaries are mainly involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Because of the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood supply to the terminal organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, sedentary lifestyle, excess weight, animal-rich diet, smoking, alcohol, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences such as obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, aging, and death (2, 3). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and aging, endothelial changes can not be reversed completely due to their fibrotic natures. The accelerating factors and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the literature, extensively (4-6). On the other hand, sickle cell diseases (SCD) are chronic inflammatory process on vascular endothelium, initiated at birth and terminated with accelerated atherosclerosis induced end-organ failures in early years of life (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Probably loss of elasticity instead of shape is the main problem since sickling is rare in peripheric blood samples of the patients with associated thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammations, infections, and emotional stress in the body. The hardened RBC 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, the SCD may keep vascular endothelium particularly at the capillaries which are the main distributors of the hardened RBC into the tissues (10, 11). The hardened cells induced chronic endothelial damage builds up an advanced atherosclerosis in early years of life. Vascular narrowing and occlusions induced tissue ischemia and infarctions are the final consequences of the SCD, so the mean life expectancy is decreased by 25 to 30 years in them (8).

Material and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD were studied. The SCD were diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, painful crises per year, transfused units of RBC in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the Same Internist, and patients with disseminated teeth losses (<20 teeth present) were detected. Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (12). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since the SCD with associated thalassemia minors show a milder clinic than the sickle cell anemia (SCA) alone (13). Systolic BP of the pulmonary artery of ≥40 mmHg are accepted as PHT (14). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of <70% (15). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (16). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. CRD is diagnosed with a persistent serum creatinine level of ≥1.3 mg/dL in males and ≥1.2 mg/dL in females. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is >1.0, and with the presence of Schamroth's sign (17, 18). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in

with the echocardiographic findings, too. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, mean age, associated thalassemia minors, smoking, alcohol, painful crises per year, transfused units of RBC in their lives, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, stroke, PHT, autosplenectomy, DVT and/or varices and/or telangiectasias, rheumatic heart disease, avascular necrosis of bones, sickle cell retinopathy, epilepsy, ACS, mortality, and mean age of mortality were detected in both genders, and 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 434 patients with the SCD (222 males and 212 females). Mean ages of the patients were similar in males and females (30.8 versus 30.3 years, $p>0.05$, respectively). Prevalences of associated thalassemia minors were similar in both genders, too (72.5% versus 67.9%, $p>0.05$, respectively). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were higher in males, significantly ($p<0.001$ for both) (Table 1). Similarly, transfused units of RBC in their lives (48.1 versus 28.5, $p=0.000$), disseminated teeth losses (5.4% versus 1.4%, $p<0.001$), ileus (7.2% versus 1.4%, $p<0.001$), cirrhosis (8.1% versus 1.8%, $p<0.001$), leg ulcers (19.8% versus 7.0%, $p<0.001$), digital clubbing (14.8% versus 6.6%, $p<0.001$), CHD (18.0% versus 13.2%, $p<0.05$), CRD (9.9% versus 6.1%, $p<0.05$), COPD (25.2% versus 7.0%, $p<0.001$), and stroke (12.1% versus 7.5%, $p<0.05$) were all higher in males, significantly. On the other hand, prevalences of ACS (2.7% versus 3.7%, $p>0.05$), PHT (12.6% versus 11.7, $p>0.05$), and DVT and/or varices and/or telangiectasias were similar in both genders (9.0% versus 6.6%, $p>0.05$), significantly (Table 2). Interestingly, mean ages of the stroke (33.5 years), COPD (33.6 years), digital clubbing (35.4 years), CHD (35.7 years), cirrhosis (37.0 years), and CRD (39.4 years) were the highest among the other atherosclerotic consequences in the SCD (Table 3).

Table 1: Characteristic features of the study cases

Variables	Male patients with SCD*	p-value	Female patients with SCD
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated thalassemia minors	72.5% (161)	Ns	67.9% (144)
Smoking	***23.8% (53)***	***<0.001***	***6.1% (13)***
Alcoholism	***4.9% (11)***	***<0.001***	***0.4% (1)***

*Sickle cell diseases †Nonsignificant (p>0.05)

Table 2: Associated pathologies of the study cases

Variables	Male patients with SCD*	p-value	Female patients with SCD
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBC‡	***48.1 ± 61.8 (0-434)***	***0.000***	***28.5 ± 35.8 (0-206)***
Disseminated teeth losses (<20 teeth present)	***5.4% (12)***	***<0.001***	***1.4% (3)***
COPD§	***25.2% (56)***	***<0.001***	***7.0% (15)***
Ileus	***7.2% (16)***	***<0.001***	***1.4% (3)***
Cirrhosis	***8.1% (18)***	***<0.001***	***1.8% (4)***
Leg ulcers	***19.8% (44)***	***<0.001***	***7.0% (15)***
Digital clubbing	***14.8% (33)***	***<0.001***	***6.6% (14)***
CHD¶	***18.0% (40)***	***<0.05***	***13.2% (28)***
CRD*	***9.9% (22)***	***<0.05***	***6.1% (13)***
Stroke	***12.1% (27)***	***<0.05***	***7.5% (16)***
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
ACS*****	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ± 8.4 (19-50)	Ns	33.3 ± 9.2 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary disease ¶Coronary heart disease **Chronic renal disease ***Pulmonary hypertension ****Deep venous thrombosis *****Acute chest syndrome

Table 3: Mean ages of the consequences of the sickle cell diseases

Variables	Mean age (year)
Ileus	29.8 ± 9.8 (18-53)
Hepatomegaly	30.2 ± 9.5 (5-59)
ACS*	30.3 ± 10.0 (5-59)
Sickle cell retinopathy	31.5 ± 10.8 (21-46)
Rheumatic heart disease	31.9 ± 8.4 (20-49)
Autosplenectomy	32.5 ± 9.5 (15-59)
Disseminated teeth losses (<20 teeth present)	32.6 ± 12.7 (11-58)
Avascular necrosis of bones	32.8 ± 9.8 (13-58)
Epilepsy	33.2 ± 11.6 (18-54)
Priapism	33.4 ± 7.9 (18-51)
Left lobe hypertrophy of the liver	33.4 ± 10.7 (19-56)
Stroke	***33.5 ± 11.9 (9-58)***
COPD†	***33.6 ± 9.2 (13-58)***
PHT‡	34.0 ± 10.0 (18-56)
Leg ulcers	35.3 ± 8.8 (17-58)
Digital clubbing	***35.4 ± 10.7 (18-56)***
CHD§	***35.7 ± 10.8 (17-59)***
DVT¶ and/or varices and/or telangiectasias	37.0 ± 8.4 (17-50)
Cirrhosis	***37.0 ± 11.5 (19-56)***
CRD*	***39.4 ± 9.7 (19-59)***

*Acute chest syndrome †Chronic obstructive pulmonary disease ‡Pulmonary hypertension §Coronary heart disease ¶Deep venous thrombosis **Chronic renal disease

Discussion

ACS is a significant cause of mortality in the SCD (19). It occurs most often as a single episode, and a past history is associated with a high mortality rate (19). Similarly, all of 14 cases with the ACS had just a single episode, and two of them were fatal in spite of the rigorous RBC and ventilation supports and antibiotic therapy in the present study. The remaining 12 patients are still alive without a recurrence at the end of the ten-year follow up period. ACS is the most common between the ages of 2 to 4 years, and its incidence decreases with aging (20). As a difference from atherosclerotic consequences, the incidence of ACS did not show an increase with aging in the present study, too, and the mean ages of the ACS and SCD were similar (30.3 and 30.5 years, $p>0.05$, respectively). 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 system. Probably, ACS shows an inborn severity of the SCD, and the incidence of ACS is higher in severe cases such as cases with the SCA or higher white blood cells (WBC) counts (19, 20). According to our experiences, the increased metabolic rate during infections accelerates sickling, thrombocytosis, leukocytosis, and capillary endothelial damage, and terminates with end-organ insufficiencies. Although ACS may be thought as a collapse of the lungs during such infections, all capillary systems of the body may probably be involved in the process, and an exaggerated and diffuse immune response syndrome against some infectious pathogens and abnormal RBC may be the cause of diffuse capillary endothelial damage, inflammation, and edema all over the body, and may even terminate with a sudden stroke or myocardial infarction. A preliminary result from the Multi-Institutional Study of Hydroxyurea in the SCD 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 WBC and platelets (PLT) (21). Similarly, we strongly recommend hydroxyurea therapy for all patients with the SCD that may also be the cause of the low incidence of ACS among our follow up cases (2.7% in males and 3.7% in females). Although the ACS did not show an infectious etiology in 66% of cases (19, 20), and 12 of 27 cases with ACS had evidence of fat embolism in the other study (22), and some authors indicated that antibiotics do not shorten the clinical course (23), some viral causes as in the coronavirus disease (COVID-19) may actually take role here, and the main cause of the exaggerated and diffuse immune response syndrome may be such viruses, and the anti-inflammatory and immunomodulatory drugs including dexamethasone may be important just after the RBC support in the treatment of ACS. On the other hand, RBC support must be given early in the course of ACS since it has also prophylactic benefit. RBC support has the obvious benefits of decreasing sickle cell concentration directly, and suppressing bone marrow for the production of abnormal RBC and excessive WBC and PLT. So they prevent further sickling and the exaggerated immune response induced endothelial damage, not in the lungs alone instead all over the body. According to our experiences, simple and repeated transfusions are superior to RBC exchange (24, 25). First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or more provides time to doctors to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBC suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their surroundings, since RBC transfusions probably have the strongest analgesic effects during the severe painful crises. Actually, the decreased severity of pain by transfusions may also indicate the decreased inflammation all over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications such as infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may 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.

PHT is a condition of increased BP 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. An increase in pulmonary artery systolic pressure, estimated noninvasively by the echocardiography, helps to identify patients with PHT (26). The cause is often unknown. The underlying mechanism typically involves inflammation, fibrosis, and subsequent remodelling of the arteries. PHT affects about 1% of the world population, and its prevalence may reach 10% above the age of 65 years (27). Onset is typically seen between 20 and 60 years of age (28). The most common causes are left heart diseases and chronic inflammatory pathologies of the lung such as CHD and COPD (28, 29). The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy (30). 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 (30). In fact, all layers of the vessel wall appear to be involved with prominent intimal changes (30). 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 (30). According to World Health Organization, 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 (28). On the other hand, PHT is also a common consequence of the SCD (31), and its prevalence was detected between 20% and 40% in the SCD (32). Whereas we detected the

ratio as 12.2% in the present study. Although the higher prevalences of smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CRD, COPD, and stroke-like atherosclerotic risk factors or endpoints in males, and the male gender alone is a risk factor for the systemic atherosclerosis, the similar prevalences of PHT and ACS in both genders also support their nonatherosclerotic nature in the SCD in the present study. As a risk factor for pulmonary thromboembolic events, frequencies of DVT and/or varices and/or telangiectasias were also similar in males and females (9.0% versus 6.6%, p>0.05, respectively), parallel to ACS and PHT in the present study. Similarly, CHD is the other most common cause of PHT in the society (33), and although the higher prevalence of CHD in males in the present study (18.0% versus 13.2%, p<0.05), PHT was not higher in them, again. In another definition, PHT may have a chronic, whereas ACS may have an acute inflammatory background in the SCD (34, 35) since the mean age of ACS is much lower (30.3 and 34.0 years, p<0.05), and its mortality is much higher than the PHT (19, 20, 28). As a difference from the atherosclerotic risk factors and endpoints, COVID-19-like viral infections-induced exaggerated and disseminated immune response syndromes at the capillary level may actually be important both for the PHT and ACS.

COPD is the third leading cause of death all over the world (36, 37). Male gender alone, aging, smoking, and excess weight may be the major risk factors. As also observed in the present study, regular alcohol consumption may also be important in the pulmonary and systemic inflammatory process. For instance, COPD was one of the most common diagnoses in alcohol dependence (38). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (39). Probably an accelerated atherosclerotic process is the main structural background of functional changes, characteristics of the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced atherosclerosis, fibrosis, and pulmonary losses. COPD may actually 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 (40, 41). For example, there may be close relationships between COPD, CHD, PAD, and stroke (42). Furthermore, two-third of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (43). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (43). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (44). So COPD may have an atherosclerotic background, and low-dose aspirin plus low-dose warfarin may be life-saving treatment regimens in moderate and severe COPD cases (45). Similarly, COPD may be the pulmonary consequence of the systemic atherosclerotic process caused by the hardened RBC in the SCD (36).

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 (46). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (47). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, or hepatic diseases or smoking which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs those affect their functions in a short period of time. On the other hand, digital clubbing is also common in patients with the SCD, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated capillary damage, inflammation, edema, and fibrosis in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% versus 6.6%, p<0.001) may also show some additional role of male gender on the systemic atherosclerosis.

Leg ulcers are seen in 10% to 20% of the SCD (48), and the ratio was 13.5%, here. Its prevalence increases with aging, male gender, and SCA (49). Similarly, its ratio was higher in males (19.8% versus 7.0%, p<0.001), and mean age of the leg ulcer cases was higher than the others (35.3 versus 29.8 years, p<0.000) in the present study. The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (48). As an evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (48). The hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the major cause in the SCD (49). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC induced venous insufficiencies may also accelerate the 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, probably pooling of blood is the 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. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCD (50). It is an orally-administered, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (11). Its main action may be the suppression of hyperproliferative WBC and PLT in the SCD (51). Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the immune system. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts

may decrease severity of pain and tissue damage (52). According to our experiences, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be due to increased WBC and PLT counts induced exaggerated capillary inflammation and edema instead of terminal fibrosis in early cases.

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (6). Although improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged lifespan and increased prevalence of excess weight all over the world. For instance, 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 (53). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerotic process (53). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases (54). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (55). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCD (9, 56). Probably smoking also takes role in the endothelial inflammatory process of the liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (57). 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 prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious or inflammatory processes may also terminate with an accelerated atherosclerosis in whole body (58). 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 (58, 59). As a result, cirrhosis may also be found among the systemic atherosclerotic consequences of the SCD.

The increased frequency of CRD may also be explained by prolonged lifespan and increased prevalence of excess weight all over the world (60, 61). Aging, physical inactivity, excess weight, smoking, alcohol, and inflammatory or infectious processes may be the major 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 and tissue hypoxia and infarcts. Excess weight induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause tissue inflammation and immune cell activation (62). For example, age (p= 0.04), high-sensitivity C-reactive protein (p= 0.01), mean arterial BP (p= 0.003), and DM (p= 0.02) had significant correlations with the CIMT (61). 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 BP with excess weight (63). Excess weight also causes renal vasodilation and glomerular hyperfiltration those initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (63). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (64). 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 more easily (63). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (65). The inflammatory and atherosclerotic effects of smoking are much more prominent in the respiratory endothelium due to the highest concentrations of its metabolites there. Although some authors reported that alcohol was not related with the CRD (65), various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the renal vascular endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis on the renal endothelium (58). Although CRD is mainly be an advanced atherosclerotic process of the renal vasculature, there are close relationships with the other consequences of the metabolic syndrome (66). For example, the most common causes of death were the cardiovascular diseases in the CRD again (67). In another definition, CRD may also be one of the several atherosclerotic consequences of the metabolic syndrome and SCD (68).

Stroke is an important cause of death, and an acute thromboembolic event on the atherosclerotic background is the most common cause. Male gender, aging, smoking, alcohol, and excess weight and its terminal consequences may be the major triggering causes. Stroke is also a common complication of the SCD (69, 70). Similar to the leg ulcers, stroke is particularly higher in cases with the SCA and higher WBC counts (71). Sickling induced endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic endothelial inflammation, edema, and fibrosis (72). Probably, stroke is the terminal event in the SCD, and it may not have a macrovascular origin, instead disseminated capillary inflammation, edema, and fibrosis may be much more important. Infections and other stresses may precipitate, since increased metabolic rate during such events may accelerate sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of stroke cases develops secondary to the increased WBC and PLT induced exaggerated inflammation, edema, and fibrosis at the capillary level (21).

The venous endothelium is also involved in the SCD (73). For instance, varices usually occur in the lower extremities as the abnormally dilated veins with tortuous courses. Normally, leg muscles pump veins against the gravity, and the veins have pairs of leaflets of valves to prevent backward flow of blood. When the leaflets are damaged, varices and/or telangiectasias develop. DVT may also cause varicose veins. 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 upright position. Although the younger mean ages of the patients (30.8 and 30.3 years in males and females, respectively), and significantly lower body mass index of the SCD patients in the literature (10), DVT and/or varices and/or telangiectasias of the lower limbs were higher in the present study (9.0% versus 6.6% in males and females, p>0.05, respectively), indicating an additional venous involvement of the SCD. 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 (74). It is an emergency since damage to the blood vessels may terminate with a long-lasting fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, and non-erectile penis (74). It is seen with hematological and neurological disorders including SCD, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (75, 76). Ischemic (veno-occlusive), stuttering (recurrent ischemic), and nonischemic priapisms (arterial) are the three types of priapism (77). 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 SCD, and they are very painful (74, 77). The other 5% are nonischemic (arterial) type usually caused by a blunt perineal trauma in which there is a short circuit of the vascular system (74). Treatment of arterial type is not as urgent as the veno-occlusive type due to the absence of risk of ischemia (74). RBC support is the treatment of choice in acute phase (78, 79). Whereas in chronic phase, hydroxyurea should be the treatment of choice. According to our experiences, hydroxyurea is an effective drug 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 capillary walls if initiated later in life.

As a conclusion, smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, COPD, and stroke-like atherosclerotic risk factors or terminal endpoints were all higher in male gender with the SCD. Since aging alone may be the major associated factor of the systemic atherosclerosis, stroke, COPD, digital clubbing, CHD, cirrhosis, and CRD may be the terminal endpoints of systemic atherosclerotic processes in human body since the mean ages of the above pathologies were the highest among the other atherosclerotic consequences in the SCD.

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. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365(9468): 1415-28.
3. Franklin SS, Barboza MG, Pio JR, Wong ND. Blood pressure categories, hypertensive subtypes, and the metabolic syndrome. J Hypertens 2006; 24(10): 2009-16.
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. 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.
13. 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.
14. 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.
15. 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.
16. Davies SC, Luce PJ, Win AA, Riordan JF, Brozovic M. Acute chest syndrome in sickle-cell disease. Lancet 1984; 1(8367): 36-8.
17. 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.

18. Schamroth L. Personal experience. S Afr Med J 1976; 50(9): 297-300.
19. Poncz M, Kane E, Gill FM. Acute chest syndrome in sickle cell disease: etiology and clinical correlates. J Pediatr 1985; 107(6): 861-6.
20. 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.
21. 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.
22. 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.
23. 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.
24. 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.
25. Helvaci MR, Ayyildiz O, Gundogdu M. Red blood cell transfusions and survival of sickle cell patients. HealthMED 2013; 7(11): 2907-12.
26. Gordeuk VR, Castro OL, Machado RF. Pathophysiology and treatment of pulmonary hypertension in sickle cell disease. Blood 2016; 127(7): 820-8.
27. 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.
28. 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.
29. Naeije R, Barbera JA. Pulmonary hypertension associated with COPD. Crit Care 2001; 5(6): 286-9.
30. 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.
31. 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.
32. Castro O. Systemic fat embolism and pulmonary hypertension in sickle cell disease. Hematol Oncol Clin North Am 1996; 10(6): 1289-303.
33. 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.
34. Oudiz RJ. Classification of pulmonary hypertension. Cardiol Clin 2016; 34(3): 359-61.
35. 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.
36. Helvaci MR, Erden ES, Aydin LY. Atherosclerotic background of chronic obstructive pulmonary disease in sickle cell patients. HealthMED 2013; 7(2): 484-8.
37. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: definition, assessment, and prevention. Lancet 2015; 385(9979): 1778-88.
38. 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.
39. 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.
40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. Helvaci MR, Pappel V, Piral K, Camlibel M, Sencan H, Davran R, Yaprak M, Abyad A, Pocock L. Low-dose aspirin plus low-dose warfarin may be life-saving treatment regimens in cases with severe chronic obstructive pulmonary disease. Biomed J Sci and Tech Res 2023; 53(2).
46. Myers KA, Farquhar DR. The rational clinical examination. Does this patient have clubbing? JAMA 2001; 286(3): 341-7.
47. Toovey OT, Eisenhauer HJ. A new hypothesis on the mechanism of digital clubbing secondary to pulmonary pathologies. Med Hypotheses 2010; 75(6): 511-3.
48. Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. Adv Skin Wound Care 2004: 17(8); 410-6.
49. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg ulcers in sickle cell disease. Am J Hematol 2010; 85(10): 831-3.

50. Yawn BP, 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.
51. 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.
52. Charache S. Mechanism of action of hydroxyurea in the management of sickle cell anemia in adults. Semin Hematol 1997; 34(3): 15-21.
53. 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.
54. 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.
55. Mawatari S, Uto H, Tsubouchi H. Chronic liver disease and arteriosclerosis. Nihon Rinsho 2011; 69(1): 153-7.
56. Bugianesi E, Moscatiello S, Ciaravella MF, Marchesini G. Insulin resistance in nonalcoholic fatty liver disease. Curr Pharm Des 2010; 16(17): 1941-51.
57. 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.
58. 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.
59. 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.
60. 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.
61. 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.
62. 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.
63. 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.
64. 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.
65. 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.
66. Bonora E, Targher G. Increased risk of cardiovascular disease and chronic kidney disease in NAFLD. Nat Rev Gastroenterol Hepatol 2012; 9(7): 372-81.
67. 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.
68. Helvaci MR, Aydin Y, Aydin LY. Atherosclerotic background of chronic kidney disease in sickle cell patients. HealthMED 2013; 7(9): 2532-7.
69. 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.
70. 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.
71. 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.
72. Kossorotoff M, Grevent D, de Montalembert M. Cerebral vasculopathy in pediatric sickle-cell anemia. Arch Pediatr 2014; 21(4): 404-14.
73. 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.
74. Kaminsky A, Sperling H. Diagnosis and management of priapism. Urologe A 2015; 54(5): 654-61.
75. Anele UA, Le BV, Resar LM, Burnett AL. How I treat priapism. Blood 2015; 125(23): 3551-8.
76. Bartolucci P, Lionnet F. Chronic complications of sickle cell disease. Rev Prat 2014; 64(8): 1120-6.
77. Broderick GA. Priapism and sickle-cell anemia: diagnosis and nonsurgical therapy. J Sex Med 2012; 9(1): 88-103.
78. 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.
79. Helvaci MR, Cayir S, Halici H, Sevinc A, Camci C, Sencan H, Davran R, Abyad A, Pocock L. Acute chest syndrome and coronavirus disease may actually be genetically determined exaggerated immune response syndromes particularly in pulmonary capillaries. World Family Med 2024; 22(3): 6-16.

Locked in Sleep, a personal experience

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Abstract

I have had for some years I can't count, a daily terrible night experience, and so disturbing that I feared the night when it fell and released its curtain down. I knew that on sleeping it would visit me and would horrify me, causing extreme distress. It's like witnessing death; I can't talk, I can't shout for help or scream or cry out. I can't move, I can't open my eyes, despite struggling hard. I just feel impending doom on my chest squeezing me very hard, where I can't breathe in fully, along with hearing buzzing and hissing sounds loudly for a few seconds, maybe minutes and then it releases as I am brought back to life, to reality, reborn as a spell lets go and passes away after a great struggle.

I never knew what it was until I heard about sleep paralysis and narcolepsy. So, I wanted to dig deep to find out why and what triggers this scary nocturnal phenomenon.

Keywords: sleep paralysis, myths, dream, muscle atonia, REM sleep, sleep disorder, narcolepsy.

Introduction and aetiology

Sleep paralysis (Parasomnia) happens when you cannot move your muscles as you are waking up or falling asleep and are not able to act out dreams. This is because you are in sleep mode but your brain is active, so the sleeper is awake or half awake and is aware of what is happening but can't move. It's not clear why sleep paralysis occurs but it has been linked with insomnia (2), sleeping supine, substance abuse, shifted nights, and the body not moving smoothly between different sleep phases. It can also be genetic and run in families.

Sleep paralysis is a period of paralysis at either sleep onset or upon awakening and is often accompanied by terrifying hallucinations (3).

A typical night's sleep has phases of 4-5 sleep cycles, with progression from non-rapid eye movement which takes 75% of our sleep phase, until the last phase of rapid eye movement where it shifts and the eye moves quickly and dreams happen along with complete relaxation of the body and the muscles turned off. If you become aware of REM, then you can't talk or breathe and feel paralysed. The REM accounts for 20-25% of every 7-8 hours spent in bed, and a complete sleep cycle takes about 90-110 minutes to finish.

During rapid eye movement (REM) sleep, your body is relaxed and your muscles don't move. Sleep paralysis occurs when the sleep cycle is shifting between stages. When you wake up suddenly from REM, your brain is awake, but your body is still in REM mode and can't move, causing you to feel like you're paralysed.

During these episodes, individuals remain aware of their surroundings and can open their eyes, despite the momentary inability to speak or move their muscles. Extreme fear reactions and hypnagogic and hypnopompic hallucinations can occur (i.e., seeing, hearing, and feeling things that are not there)(8). Sleep difficulties can serve as predisposing factors that may make episodes more likely to occur.

Research denotes likely influencing factors such as the intensification of anxiety symptoms, a tendency to apprehension, the presence of post-traumatic stress disorder (PTSD) symptoms, and behavioural factors such as the consumption of psychoactive substances (caffeine, alcohol, nicotine), sleep deprivation, along with poor sleep hygiene (2).

In countries like Libya, Egypt, and some Arab countries, they think it's a sort of evil occupying your body and is called 'Gotama', "jinn attack", as a result of aliens, spirits, or ghost visits during sleep. Similarly, China believes it is ghost oppression.

Figure 1https://vrglovevs.life/product_details/4218034.html access on 28/03/2024

A study in Denmark supported and ascribed causes such as brain malfunctioning and reduced blood flow in the brain to their sleep paralysis episodes rather than supernatural creatures (1).

Analysis and Conclusion

Often this experience is associated with hearing loud buzzing in the ears, sensations of flying, along with difficulties in breathing. Some researchers thought it was connected with some sort of 'alien abduction'.

There is, however, no cure for sleep paralysis, but advocacy about changing sleep positions, adjusting sleep environment and patterns, as well as the use of various relaxation techniques can be helpful to prevent sleep paralysis episodes. Also, attempting to move extremities and smaller body parts (e.g., fingers and toes) as well as trying to "calm down" at the moment were reported to be the most effective disruption techniques. The treatment consists of managing the risk factors that trigger the condition. In many cases, sleep paralysis is a one-off occurrence and the person does not have a recurrence. Most of us may expect to experience sleep paralysis at least once in our lives.

Sleep paralysis is a temporary inability to move or speak when you're waking up or falling asleep. It's not harmful and should pass quickly, but can be frightening. It can affect anyone but is most common in young adults. I recall I was terrified to go to sleep in bed as I knew what I was expecting.

Most descriptions of sleep paralysis demons have two things in common: 'being unable to move or speak', as well as 'the sense of being held down by a malevolent, often supernatural, intruder'. Many people also describe a feeling of their chest being crushed. I recall how my chest was squeezed so hard to the level I couldn't shout or cry out. I was just trying to get a release of that power compressing me.

It's entirely safe to wake someone up from sleep paralysis. In fact, they will probably be hugely grateful. If you suspect your bed partner is experiencing sleep paralysis, you could try talking to them, tapping their shoulder, or gently shaking them.

Sleep paralysis can occur in otherwise normal sleepers, and is surprisingly common in its occurrence and universality. It has also been linked to certain conditions such as increased stress, excessive alcohol consumption, sleep deprivation, and narcolepsy which is a sleep disorder in which the brain fails its ability to regulate sleep.

After an episode of sleep paralysis, you may feel absolutely exhausted. The experience may be emotionally overwhelming, and draining and some patients wake up gasping or crying. Other symptoms are sometimes reported, such as a rapid heart rate.

During an episode of sleep paralysis, you might have the sensation of a harmful presence in your bedroom, or pressing down on you — but you can't move or scream.

Sleep paralysis refers to the phenomenon in which resumption of consciousness occurs while muscle atonia of REM (rapid eye movement) sleep is maintained, leading to intense fear and apprehension in the patient as the patient lies awake without the ability to use any part of their body. It is often complemented by visual hallucinations of the intruder and Incubus array. The former involves the observation of a dangerous person or existence in the room, while the latter is categorised by a hallucination with a feeling of pressure on the thorax, and is supplemented by feelings of extreme anxiety, and paralysis, along with feelings of suffocation.

The usual phase of the sleep cycle in which it manifests is the REM sleep phase. During non-REM sleep, there is an increase in parasympathetic tone and a decrease in sympathetic tone, while during phasic REM sleep, there are surges in sympathetic tone. It prevents movement of body parts in response to the dreams and muscles of the body become paralyzed temporarily. If the patient achieves wakefulness in this state, it creates the dissociation between perception and motor control that is characteristic of sleep paralysis (5).

Another condition is called narcolepsy, which is a disorder of rapid onset rapid eye movement (REM) sleep characterized mainly by excessive daytime sleepiness (EDS), frequent uncontrollable sleep episodes as well as sleep fragmentation and can be associated with cataplexy, sleep paralysis, and hypnagogic hallucinations (4). It is a chronic, long-term neurological disorder characterized by a decreased ability to regulate sleep-wake cycles.

Some clinical symptoms enter into differential diagnosis with other neurological diseases.

The majority of people with narcolepsy experience cataplexy, which is a loss of muscle tone. Many people experience neurological complications such as sleep cycle disruption, hallucinations, or sleep paralysis. Because of the associated neurological conditions, the exact pathophysiology of narcolepsy is unknown (6).

There is another phenomenon, called Isolated sleep paralysis which is a benign nonetheless fear-provoking condition characterised by a momentary failure to move at sleep onset or upon awakening.

To conclude, nightmare disorder can cause insomnia due to the distress of falling asleep through dread of nightmare occurrence. After all, sleep paralysis signifies a dissociated state, with the persistence of REM atonia into wakefulness. It's postulated that deviations in circadian rhythm genes could be the culprits. Inclining problems include sleep deprivation, irregular sleep-wake schedules, medications such as sertraline(9), and jetlag(7). The most effective therapy consists of avoiding those factors(7).

References

1. Rauf B, Sharpless BA, Denis D, Perach R, Madrid-Valero JJ, French CC, Gregory AM. Isolated sleep paralysis: Clinical features, perception of aetiology, prevention and disruption strategies in a large international sample. Sleep Med. 2023 Apr; 104:105-112. doi: 10.1016/j.sleep.2023.02.023. Epub 2023 Mar 2. PMID: 36934464.
2. Wróbel-Knybel P, Flis M, Rog J, Jalal B, Karakuła-Juchnowicz H. Risk factors of sleep paralysis in a population of Polish students. BMC Psychiatry. 2022 Jun 7;22(1):383. doi: 10.1186/s12888-022-04003-0. PMID: 35672736; PMCID: PMC9171979.
3. Cui N, van Looij MA, Kasius KM. Successful treatment of sleep paralysis with the Sleep Position Trainer: a case report. J Clin Sleep Med. 2022 Sep 1;18(9):2317-2319. doi: 10.5664/jcsm.9996. PMID: 35473768; PMCID: PMC9435325.
4. Slowik JM, Collen JF, Yow AG. Narcolepsy. 2022 Jun 21. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 29083681.
5. Farooq M, Anjum F. Sleep Paralysis. 2023 Apr 27. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 32965993.
6. Chavda V, Chaurasia B, Umana GE, Tomasi SO, Lu B, Montemurro N. Narcolepsy-A Neuropathological Obscure Sleep Disorder: A Narrative Review of Current Literature. Brain Sci. 2022 Oct 30;12(11):1473. doi: 10.3390/brainsci12111473. PMID: 36358399; PMCID: PMC9688775.
7. Stefani A, Högl B. Nightmare Disorder and Isolated Sleep Paralysis. Neurotherapeutics. 2021 Jan;18(1):100-106. doi: 10.1007/s13311-020-00966-8. Epub 2020 Nov 23. PMID: 33230689; PMCID: PMC8116464.
8. Sleep Paralysis. Edinb Med J. 1942 Mar;49(3):204. PMID: 29647837; PMCID: PMC5305875.
9. Sohi M, Jain L, Ang-Rabanes M, Mogallapu R. Sertraline-Induced Sleep Paralysis: A Case Report. Cureus. 2023 Nov 18;15(11):e49014. doi: 10.7759/cureus.49014. PMID: 38024073; PMCID: PMC10657016.