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In this issue Hamdan, et al., explored the barriers toward colorectal cancer screening. The authors stressed that Colorectal cancer is the third most common cancer and the second leading cause of death worldwide. Bowel cancer screening helps prevent colon cancer by early detection of polyps, leading to efficient treatment and reduced mortality. Within Qatar, primary health facilities promote bowel screening by using the faecal occult blood test. However, the popularity and use of this test are still low. Cronin's five step framework for literature reviews was utilized for this paper. This review included nine articles that were peer-reviewed and published between 2009 and 2019. The nine articles were appraised by using the Mixed Methods Appraisal Tool. This tool has separate criteria to assess the quality of the qualitative, quantitative, and mixed-method studies. The authors noted three main barriers to bowel cancer screening included knowledge deficit, personal beliefs, and organizational barriers. The authors stressed that the main barriers are related to the patients' lack of knowledge and personal beliefs. Overcoming these barriers is essential to raising awareness about this issue among all nurses, physician, and patients. It is necessary to involve stakeholders in order to mitigate barriers. Developing educational activities for healthcare professionals will provide information that they can share with patients to encourage screening and decrease the fear of the test. Developing a pamphlet to increase patient awareness will also encourage screening and work toward decreasing fear.

Helvaci et al., tried to understand prognosis of sickle cell diseases (SCD) in both genders. All cases with the SCD in the absence of smoking and alcohol were included. The study included 368 patients (168 males and 200 females). Mean age (29.4 versus 30.2 years), associated thalassemia minors (72.0% versus 69.0%), and body mass index (BMI) (21.7 versus 21.6 kg/m2) were similar in males and females, respectively ($p>0.05$ for all). Whereas total bilirubin value of the plasma (5.2 versus 4.0 mg/dL, $p=0.011$), transfused units of red blood cells (RBC) in their lives (46.8 versus 29.2, $p=0.002$), disseminated teeth losses (4.7% versus 1.0%, $p<0.001$), chronic obstructive pulmonary disease (COPD) (20.8% versus 6.0%, $p<0.001$), ileus (5.3% versus 2.0%, $p<0.01$), cirrhosis (5.9% versus 1.5%, $p<0.001$), leg ulcers (16.0% versus 7.5%, $p<0.001$), digital clubbing (13.0% versus 5.5%, $p<0.001$), and chronic renal disease (CRD) (10.7% versus 6.5%, $p<0.05$) were all higher in males, significantly. The authors concluded that SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of the hardened RBC into tissues. Although the similar mean age, associated thalassemia minors, and BMI and absence of smoking and alcohol, the higher total bilirubin value of the plasma, transfused units of RBC in their lives, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, and CRD in males may be explained by the dominant role of male sex in life according to the physical power that may accelerate systemic atherosclerotic process all over the body.

Mehmet et al., tried to understand presence of any atherosclerotic background of cirrhosis in patients with sickle cell diseases (SCDs). The study was performed in the Hematology Service of the Mustafa Kemal University on SCDs patients between March 2007 and June 2012. The study included 256 patients with SCDs (127 females). The mean age of them was 29.3 years. Cirrhosis was detected in 5.8% (15) of the SCDs patients without any gender difference (6.2% of females versus 5.4% of males, $p>0.05$). There were 15 (5.8%) patients with chronic obstructive pulmonary disease with a highly significant male predominance (3.1% versus 8.5%, $p<0.001$). Digital clubbing and pulmonary hypertension were also higher in males, but the differences were nonsignificant in between (4.7% versus 6.2% and 11.0% versus 12.4%, respectively). Similarly, the leg ulcers were significantly higher in males, too (5.5% versus 16.2%, $p<0.001$). The significant male predominance was also observed in stroke and smoking (3.1% versus 6.2%, $p<0.05$ and 3.9% versus 11.6%, $p<0.001$, respectively). There were 14 (5.4%) mortal patients during the five-year follow-up period (6.2% of females and 4.6% of males, $p>0.05$), and the mean ages were 31.0 and 26.8 years, respectively ($p>0.05$).
The authors concluded that probably cirrhosis is a systemic inflammatory process prominently affecting the hepatic vasculature, and an eventual accelerated atherosclerotic process is the main underlying cause of characteristics of the disease. SCDs are accelerated systemic atherosclerotic processes, too, and the higher prevalence of cirrhosis in SCDs patients may indicate the underlying atherosclerotic background of cirrhosis.

Dr Elghblawi looked at the the nocturnal kissing of a nuisance mosquito; unusual insect bite reaction, through a case report and a literature review. Insects represent more than half of all known living organisms in the world. Both human beings and insects share a common biodiversity and the influence of insects on human life is enormous. They share an intimate relationship in which human beings are both benefitted and harmed. Insects inflict harm by stinging, biting or transmitting diseases. Rarely, humans are harmed by inadvertently coming in contact with the toxin of an insect. Insect dermatitis is characterized by tingling and burning within 10 minutes of contact, and sometimes the incurred dermatitis is a self-healing condition. Such cases usually happen while asleep when there is a lag time between the crash of the insect and waking up on the morning. A case while sleeping, heard the insect fly around her bare chest, at summer time, and on waving it away instinctively while sleeping, and the insect had crashed on her bare upper chest skin, incurring a subsequent skin reaction without the typical red bite mark followed by an evolved burning ulcerative skin lesion, that took a while to subside and heal up completely.

EXPLORING THE BARRIERS TOWARD COLORECTAL CANCER SCREENING: A LITERATURE REVIEW

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Abstract

Background: Colorectal cancer is the third most common cancer and the second leading cause of death worldwide. Bowel cancer screening helps prevent colon cancer by early detection of polyps, leading to efficient treatment and reduced mortality. Within Qatar, primary health facilities promote bowel screening by using the faecal occult blood test. However, the popularity and use of this test is still low.

Aim: The aim of this literature review is to explore barriers related to colorectal cancer bowel screening using the faecal occult blood test in primary health care settings to facilitate colorectal cancer screening in Qatar.

Method: Cronin's five step framework for literature reviews was utilized for this paper. This review included nine articles that were peer-reviewed and published between 2009 and 2019. The nine articles were appraised by using the Mixed Methods Appraisal Tool. This tool has separate criteria to assess the quality of the qualitative, quantitative, and mixed-method studies.

Result: Three main barriers to bowel cancer screening included knowledge deficit, personal beliefs and organizational barriers.

Conclusion: The main barriers are related to the patients' lack of knowledge and personal beliefs. Overcoming these barriers is essential to raising awareness about this issue among all nurses, physicians, and patients. It is necessary to involve stakeholders in order to mitigate barriers. Developing educational activities for healthcare professionals will provide information that they can share with patients to encourage screening and decrease the fear of the test. Developing a pamphlet to increase patient awareness will also encourage screening and work toward decreasing fear.

Key words: faecal occult blood test, faecal immunochemical test, barriers

Introduction

Colorectal cancer (CRC) is considered the third most common type of cancer diagnosis and the second leading cause of death worldwide (Guo et al., 2020). The American Cancer Society (2017) stated that around 1 in 24 women (4.2%) and 1 in 22 men (4.6%) will be diagnosed with CRC in the USA. The American Cancer Society (2017) defines CRC as the division and growth of abnormal cells in the rectum or colon. CRC usually begins as a non-cancerous benign tumor known as an adenoma that develops in the colon or rectal inner lining and grows slowly during a period of 10 to 20 years (Goede et al., 2017). It is estimated that one-third to one-half of all individuals will ultimately develop one or more adenomas during their lifetime (Schreuders et al., 2016). In contrast, all adenomas have the potential to be converted to cancer when they become enlarged, while only less than 10% are expected to progress to cancer (American Cancer Society, 2017). The CRC cancer stages are generally considered from the time of diagnosis. For this reason, it is essential to have early detection and diagnosis to prevent its progression to cancer (Ramazani et al., 2020).

While the morbidity and mortality rates have decreased in the Western countries related to the effectiveness of screening programs there remains an increase in middle to high-income countries in South America, Eastern Europe, and Asia (Al-Dahshan et al., 2020). Wong (2015) stated that bowel cancer screening proved efficient to decrease the cancer mortality rate by 33%. However, without adequate uptake of bowel screening within these countries, the number of colon cancer cases is expected to increase to 2.2 million and result in 1.1 million deaths by 2030 (Al-Dahshan et al., 2020). According to Chiu et al. (2015), the mortality and morbidity rates of CRC have risen in the last decade especially in these Asia-Pacific regions. Thus, the purpose of this literature review is to identify the barriers related to the uptake of bowel screening in order to prevent colorectal cancer.

Methods

Cronin et al.'s (2008) framework was used for this literature review. This framework consists of five steps which include determining a review topic, searching the literature, analyzing and synthesizing literature, writing the review including adding references (Cronin et al., 2008).

A literature search of the following databases was done: CINAHL, MEDLINE, and Academic Search Complete. The search terms included: barrier, fecal occult blood test, cancer screening, perception, FIT, gFOBT, FOBT, and beliefs. Boolean operators AND and OR were used to make this search more precise. A total of 432 articles were evaluated for inclusion in this literature review. The titles of these articles were reviewed based on both the inclusion and exclusion criteria. Inclusion criteria consisted of (a) primary studies published in English between 2009 and 2020 and (b) quantitative, qualitative, or mixed method studies, studies that focused primarily on the barriers to FOBT, gFOBT, and FIT screening among men and women from the ages of 50 to 75 years old. Exclusion criteria were (a) non-peer reviewed studies, (b) studies that did not report the barriers to FOBT, gFOBT and FIT and focused only on colonoscopy (c) studies not published in English (d), studies published before 2009 (e), studies not conducted in primary care settings, and (f) studies that included people less than 50 years of age. The initial search resulted in 432 articles of which 289 remained after applying limiters. The remining 289 were then screened for duplication which left 143 articles. After reviewing titles and abstracts, 87 remained for further assessment of inclusion and exclusion criteria. The remaining 87 articles were checked for eligibility and resulted in a further 38 studies being excluded. After full text review of the remaining 49 articles, 40 were excluded because they did not discuss the barriers specifically to FOBT, gFOBT and FIT. In all, a total of 9 articles were included in this review (see Figure 1).

Findings

The nine retrieved studies published between the years 2009-2020 were primary studies that used three different approaches: quantitative, qualitative, and mixed methods. These studies focused on those articles that discussed the barrier of FOBT. These studies were conducted in different countries: United States (n = 2), United Kingdom (n = 2), France (n = 1), Turkey (n = 2), and Australia (n = 2). In all, there were five quantitative studies, three qualitative, and one mixed method study in this review. The three major themes that emerged were (a) knowledge deficits, (b) personal beliefs and attitudes, (c) and organizational barriers (see Figure 2).

Figure 1: Search Strategy

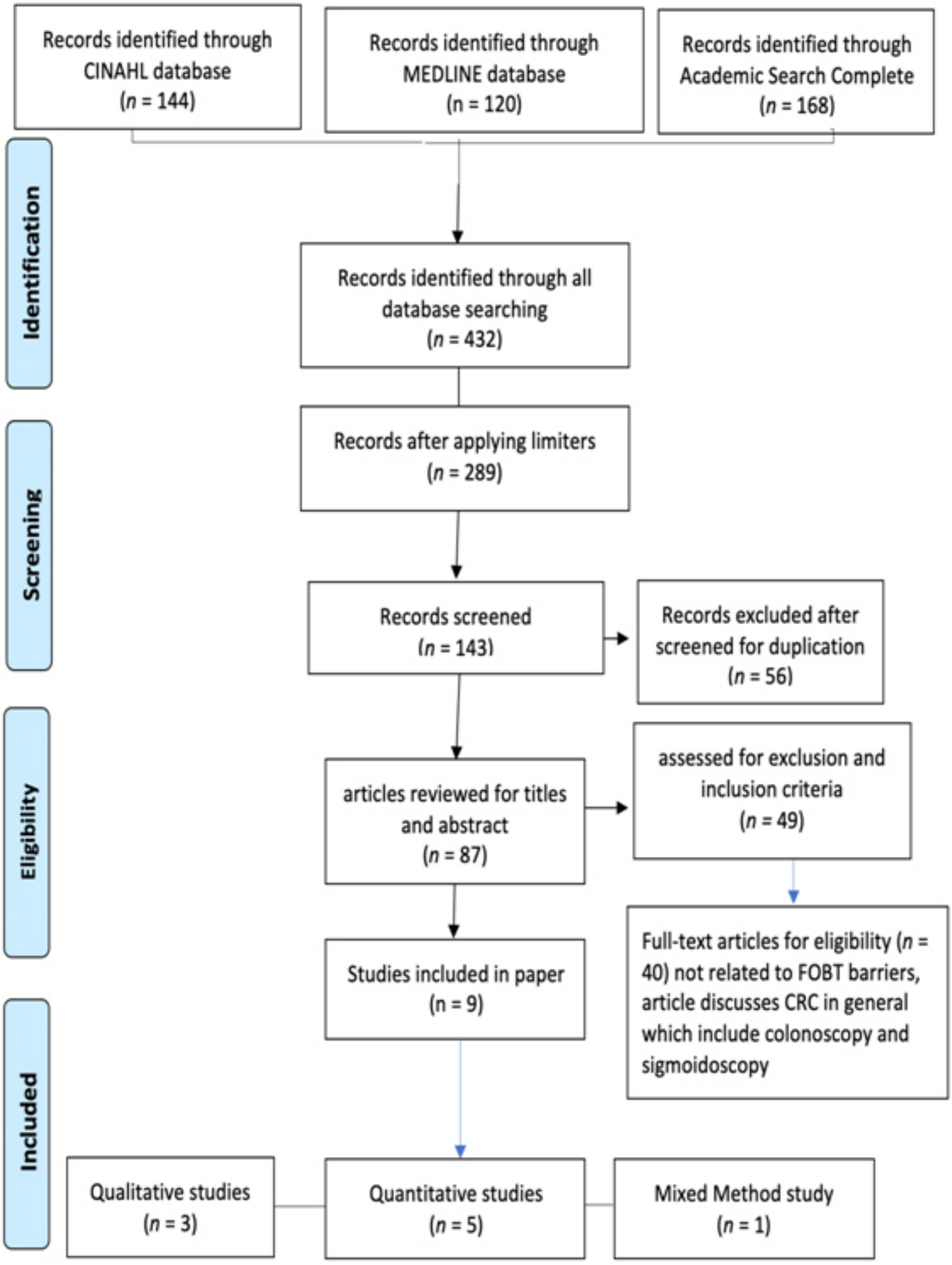
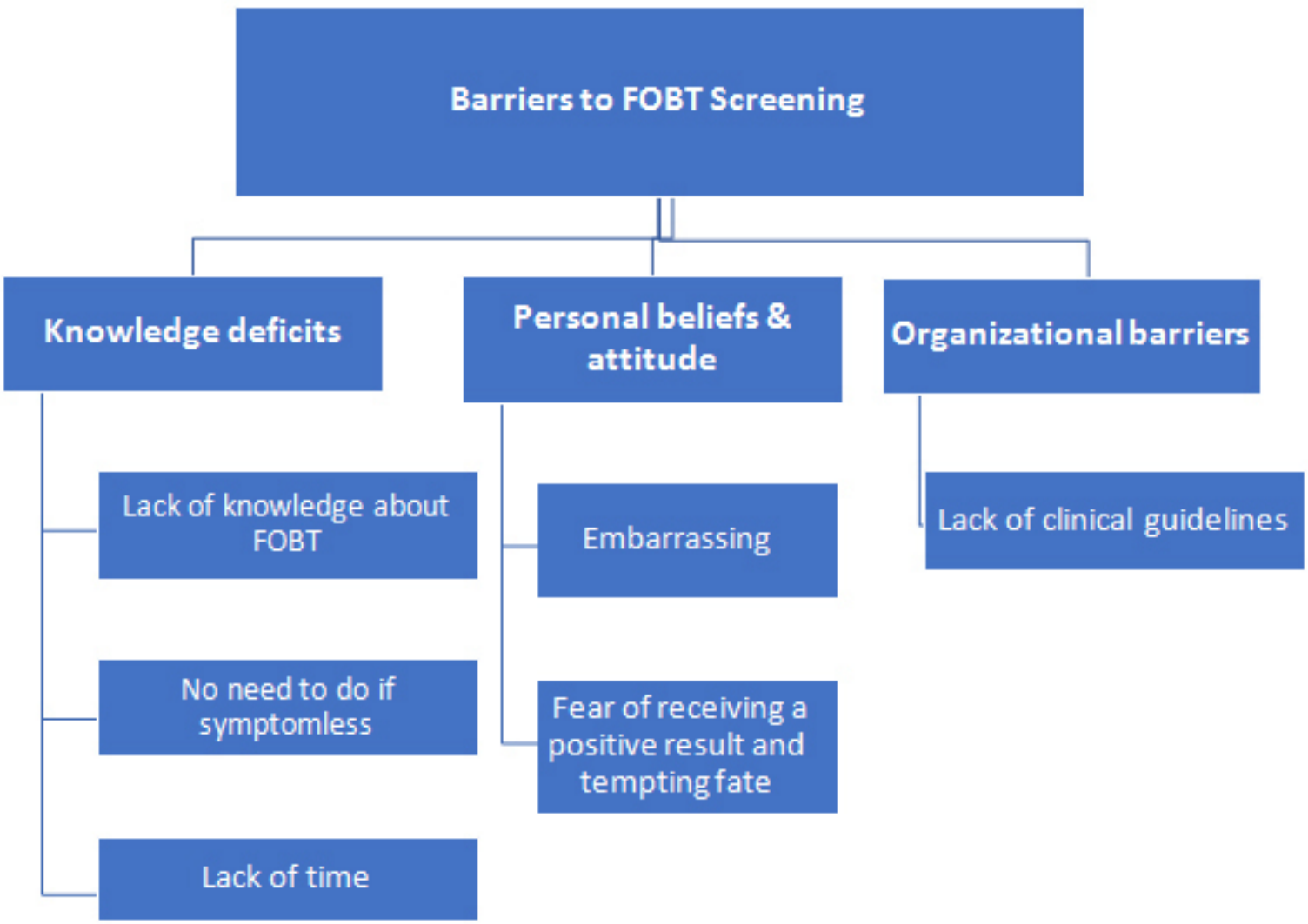


Figure 2: Identified Themes



Discussion

In order to mitigate the rise seen in CRC cases in Qatar, it is essential to explore the barriers people have for not performing the available tests necessary to detect CRC. This literature review identified the barriers noted for the lack of uptake to CRC screening. These barriers were knowledge deficits, personal beliefs and attitudes, and organizational barriers.

Knowledge Deficits.

Lack of Knowledge about FOBT

Knowledge plays an active and essential role in a patient's decisions, which affects the quality of life. This review highlighted the following barriers regarding knowledge deficits: lack of awareness regarding the importance of CRC screening, fear of receiving positive cancer result, absence of symptoms, and lack of time. Several studies have agreed that decreased awareness is a significant factor associated with CRC screening uptake. Saad et al. (2020) conducted a study in Dearborn, Michigan, to assess Arabic-speaking participants' knowledge of CRC. This study found that 70% of the participants lacked knowledge about colon polyps and over 89% were unaware that they are under high risk for CRC and need to do FOBT. This study also agreed that insufficient knowledge about the importance of FOBT and the risk of CRC could be a barrier to FOBT. Congruent in this literature review was that lack of knowledge was significant in influencing people's decision to do the FOBT. Warner et al.'s (2018) study which aimed to assess knowledge, barriers, and feasibility of home-based FIT in a Latina's population for CRC screening found that 30% of participant did not know about CRC screening resulting in low compliance with FOBT.

No Need to do it if Symptomless

Colorectal cancer develops without early warning signs or symptoms which will affect people's decisions not to do the FOBT screening. A person may be reluctant to do the FOBT because they believe they do not have symptoms. Lack of symptoms leads people to not be concerned, which is considered as a barrier of CRC screening (Davis et al., 2016; Warner et al., 2018). The Cancer Council Australia population surveys showed that people of advanced age believed that screening was necessary only if they developed symptoms (as cited in Lotfi-Jam et al., 2019). In addition, Lee's (2018) study, which was done in Korea, aimed to understand the awareness of CRC screening in order to implement a strategy to improve it. Many participants in this study explained that FOBT was not a priority because they

assumed that the absence of symptoms meant that they are healthy. In Le Pimpec et al.'s (2017) study, they found 16% of participants felt non-concerned to do the test in absence of symptoms. This study also noted that lack of symptoms is one of the essential barriers of FOBT.

Lack of Time

Lack of time was found as a barrier to doing the FOBT in this literature review.

Le Pimpec et al.'s (2017) study also found lack of time was frequently reported by participants. Also noted in their study was that 36% of participants age 55 to 75 years reported that they did not have time to do the test. Lack of time for FOBT was also a barrier of FOBT reported by Miranda-Diaz et al. (2015). These authors found that 17% of participants reported they did not have the time to do the FOBT for various reasons.

Personal Beliefs and Attitudes

Embarrassing

This review showed personal beliefs and attitudes affect people's decision not to do the FOBT. The most common personal belief was that of embarrassment toward collecting one's own stool sample. Congruent with the findings in Miranda-Diaz et al.'s (2015) study which looked at barriers of compliance to cancer screening among Hispanic patients, that participants were not only disgusted but embarrassed by collecting their own stool sample. In this study, 33% of participants did not have the FOBT because of feeling discomfort from doing the test. Similarly, in Davis et al.'s (2016) study, participants felt embarrassed from doing the FOBT; as one participant explained "giving stool-fecal sample for testing is really embarrassing" (p. 3). Lecky et al. (2014) did a qualitative study in the UK to examine patient's perception in providing a FOBT and found that participants felt disgusted and embarrassed by the contamination of their hands having to deal with feces. They felt disgusted while placing their hands near the toilet bowl to collect a stool sample. Congruent with the findings from this literature review, Javanparast et al. (2012) did a qualitative study to identify facilitators and barriers of CRC testing among different cultures in South Australia and one participant in this study stated "dealing with a dirty part of the body; it is why many people do not like to do it" (p. 552). In line with this literature review, another Asian study by Azeem et al. (2016) to assess the barriers of CRC screening in Asia stated that a feeling of embarrassment was a barrier to the uptake for the FOBT.

Fear of Receiving a Positive Result and Tempting Fate

One of the barriers that affects the uptake of the FOBT is fear of receiving a positive result (Qumseya et al., 2014; Taskila et al., 2009; Yong et al., 2016). Davis et al.'s (2016) study conducted in Australia found that 11% of participants felt fear of receiving positive results and tempting fate. Thus, some people felt anxious when they received the FOBT kit because they thought they were a significant CRC risk. Beeker et al.'s (2000) study, which looked at colorectal cancer screening in older men and women, also found that the biggest barrier to doing the FOBT was fear of receiving a positive result. In the same study, one participant described the CRC as "the disease no one wants to talk about" (p. 274). Javanparast et al. (2012) also explained that many people believe that disease, death, and life cannot be controlled because these are in God's hands. Noted in the literature was a study conducted by Taskila et al. (2009) which aimed to identify factors affecting CRC attitude. They found that some participants believe that they were tempting fate by undergoing FOBT.

Organizational Barriers

Lack of Clinical Guidelines

This literature review showed that general practitioner's recommendation for CRC screening is crucial to encourage patients to undergo FOBT. A lack of physician recommendation owing to an absence of clear clinical guidelines is a barrier to FOBT. This was found in Le Pimpec et al.'s (2017) study who recommended that physicians encourage patients to do bowel cancer screening because physicians can convince patients by explaining the importance of screening. A similar finding was found in Leung et al. 's (2016) quantitative study done in China to identify the factors that stop Chinese people from participating in CRC screening. This study found that physician recommendation was considered as the strongest factor associated with FOBT. In the same study, participants who did not receive advice or a recommendation from their physician were less likely to do the FOBT. In line with this literature review finding, GPs are not likely to advise patients to have the CRC screening due to lack of clinical guidelines (Nguyen et al., 2017; Sewitch et al., 2007; Wee et al., 2005;). Javanparast et al. (2012) stated that a trusting relationship between the physician and patient is considered essential in order to encourage and influence their decision regarding FOBT. As stated by a participant in their study, "if my doctor asked me to do it I will do it" (p. 522). A qualitative study that explored barriers and facilitators of CRC among Vietnamese people in the USA (Kimura et al. (2015) found that male and female participants mentioned that physician recommendations are essential facilitators to CRC screening.

An appropriate medical system with clear guidelines is required to increase the screening rate of FOBT. Lack of a supportive medical system will affect the medical team's ability to identify patients' need for screening and family history about CRC, follow up, and sending reminders. As explained in the study done in New Mexico by Hoffman et al. (2011), which explored the barriers to CRC screening, lack of electronic medical records and tracking systems was considered a significant barrier for FOBT. Yong et al (2016) also noted that 28.9% of participants did not do the FOBT because of a lack of a reminder. Thus, it is necessary to provide adequate guidelines for CRC screening to facilitate tracking and identification of patients who need FOBT screening.

Implications and Recommendations

This literature review highlighted the barriers related to bowel screening such as the FOBT in order to detect colorectal cancer. One of the barriers at the organizational level necessitates clear policies within hospitals in order that physicians are all on the same page and recommending necessary screening with all eligible patients. The majority of the barriers were related to knowledge deficit and personal beliefs of the patients. Therefore, it is necessary to address these with patients in order to increase the uptake of bowel screening. In order to do this, it is necessary to raise awareness about this issue among all nurses and physicians and patients. Thus, a recommendation is to develop educational activities that include materials for both patients and healthcare personnel that will offer patients information that can allay those fears and healthcare personnel information they can share with patients.

Strengths and Limitations

The strength is that all articles included were peer reviewed and published between 2009 and 2019. This review also includes a study that used mixed method paradigms that consider strength because both quantitative and qualitative data gives a comprehensive view of the barriers of FOBT. However, a limitation of this review is that most studies examined the barriers related to colonoscopy and sigmoidoscopy and not that of the FOBT.

Conclusion

Bowel cancer screening is essential to discover colorectal cancer at an early stage.

Colorectal cancer is preventable if screened appropriately and on time. There are several barriers to colorectal cancer screening. Understanding barriers to FOBT is essential to overcome these barriers and increase screening rates to improve quality of life. Lack of knowledge was the most critical barrier linked to the majority of other barriers. These barriers could affect people from undergoing FOBT for early detection, prevention, and treatment of CRC. Health care providers play an essential role in encouraging patients to undergo screening by increasing awareness about the importance of FOBT. Also, the availability of appropriate medical systems is important for improving CRC screening rate. Therefore, colorectal cancer screening is a cost-effective and useful test for preventing and controlling colon cancer worldwide.

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Appendix A: Data Extraction Matrix for Articles

Author and Country	Methods	Barriers
Sahin et al., (2016) Barriers to Colorectal Cancer Screening as perceived by PHCP in Turkey	Quantitative N= 478 primary health care providers (physicians and family health personal 1. Questionnaire developed for study, three main sections (socio-demographics, knowledge attitudes and practices, and 3) barriers 2. Data transfer onto SPSS 22.0 and analyzed as percentage and numbers.	• Fear of bad test results • Embarrassing • Hearing unpleasant things about the test from others • Healthcare provider not recommending the test
Smith et al., (2016) Barriers and facilitators to FOBT screening UK	1. Quantitative 2. N= 8576, age range 45 to 59.5 years of age. The majority were married, white, employed, good level of self-reported health 54.2% had high school, 32.1 % university. 3. Questionnaire – (five questions assessed barriers to FOBT) 4. Descriptive and logistic regression	• Doing a FOBT would be disgusting, (16.6%) • Embarrassed if others knew I had done the FOBT (6.9%) • Doing a FOBT would make me worry about bowel cancer (16.8 %) • Afraid of getting an abnormal result (56.6%) • Patient would not want to keep stool sample in the house, • No privacy to do FBOT test, • No time to do the test
Broc et al., (2017) Motivational process underlying decision-making in FOBT participation France	1. Mixed method 2. 5894 (men & women) Female N- 3401 (57.7%) age 50-74. Mean age 60 yrs. (SD=6.9). 3. Telephone survey, three nurses, and one psychologist conducted semi-structured interviews. 4. Used a similarity tree (facilitates capture of barriers and motivation to screening)	• Previous screening, no cancer consultation fees • "No time" • Healthy life (no symptoms) • Not concerned (too young/old) • Afraid, Family pressure • Discourage by GP
Green et al., (2017) Barriers and facilitators reported by patients with suboptimal screening adherence to refine interventions of starting ongoing adherence to CRC screening USA	1. Qualitative 2. Purposive sampling- N=41; (44 %) male & (30 %) female (wrong number 44 plus 0 = 74 need 100% age ranged 50-73 years; 23 completed 1 FOBT and 18 did not during the three-year study despite reminders 3. Phone interview, audio-recorded 4. Thematic analysis	• "Avoidance" (i.e. not paying attention, remembering, taking time for test, or procrastinating.) • "Fear" (i.e. fear of cancer diagnosis and fear in general). • "Test specific barriers (i.e. Handling the stool) • "Health concerns" for example a "never" screener listed multiple health conditions and the need to prioritize. Other participants mentioned the same. Also, health concerns about medication

Appendix A: Data Extraction Matrix for Articles (continued)

Dharni et al., (2016) Factors affecting CRC screening in socio-economically and ethnically diverse inner-city population UK	1. Qualitative study, guided by the Theoretical Domains Framework 2. Purposive 50 participants, 29 males; 21 female, age range 55-75 years of age, 21 SES 34% low, 44% intermediate & 20% high 13 Black African, 15 black Caribbean, 17 white British (n=17) and 2 black others and 3 white others. 3. Face to face interviews, recorded 4. Framework analysis.	Result: lack of awareness of CRC was barrier of screening, the majority of participants reported they knew very little about CRC. • Lack of awareness • Fear of cancer /screening outcome • Faith in God • Misunderstanding instruction for completing FOBT • Collecting fecal sample (hygiene and potential smell) • Existing physical /mental health issues, • Being too busy or stressed at work & having to care for elderly person, • Mobility or physical limitations. • Different ethnic groups may have different beliefs about health, illness & prevention
Bulduk et al., (2017) Colorectal Cancer risks of individuals aged over 50 and their attitudes towards having FOBT Turkey	1. Quantitative, descriptive, cross-sectional 2. N= 1500, mean age 64.4 yrs. 3. Survey using Scale for Assessment of Benefits and Barriers of Colorectal Cancer Screening-FOBT. 8 items related to barriers.	• Doing a FOBT is unpleasant • Don't know how to do test • Embarrassing • No problems • Afraid of results • Cost, no health insurance. • No Time • No privacy to do test
Dawson et al., (2016) To understand the factors that influence personal behavior of uptake of the bowel screening: A health belief model used to guide study. Australia	1. Qualitative 2. Purposive sample, N=61 age 45-69 yrs. 3. Seven focus group 4. Thematic analysis	Six main themes emerged • Health awareness and its influence on health behaviors (fatalism) may manifest itself as denial & avoidance of health care system. • Conceptualizing the risk of bowel cancer: • Awareness of screening • Perceived value of screening • Motivators and barriers to FOBT • Knowledge & Its impact on intentions to screen.
Davis et al., (2013) The differences in CRC screening knowledge, beliefs, barriers & health system experiences among rural & urban patients who were not up-to-date with CRC screening USA	1. Quantitative 2. Interview, survey administered orally. N= 972 Age 50 to 70 Descriptive & logistic regression	• Afraid the FOBT instructions will be confusing • Doing FOBT is embarrassing • Doing an FOBT is a lot of trouble. • Doing an FOBT is messy. • Lack of time • Cost and low income, lack of interest of screening • Worried from bad result

Appendix A: Data Extraction Matrix for Articles (continued)

Todorov et al., (2018) To examine knowledge, and reasons for use or non-use (FOBT) for colorectal cancer (CRC) Australia	1. Quantitative 2. Questionnaire survey years 2011, 2012, and 2014 3. N= 2732 4. 4. 51.8% Men & 48.2 women 50–75 years 5. Logistic regression analysis	• Reasons given for non -use of FOBT • Had no symptoms • Lack of physician recommendation • Too busy or lack of time • Did not know that that this should be done every two years • Not interested and can't be bothered • Not aware about the FOBT • No family history of bowel cancer • Too embarrassed to do the test • Have other bowel examinations • Have regular colonoscopies

WORSE PROGNOSIS OF SICKLE CELL DISEASES IN MALES EVEN IN THE ABSENCE OF SMOKING AND ALCOHOL

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Abstract

Background: We tried to understand the prognosis of sickle cell diseases (SCD) in both genders.

Methods: All cases with the SCD in the absence of smoking and alcohol were included.

Results: The study included 368 patients (168 males and 200 females). Mean age (29.4 versus 30.2 years), associated thalassemia minors (72.0% versus 69.0%), and body mass index (BMI) (21.7 versus 21.6 kg/m2) were similar in males and females, respectively (p>0.05 for all). Whereas total bilirubin value of the plasma (5.2 versus 4.0 mg/dL, p=0.011), transfused units of red blood cells (RBC) in their lives (46.8 versus 29.2, p=0.002), disseminated teeth losses (4.7% versus 1.0%, p<0.001), chronic obstructive pulmonary disease (COPD) (20.8% versus 6.0%, p<0.001), ileus (5.3% versus 2.0%, p<0.01), cirrhosis (5.9% versus 1.5%, p<0.001), leg ulcers (16.0% versus 7.5%, p<0.001), digital clubbing (13.0% versus 5.5%, p<0.001), and chronic renal disease (CRD) (10.7% versus 6.5%, p<0.05) were all higher in males, significantly.

Conclusion: SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of the hardened RBC into tissues. Although the similar mean age, associated thalassemia minors, and BMI and absence of smoking and alcohol, the higher total bilirubin value of the plasma, transfused units of RBC in their lives, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, and CRD in males may be explained by the dominant role of male sex in life according to the physical power that may accelerate systemic atherosclerotic process all over the body.

Key words: Sickle cell diseases, male sex, chronic endothelial damage, atherosclerosis, metabolic syndrome, early aging, premature death

Introduction

Chronic endothelial damage may be the leading cause of aging and death by causing disseminated tissue hypoxia all over the body. Probably whole afferent vasculature including capillaries are mainly involved in the process since much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent endothelial injuries. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature which reduces blood flow and increases systolic BP further. Some of the well-known accelerators of the systemic atherosclerotic process are physical inactivity, excess weight, smoking, alcohol, prolonged infections such as tuberculosis, and chronic inflammatory processes including sickle cell diseases (SCD), rheumatologic disorders, and cancers for the development of terminal endpoints including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PHT), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). Although early withdrawal of the causative factors may delay terminal endpoints, the endothelial changes cannot be reversed completely after the development of obesity, HT, DM, PAD, COPD, PHT, CRD, CHD, or stroke due to their fibrotic nature (3, 4). Similarly, SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level terminating with accelerated atherosclerosis induced end-organ failures in early years of life. We tried to understand the prognosis of the SCD in both genders in the present study.

Material and methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD in the absence of smoking and alcohol were included into the study. The SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including painful crises per year, epilepsy, deep venous thrombosis, transfused units of red blood cells (RBC) in their lives, surgical operations, leg ulcers, and stroke were learnt. Due to the cumulative atherosclerotic effects of smoking and alcohol together with the SCD, current and/or previous regular smokers or drinkers at least for a period of one year were excluded from the study. A complete physical examination was performed by the Same Internist. Body mass index (BMI) of each patient was calculated by the measurements of the Same Internist instead of verbal expressions. Weight in kilogram is divided by height in meter squared. Patients with disseminated teeth loss (<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, total bilirubin, creatinine, liver function tests, markers of hepatitis viruses A, B, C and human immunodeficiency virus, 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 (AVN) was diagnosed via MRI (5). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since the SCD with associated thalassemias show a milder clinic than the sickle cell anemia (SCA) alone (6). Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as PHT (7). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (8). Acute chest syndrome is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (9). 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 is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher 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 greater than 1.0, and with the presence of Schamroth's sign (10, 11). 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 the cardiac walls. Rheumatic heart disease is diagnosed 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, the mean age, associated thalassemia minors, BMI, and consequences of the SCD 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 368 patients with the SCD (168 males and 200 females). Mean ages of the patients were similar in males and females (29.4 versus 30.2 years, respectively, p>0.05). Prevalence of associated thalassemia minors were also similar in both genders (72.0% versus 69.0%, respectively, p>0.05). Mean values of BMI were similar in males and females, too (21.7 versus 21.6 kg/m2, respectively, p>0.05) (Table 1). On the other hand, total bilirubin value of the plasma (5.2 versus 4.0 mg/dL, p=0.011), transfused units of RBC in their lives (46.8 versus 29.2, p=0.002), disseminated teeth losses (4.7% versus 1.0%, p<0.001), COPD (20.8% versus 6.0%, p<0.001), ileus (5.3% versus 2.0%, p<0.01), cirrhosis (5.9% versus 1.5%, p<0.001), leg ulcers (16.0% versus 7.5%, p<0.001), digital clubbing (13.0% versus 5.5%, p<0.001), and CRD (10.7% versus 6.5%, p<0.05) were all higher in males, significantly. Although the overall mortality was higher in males during the ten-year follow up period (8.3% versus 6.5%, p>0.05), the difference was nonsignificant probably due to the small sample size of the mortality cases. Similarly, although the mean age of mortality cases was lower in males, the difference was nonsignificant (29.0 versus 32.5 years, p>0.05) probably due to the same reason again (Table 2).

Table 1: Characteristics of the study cases

Variables	Males with the SCD*	*p*-value	Females with the SCD
Prevalence	45.6% (168)		54.3% (200)
Mean age (year)	29.4 ±9.9 (5-58)	Ns†	30.2 ±9.9 (8-59)
Associated thalassemiaminors	72.0% (121)	Ns	69.0% (138)
BMI‡ (kg/m²)	21.7 ±3.5 (14.3-32.5)	Ns	21.6 ±3.7 (14.5-46.4)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Body mass index

Table 2: Associated pathologies of the study patients according to the gender distribution

Variables	Males with the SCD*	*p*-value	Females with the SCD
Painful crises per year	5.0 ±7.0 (0-36)	Ns†	5.0 ±8.7 (0-52)
Total bilirubin (mg/dL)	*5.2 ± 4.9 (0.6-29.0)*	*0.011*	*4.0 ± 3.4 (0.6-22.9)*
Transfused units of RBC‡	*46.8 ± 61.0 (0-434)*	*0.002*	*29.2 ± 36.5 (0-206)*
Disseminated teeth losses (< 20 teeth present)	*4.7% (8)*	*<0.001*	*1.0% (2)*
COPD§	*20.8% (35)*	*<0.001*	*6.0% (12)*
Ileus	*5.3% (9)*	*<0.01*	*2.0% (4)*
Cirrhosis	*5.9% (10)*	*<0.001*	*1.5% (3)*
Leg ulcers	*16.0% (27)*	*<0.001*	*7.5% (15)*
Digital clubbing	*13.0% (22)*	*<0.001*	*5.5% (11)*
CHD¶	16.0% (27)	Ns	13.0% (26)
*CRD***	*10.7% (18)*	*<0.05*	*6.5% (13)*
Stroke	8.3% (14)	Ns	6.5% (13)
PHT****	10.1% (17)	Ns	12.5% (25)
Autosplenectomy	47.6% (80)	Ns	52.5% (105)
Deep venous thrombosis or varices or telangiectasias	7.1% (12)	Ns	5.5% (11)
Rheumatic heart disease	7.7% (13)	Ns	5.5% (11)
AVN*****	25.0% (42)	Ns	27.0% (54)
Sickle cell retinopathy	1.1% (2)	Ns	0.5% (1)
Epilepsy	2.9% (5)	Ns	2.5% (5)
Acute chest syndrome	2.3% (4)	Ns	3.5% (7)
Mortality	8.3% (14)	Ns	6.5% (13)
Mean age of mortality (year)	29.0 ±6.9 (19-42)	Ns	32.5 ±9.0 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary disease ¶Coronary heart disease **Chronic renal disease ***Pulmonary hypertension ****Avascular necrosis of bones

Discussion

SCD are chronic inflammatory processes on vascular endothelium terminating with an accelerated atherosclerosis induced end-organ failure and a shortened survival in both genders (12, 13). Hemoglobin S causes loss of elastic and biconcave disc shaped bodies of RBC. Probably loss of elasticity instead of shape is the major pathology since sickling is rare in peripheric blood samples of the SCD patients with associated thalassemia minors (6), and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan but it is exaggerated with inflammation, infection, and various stresses of the body. The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia all over the body (14, 15). The SCD may keep vascular endothelium particularly at the capillary level (16), since the capillary system is the main distributor of the abnormally hardened RBC into the tissues. The hardened RBC induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages of the patients. As a result, mean lifespans of the patients were 42 and 48 years in males and females in the literature, respectively (17), whereas they were 29.0 versus 32.5 years in the present study. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during emergencies in Turkey (18). Actually, RBC supports must be given immediately during all medical or surgical situations in which there is evidence of clinical deterioration in the SCD (9). RBC supports decrease sickle cell concentration in the circulation and suppress bone marrow production of abnormal RBC. So it decreases sickling-induced endothelial damage, inflammation, and edema and the subsequent tissue hypoxia all over the body.

Smoking may have a major role in systemic atherosclerotic processes such as COPD, digital clubbing, cirrhosis, CRD, PAD, CHD, stroke, and cancers (19). Its atherosclerotic effects are the most obvious in Buerger's disease and COPD. Buerger's disease is an inflammatory process terminating with obliterative changes in small and medium-sized vessels, and it has never been reported in the absence of smoking in the literature. Smoking induced endothelial damage probably affects pulmonary vasculature much more than the other organs due to the higher concentration of its products in the respiratory system. But it may even cause cirrhosis, CRD, PAD, CHD, stroke, and cancers with the transport of its products by means of the blood. COPD may also be accepted as a localized Buerger's disease of the lungs. Despite its strong atherosclerotic effects, smoking in human beings and nicotine administration in animals may be associated with some weight loss (20). There may be an increased energy expenditure during smoking (21), and nicotine may decrease caloric intake in a dose-related manner (22). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (23). BMI seems to be the highest in former, the lowest in current, and medium in never smokers (24). Similarly, smoking may also show the weakness of volition to control eating, and prevalence of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of the metabolic syndrome (25). On the other hand, smoking-induced endothelial damage may increase plasma triglycerides (26), since triglycerides may behave acute phase reactants and plasma values may not be negatively affected by pathologic weight loss (27, 28). Additionally, although CHD were detected with similar prevalence in both sexes, smoking and COPD were higher in males against the higher prevalence of BMI and its consequences including dyslipidemia, HT, and DM in females (19). Probably tobacco smoke induced acute inflammation on vascular endothelium all over the body is the major cause of loss of appetite, since the body doesn't want to eat during fighting. On the other hand, when we think of some antidepressant properties of smoking and alcohol, the higher prevalence of them in males may also show some additional stresses on male sex in life and a shorthened survival (29).

Probably alcohol causes a vascular endothelial inflammation all over the body, too (30). Smoking and alcohol restrictions were the cause of female predominancy in the present study since both of them are much higher in males (29). Similar to the tobacco smoke, alcohol leads to an increased proinflammatory cytokine secretion and reactive oxygen species (ROS) production by tissue macrophages which damage organs via oxidative stresses, and these effects lie far beyond lungs and liver. Against the harmful effects of the ROS, there are various enzymatic and non-enzymatic antioxidants in the body. Enzymatic ones include catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase, and non-enzymatic ones include glutathione, carotene, bilirubin, tocopherol, uric acid, and metal ions (31). Both tobacco smoke and ethyl alcohol resulted in a change of glutathione levels in serum and tissues in rats (31), and tobacco smoke had the strongest effect on protein nitrozylation in the brain (31). Ethyl alcohol affected glutathione levels in serum, kidney, and brain and superoxide dismutase activity in the brain (31). Vascular endothelial effects of alcohol may even be seen in the absence of a significant liver disease. For example, erectile dysfunction was higher among aborigines with alcohol dependence (32). There was a significant increase in leukocyte adhesion after chronic alcohol exposition in pancreas, and histological changes and cytokine levels correlated with the duration of exposition in rats (33). Probably, cirrhosis also has a capillary endothelial inflammation terminating with disseminated hepatic destruction, and it may even be accepted as a localized Buerger's disease of the liver caused by alcohol. Stromal cells including hepatic stellate and endothelial cells were proposed to control the balance between hepatic fibrosis and regeneration, but chronic damage eventually leads to progressive substitution of hepatic parenchyma by scar tissue in cirrhosis (34). Although the atherosclerotic effect of alcohol is the most obviously seen in the liver due to

the highest concentrations of its products via the portal blood flow there (30), alcohol may even cause COPD, digital clubbing, CRD, PAD, CHD, stroke, and cancers-like other atherosclerotic endpoints by the transport of its products in the blood.

COPD is the third leading cause of death in the world (35). It is an inflammatory disorder that mainly affects the pulmonary vasculature. Aging, smoking, and excess weight may be the major underlying causes of COPD. Regular alcohol consumption may also be important in the inflammatory process of COPD. For example, COPD was one of the most frequent diagnoses in patients with alcohol dependence (36). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (37). Probably an accelerated atherosclerotic process is the major structural background of functional changes seen in the COPD. The inflammatory process on vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced atherosclerosis, fibrosis, and pulmonary losses. Although the COPD may mainly be an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body (38, 39). For example, there may be close relationships between COPD, CHD, PAD, and stroke (40). Furthermore, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in COPD, and the CHD was the most common cause in a multi-center study of 5,887 smokers (41). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (41). In another study, 27% of all mortality cases were due to the cardiovascular diseases in the moderate and severe COPD patients (42). Similarly, COPD may just be one of the terminal endpoints including priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the SCD (43).

Digital clubbing is characterized by an increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (44). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (45). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (11). But according to our experiences, digital clubbing is frequently associated with smoking and pulmonary, cardiac, renal, and hepatic disorders which are characterized by chronic tissue hypoxia (3). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs that affect each other 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 previous study (29). It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of clubbing in males in the present study (13.0% versus 5.5%, $p<0.001$) may also show some additional role of male sex on clubbing.

Leg ulcers are seen in 10-20% of patients with the SCD (46), and the ratio was 11.4% in the present study. Its incidence increases with age, male sex, and SCA alone (47). Similarly, its ratio was higher in males (16.0% versus 7.5%, $p<0.001$), and mean age of the patients with leg ulcers was significantly higher than the others (34.6 versus 29.2 years, $p<0.000$) in the present study. The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (46). As evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (46). The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the major underlying cause in the SCD (47). 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 hardened bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood probably delays wound and fracture healing in the lower extremities. Beside the hardened bodies, smoking and alcohol may also have some additional effects on the leg ulcers since both of them are much more common in males (29). Hydroxyurea is the first drug that was approved by Food and Drug Administration for the treatment of SCD (16). 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 (18). Its main action may be the suppression of hyperproliferative white blood cells (WBC) and platelets (PLT) in the SCD (48). Although presence of continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. 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 (49). According to our ten-year experiences, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the leg ulcers may be secondary to the increased WBC and PLT counts induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD.

Cirrhosis is increasing in the world, and it was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (4). Although the improvement of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being and increased prevalence of excess weight all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it became the most common cause of chronic liver disease even at childhood at the moment (50). NAFLD is a marker of pathological fat deposition combined with a low-grade chronic inflammation, which results with hypercoagulability, endothelial dysfunction, and

an accelerated atherosclerosis (50). Beside terminating with cirrhosis, NAFLD is associated with a higher overall mortality rate as well as an increased prevalence of cardiovascular diseases (51). Authors reported independent associations between the NAFLD and an impaired flow-mediated vasodilation and an increased mean carotid artery intima-media thickness (CIMT) (52). The NAFLD may be considered as the hepatic consequence of the metabolic syndrome and SCD (53). Probably smoking also takes a 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 (54). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Chronic infectious and inflammatory processes may also terminate with an accelerated atherosclerotic process all over the body including the liver (55). For example, chronic hepatitis C virus infection raised CIMT (55). As a result, similar with the disseminated teeth losses, COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, stroke, PHT, and AVN, cirrhosis may actually be one of the several atherosclerotic endpoints of the SCD and metabolic syndrome.

CRD is increasing all over the world, too (56). The increased prevalence and complications of the CRD may be explained by prolonged survival of the human being and increased prevalence of excess weight all over the world (57). Excess weight, smoking, alcohol, chronic inflammations, prolonged infections, and aging may be the major underlying causes of the endothelial inflammation of the kidneys. The inflammatory process is enhanced by releases of various chemicals by lymphocytes to repair the damaged renal endothelium, particularly the endothelial cells of renal arteriols. Secondary to the continuous irritation of the endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, fibrosis, tissue hypoxia, and infarcts. Excess weight induced metabolic abnormalities such as hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause various cellular stresses for acceleration of tissue inflammation and immune cell activation (58). 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 (57). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous and renin-angiotensin systems, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess weight (59). Excess weight also causes renal vasodilation and glomerular hyperfiltration thatinitially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (59). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in the long term that causes chronic endothelial damage (60). With prolonged weight excess, there are increased urinary protein excretion, loss of nephron functions, and exacerbated HT. With the development of dyslipidemia and DM in the overweight and obese individuals, CRD progresses much more easily (59). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the etiology of CRD (61). Similarly, although some authors reported that alcohol was not associated with the CRD (61), it is not logical since various metabolites of alcohol circulate even in the blood vessels of the kidneys while damaging the renal vascular endothelium. Chronic inflammatory and infectious disorders may also terminate with the accelerated atherosclerosis on the renal endothelium (55). On the other hand, although CRD is mainly an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic endpoints of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (62). For example, the most common cause of death was the cardiovascular diseases in the CRD rather than the renal failure again (63). In another definition, CRD may just be one of the several atherosclerotic endpoints of the metabolic syndrome and SCD again (64).

As a conclusion, SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of the hardened RBC into the tissues. Although the similar mean age, associated thalassemia minors, and BMI and absence of smoking and alcohol, the higher total bilirubin value of the plasma, transfused units of RBC in their lives, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, and CRD in males may be explained by the dominant role of male sex in life according to the physical power that may accelerate systemic atherosclerotic process all over the body.

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ATHEROSCLEROTIC BACKGROUND OF CIRRHOSIS IN SICKLE CELL PATIENTS

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Abstract

Background: We tried to understand the presence of any atherosclerotic background of cirrhosis in patients with sickle cell diseases (SCDs).

Methods: The study was performed in the Hematology Service of the Mustafa Kemal University on SCDs patients between March 2007 and June 2012.

Results: The study included 256 patients with SCDs (127 females). Their mean age was 29.3 years. Cirrhosis was detected in 5.8% (15) of the SCDs patients without any gender difference (6.2% of females versus 5.4% of males, p>0.05). There were 15 (5.8%) patients with chronic obstructive pulmonary disease with a highly significant male predominance (3.1% versus 8.5%, p<0.001). Digital clubbing and pulmonary hypertension were also higher in males, but the differences were nonsignificant in between (4.7% versus 6.2% and 11.0% versus 12.4%, respectively). Similarly, the leg ulcers were significantly higher in males, too (5.5% versus 16.2%, p<0.001). The significant male predominance was also observed in stroke and smoking (3.1% versus 6.2%, p<0.05 and 3.9% versus 11.6%, p<0.001, respectively). There were 14 (5.4%) mortal patients during the five-year follow-up period (6.2% of females and 4.6% of males, p>0.05), and the mean ages were 31.0 and 26.8 years, respectively (p>0.05).

Conclusion: Probably cirrhosis is a systemic inflammatory process prominently affecting the hepatic vasculature, and an eventual accelerated atherosclerotic process is the main underlying cause of characteristics of the disease. SCDs are accelerated systemic atherosclerotic processes, too, and the higher prevalence of cirrhosis in SCDs patients may indicate the underlying atherosclerotic background of cirrhosis.

Key words: Atherosclerosis, metabolic syndrome, cirrhosis, sickle cell diseases

Introduction

Atherosclerosis may be the major underlying cause of aging of human beings that decreases quality and duration of lifespan. Probably it is an irreversible process that is accelerated by many factors. Smoking, dyslipidemia, obesity, diabetes mellitus (DM), hypertension (HT), and various systemic inflammatory or infectious disorders may be the accelerating causes of the systemic process. Such preventable causes of the systemic atherosclerotic process are mainly collected under the heading of metabolic syndrome (1-6). The syndrome is characterized by a group of metabolic risk factors including overweight, dyslipidemia, elevated blood pressure, insulin resistance, and a prothrombotic and proinflammatory state for the development of irreversible diseases such as obesity, HT, DM, coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), peripheric artery disease (PAD), and stroke (7). Similary, cirrhosis is also a frequent and continuously increasing cause of morbidity and mortality in the world (8), and it may not solely be a hepatic disease instead it may just be one of the terminal consequences of a systemic atherosclerotic process.

Sickle cell diseases (SCDs) are chronic endothelial dysfunctions that are characterized by sickle-shaped red blood cells which is caused by homozygous inheritance of the hemoglobin S (Hb S). Polymerisation of the Hb S distorts red blood cells into a sickle shape and decreases their elasticity. The polymerisation process probably takes place during the whole life, although its severity may increase during stressful conditions. The abnormal shape and decreased elasticity cause chronic endothelial damage terminating with an accelerated atherosclerotic process that may be the underlying cause of significantly shortened survival in SCDs patients (9). We tried to understand the presence of any atherosclerotic background of cirrhosis in patients with SCDs in the present study.

Material and methods

The study was performed in the Hematology Service of the Mustafa Kemal University between March 2007 and June 2012. All patients with SCDs were enrolled into the study. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography. Their medical histories including smoking habit, regular alcohol consumption, leg ulcers, and stroke were learnt, and cases with a history of one pack-year were accepted as smokers. A check up procedure including liver function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, an abdominal ultrasonography, a Doppler ultrasonography to evaluate the portal blood flow, an endoscopy to detect esophageal varices just in suspected cases, and a computed tomography of the brain was performed. Cases with acute painful crisis, infections, or inflammatory events were treated at first, and then spirometric pulmonary function tests to diagnose COPD and a Doppler echocardiography to measure the systolic blood pressure of pulmonary artery were performed on a silent phase. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70% (10). Systolic blood pressure of the pulmonary artery at and above 40mmHg during the silent phase was accepted as pulmonary hypertension (11). Clubbing is diagnosed by determining the ratio of distal phalangeal diameter to interphalangeal diameter which is required to be >1.0 and with the presence of Schamroth's sign (12,13). Cirrhosis is diagnosed with serum laboratory tests, ultrasonographic findings, esophageal varices, and ascites without any histologic procedure in the absence of any indication. Eventually, SCDs patients with pulmonary hypertension, leg ulcers, smoking, cirrhosis, COPD, clubbing, stroke, and exitus were detected and compared between the sexes. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 256 patients with SCDs (127 females and 129 males). The mean age of them was 29.3 ± 9.5 (14-59) years. There was not any patient with regular alcohol consumption. Cirrhosis was detected in 5.8% (15) of the SCDs patients without any gender difference (6.2% of females versus 5.4% of males, $p>0.05$) (Table 1). Although antiHCV was positive in two of the cirrhotic cases, HCV RNA was negative by polymerase chain reaction method in both of them. Histological diagnosis of cirrhosis was required in none of the study cases. On the other hand, there were 15 (5.8%) patients with COPD with a highly significant male predominance (3.1% versus 8.5%, $p<0.001$). Digital clubbing and pulmonary hypertension were also higher in males, but the differences were nonsignificant in between (4.7% versus 6.2% and 11.0% versus 12.4%, respectively). Similarly, the leg ulcers were significantly higher in males, too (5.5% versus 16.2%, $p<0.001$). The significant male predominance was also observed in stroke and smoking (3.1% versus 6.2%, $p<0.05$ and 3.9% versus 11.6%, $p<0.001$, respectively). On the other hand, there were 14 (5.4%) mortal patients during the five-year follow-up period without any significant gender difference (6.2% of females and 4.6% of males, $p>0.05$), and the mean ages were 31.0 and 26.8 years, respectively ($p>0.05$) (Table 2).

Table 1: Characteristic features of the sickle cell cases

Variables	Prevalence	Mean age (year)	Female cases	Male cases	*p*-value
Pulmonary hypertension	11.7% (30)	30.4 ±10.9 (19-56)	11.0% (14)	12.4% (16)	ns*
Leg ulcers	10.9% (28)	*35.7 ± 7.6 (17-58)*	*5.5% (7)*	*16.2% (21)*	*<0.001*
Smoking	7.8% (20)	*33.1 ± 9.3 (21-54)*	*3.9% (5)*	*11.6% (15)*	*<0.001*
Cirrhosis	5.8% (15)	33.6 ±12.5 (19-56)	6.2% (8)	5.4% (7)	ns
COPD†	5.8% (15)	*35.0 ± 8.7 (23-54)*	*3.1% (4)*	*8.5% (11)*	*<0.001*
Clubbing	5.4% (14)	36.1 ±12.1 (21-56)	4.7% (6)	6.2% (8)	ns
Stroke	4.6% (12)	*32.5 ± 9.2 (17-47)*	*3.1% (4)*	*6.2% (8)*	*<0.05*

*Nonsignificant (p>0.05) †Chronic obstructive pulmonary disease

Table 2: Features of the mortal patients

Variables	Female cases	Male cases	*p*-value
Prevalence	6.2% (8)	4.6% (6)	ns*
Mean age (year)	31.0 ±10.6 (19-45)	26.8 ±7.1 (19-39)	ns

*Nonsignificant (p>0.05)

Discussion

Probably cirrhosis is a systemic inflammatory process prominently affecting the hepatic vasculature, and an eventual accelerated atherosclerotic process is the main underlying cause of characteristics of the disease. The origin of the inflammation is unclear but aging, smoking, regular alcohol consumption, local or systemic inflammatory or infectious processes, and excess weight may be the major ones of the several possible causes. The inflammatory process is enhanced by release of various chemical factors by lymphocytes to repair the damaged hepatic tissues, especially endothelial cells of the hepatic arteriols (14). Due to the continuous irritation process of the endothelial cells in the case of aging, smoking, regular alcohol consumption, local or systemic inflammatory or infectious processes, or excess weight, prominent changes develop in the architecture of the hepatic tissue, since the chronic inflammatory process of the endothelial cells terminates with atherosclerosis, tissue hypoxia, and fibrosis. Metabolic abnormalities such as dyslipidemia, hyperglycemia, and insulin resistance cause various cellular stress responses that induce tissue inflammation and immune cell activation, which in turn exacerbate the atherosclerotic process (15). Although cirrhosis is mainly an accelerated atherosclerotic process of the hepatic vasculature, there are several items of evidence about existence of an associated systemic endothelial inflammation. For example, there may be a close relationship between cirrhosis and CHD, COPD, PAD, chronic renal disease, and stroke probably due to the underlying systemic atherosclerotic process (16). Additionally, most of the mortality cases in cirrhosis may actually be caused by cardiovascular diseases, and CHD may be the most common one among them (8). Similarly, beside the digital clubbing, pulmonary hypertension, leg ulcers, stroke, and COPD like atherosclerotic end-points, cirrhosis is just one of the final consequences of the SCDs, as accelerated systemic atherosclerotic processes, in the present study.

Both the frequency and complications of cirrhosis are increasing in the world. For example, cirrhosis and chronic liver disease were the 10th leading cause of death for men and the 12th for women in the United States in 2001, killing about 27,000 people each year (8). Although the achieved development of health services worldwide, the increased mortality and morbidity of cirrhosis may only be explained by aging of the human being and increased frequency of excess weight in the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to a third of the world population, and it has become the most common cause of chronic liver disease even in children and adolescents (17,18). The recent rise in the prevalence of excess weight likely explains the NAFLD epidemic worldwide (16). NAFLD is a marker of pathological fat deposition combined with a low-grade chronic inflammatory state, which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerotic process (17). NAFLD shares many features of the metabolic syndrome as a highly atherogenic condition, and may cause hepatic inflammation and liver cell injury especially at the endothelial level. Beside terminating with cirrhosis, NAFLD is associated with a significantly greater overall mortality as well as with an increased prevalence of cardiovascular diseases (18). Authors have reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased carotid artery intimal medial thickness as the reliable markers of subclinical atherosclerosis (18), so NAFLD may also be a predictor of cardiovascular disease (19,20). NAFLD and cirrhosis may be considered as the hepatic components of the accelerated systemic atherosclerotic process, metabolic syndrome, and hepatic fat is highly correlated with all components of the syndrome (21). On the other hand, the systemic inflammatory effects of smoking on endothelial cells is already known with Buerger's disease and COPD (7). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic inflammatory and eventual atherosclerotic process in smokers. The inflammatory and eventually atherosclerotic effects of alcohol is prominent in hepatic endothelium probably due to the higher concentrations of its metabolites in liver. Similarly, aging may be another but unpreventable cause of systemic atherosclerotic process that prevents adequate tissue repair. The prevented adequate tissue repair may be a significant cause of the increased risk of cancers in elders, since immune cells cannot eradicate the malignant ones effectively due to the prevented adequate tissue circulation. Chronic inflammatory or infectious disorders may also terminate with an accelerated systemic atherosclerotic process (14). For example, chronic HCV infection had raised carotid intima-media thickness, indicating a direct effect of infection, and hepatic function normalisation with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (14).

Hb S causes red blood cells to change their elastic biconcave disc shape to a hard sickle shape especially during mild, moderate, and severe stresses. The red blood cells can take their normal elastic shapes later, but after repeated cycles of sickling and unsickling attacks, they get a permanent sickle shape with a loss of elastic motion ability that is especially important during the passage between the endothelial cells. So they cause damage on the vascular endothelial cells terminating with a chronic endothelial inflammation. Because of the lifelong duration of the chronic endothelial inflammation, an accelerated atherosclerotic process develops all over the body in SCDs patients. Although the chronic inflammatory process is exaggerated during infections, operations, or depressions like various stresses, it is usually present during the whole lives of the patients. The chronic process is usually shown by a permanent leukocytosis and thrombocytosis even in silent phases of the patients (22). The adverse effects of neutrophils on endothelium are of particular interest with regard to CHD and stroke in SCDs. For example, leukocytosis during the silent phase was an independent predictor of the severity of the disease in a previous study (23), and it was associated with the risk of stroke in another study

(24). On the other hand, due to the accelerated systemic atherosclerotic processes, SCDs may be a useful model to show the end results of systemic atherosclerosis seen with the metabolic syndrome even in early age groups (9). The very high prevalences of cirrhosis (5.8%), COPD (5.8%), digital clubbing (5.4%), pulmonary hypertension (11.7%), leg ulcers (10.9%), stroke (4.6%), and exitus (5.4%) even in the early age group (29.3 years) may be a good sample to show some end-points of the systemic atherosclerosis in the present study.

As a conclusion, probably cirrhosis is a systemic inflammatory process prominently affecting the hepatic vasculature, and an eventual accelerated atheroscerotic process is the main underlying cause of characteristics of the disease. SCDs are accelerated systemic atherosclerotic processes, too, and the higher prevalence of cirrhosis in SCDs patients may indicate the underlying atherosclerotic background of cirrhosis.

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THE NOCTURNAL KISSING OF AN ANNOYING MOSQUITO; UNUSUAL INSECT BITE REACTION, A CASE REPORT AND A LITERATURE REVIEW

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Abstract

Insects represent more than half of all known living organisms in the world. Both human beings and insects share a common biodiversity and the influence of insects on human life is enormous. They share an intimate relationship in which human beings are both benefitted and harmed. Insects inflict harm by stinging, biting or transmitting diseases. Rarely, humans are harmed by inadvertently coming in contact with the toxin of an insect.

Insect dermatitis is characterized by tingling and burning within 10 minutes of contact, and sometimes the incurred dermatitis is a self-healing condition. Such cases usually happen while asleep when there is a lag time between the crush of the insect and waking up in the morning. A case while sleeping, heard the insect fly around her bare chest, in summer time, and on waving it away instinctively while sleeping, and the insect had been crushed on her bare upper chest skin, incurring a subsequent skin reaction without the typical red bite mark followed by an evolving burning ulcerative skin lesion, that took a while to subside and heal completely.

Key words: insect bite, crash, skin reaction.

Introduction

Insects play a role in humans' life as they have in common some biodiversity. They are active and thriving mostly in the summer and tropical climates. Sporadic cases of insect bites are seen in any season when the insect is active, but large outbreaks occur particularly during the summer months where accumulation of rubbish and dirt could cause their breeding to flourish and be responsible for epidemic outbreaks as they feed on the vicinity of decaying organic matter. Moreover, bright and dim lights can attract insects to human flesh in the dark over a distance of many miles. Having said so, some human beings are more appealing and attractive to insect bites while others are not. This could be attributed to certain blood group as has been postulated by some scientists. This is determined by differences in volatile chemicals and the body odour that is created by the human body and which is detected by mosquitoes and appeals as attractive to mosquitos, through their olfaction (Fernández-Grandon et al, 2015).

For instance, studies showed that pregnant ladies, ladies with great body mass, and tall men, are more appealing to mosquitos' bites. While, for children the tendency to be bitten, is not clear if it is inherited from their parents or not (Logan et al, 2010). Additionally, those who consume garlic, vitamin B or beer would repel mosquitos (Fernández-Grandon et al, 2015).

Blood feeding is crucial for most female mosquito species' life cycles, as it provides the necessary proteins for egg production. Some insects do not bite or sting, they just wander at night and approach humans while sleeping causing nuisance. Many times, the patients are unaware of the encounter with the insect as it occurs at night during sleep when the insects are crushed in a reflex action. Since it is often noticed after getting up in the morning and because of the time lag between contact and noticing the signs, it is referred to as 'wake and see' disease, in Nigeria locally. Sometimes, insects can be transferred by clothes and sheets to our concealed remote parts of bodies. Insect's toxins are released on crushing onto the skin due to reflex brushing away of the insect. Exposed areas of the body such as the face, neck and arms are

such as the face, neck and arms are most affected, however, chest, abdomen and legs are not immune to the attack of insect's bite.

The hypothesis is that it could be due to the crushed insect releasing its secretion, toxins, and excreta which lead to skin irritation, due to direct contact. Various names are given to different insects and it is suggested the use of the term dermatitis as the most accurate description as the other terms are misleading.

Greater penetration of toxin might be facilitated by wet and sticky skin in areas of high humidity. Symptoms typically begin between 24 and 48 hours after contact with the insect, with the most common being itching and burning or smarting sensation.

The evolution of the lesion depends upon the severity of the skin reaction; dermatitis, may range from mild to severe fulminate forms.

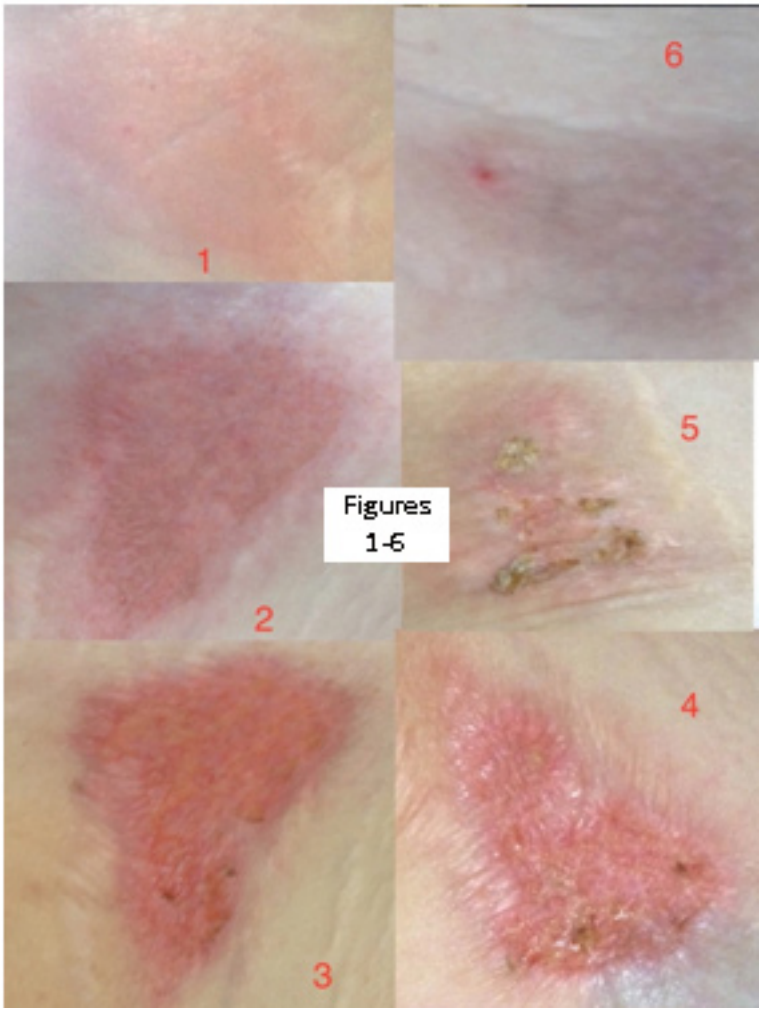
Mild cases resolve after two days with only erythema and no other lesion. Moderate cases develop significant vesiculation after four days, after which the vesicles start to dry out and exfoliate in about 7-8 days. Cutaneous necrosis can also occur.

The lesion in this case had evolved through an initial itchy erythematous phase followed by vesiculation and subsequent crusting and desquamation, leaving an open ulcerative oozing painful area. Typical mosquito bites appear as circumscribed areas of edema in the center of which a red bite mark may be seen. Complications are due to the direct effect of the toxin and secondary infection. Post inflammatory hyperpigmentation (PIH) and scarring can occur.

The patient should be managed like that of acute irritant dermatitis. The principles of management include immediate removal of the toxin and prevention of the effect of the toxin. This can be done if the patient comes in contact with the insect and seeks immediate medical attention. But most of the patients reach the hospital after the lesion has occurred.

Case report

A 45-year-old lady presented with a sudden abrupt painful and burning cutaneous lesion on the right upper quadrant of the breast (Figure 1). Approximately 2 weeks previously, while she was asleep, she heard and felt a mosquito buzz close to her chest skin. It was summer time and people tend to wear light dress due to the hot humid weather along with the continuous power cuts in the capital; Tripoli. She just tried to wave away the nuisance fly and recalled feeling it crushed upon her skin, in an attempt to keep the fly away and continue her sleep. On waking up in the morning, the skin was very uncomfortable, red and started to show some local skin reaction that had extended slowly beyond the stung area, without a central bite mark (Figure, 1, 2). It was associated with severe burning sensation and few days later it started to ooze clear serous fluid which made the lady feel uncomfortable ad in great as she could not tolerate her clothes on it (figures, 3, 4). She kept applying a clean sterile gauze to avoid the continuous rubbing and friction of her skin with the brassiere and her tops. A few weeks later, she noted a development of a 3 x 2.5 cm, macerated area with an ulcer of slightly raised edges along with surrounding erythema on the skin (figures 3, 4). The patient kept applying antibiotic cream (fusidic acid cream) to no avail. It was painful and with a burning sensation she affirmed.



Figures 1-4, showing different stages of the skin inflammations.

Figures 5-6. The patient experienced an excellent self-healing response, with some PIH.

During the next several weeks, the lesion kept oozing with painful burning sensations (figure, 3, 4). There were no other associated comorbidities. The lady is fully healthy with no chronic medical history. There were no mucocutaneous lesions noted. There was no lymphadenopathy. The lesion stayed as such for a complete month and then started to recover and heal up with PIH, as the photo can demonstrate (figure, 5, 6). The area faded with time and the skin made a full recovery.

Differentials in this unique case could be contact dermatitis, brown recluse envenomation, pyoderma gangrenosum. However, tracing up the history would rule out the stated differentials.

Discussion:

Mosquito bite and skin reactions are extremely common in Libya especially in the summer time, where rubbish keep piling up out in the street, neighbourhood areas and with the continuous power cuts in the capital, life becomes miserable, intolerable and unbearable. In fact, it causes all sorts of insects to breed and fly around mankind and bite.

Mosquitoes are nocturnal nuisance visitors, which suck blood for their food. Insects mostly are active from one hour after sunset, dawn till midnight.

Allergic reactions can vary and in children are mostly severe and can be fatal. This is because children still have not had the time to build up the required immunity yet. Normally, a human body builds up immunity to certain allergens over a period of time, and due to these children may experience severe allergic reactions to mosquito bites. Additionally, mosquitoes are selective in their bites to humans, where some humans are more likely to get bites than others. It has been explained that people with blood group O are nearly twice as frequently as those with blood group A to be stung. The lady was blood group O, and overweight with a BMI reading of 27.7. This was explored further and explained according to humans secretions and productions of CO2 due to basal high metabolic rates which consequently would attract mosquitoes to certain humans specifically and make them preferential over others. Also, genetics could play a role (Seda J and Horrall S, 2019).

Mosquito bites can inflict different ranges of widespread and disseminated cutaneous eruptions to localized blisters, ulcers, and extremely itchy papules and nodules. After a mosquito bite, an allergic reaction occurs against the protein in the salivary components of the mosquito, sometimes leading to systemic reactions in rare cases. Those released toxins serve the mosquito's purpose for feeding by inflicting local vasodilation, anticoagulation and antiplatelet functionality. In sensitized patients, a local spectrum of various reactions, of species-specific, would be appreciated (Seda J and Horrall S, 2019).

The insect bite noticeably triggered an allergic reaction and, in this case, a large local reaction incurred and resulted in a swelling that extended beyond the stung site. The patient was deeply concerned as it was looking like an unhealed skin ulcer for a month, and was extremely painful and burning as the patient exclaimed. She does not have any comorbidity associations.

Mosquito bites are skin irritating reactions, which usually resolve spontaneously without intensive medical care. However, in certain situations, mosquito bites may form a more vicious prolonged reaction (Tatsuno et al, 2015 and 2016).

Conclusion

The treatment should be individualized and tailored to suit the patient. Cooling agents such as calamine, camphor and local anesthetics like topical preparations of camphor, lidocaine, and benzocaine have been used for temporary relief of itching and burning sensations. Silver sulphadiazine has been described to give some relief of symptoms. Its antibacterial action is an added advantage.

The cornerstone of treatment is a combination of a topical steroid with an antibiotic. It has been found to be more effective than topical steroids alone. Corticosteroids act by a variety of mechanisms of action on the skin such as suppression of histamine release and mast cell inhibition. After a month, the lady made a full recovery (figure, 6).

Also, it was in a difficult area, thus keeping dry would be the ultimate goal to achieve healing and complete recovery. She was applying gauze on a regular basis to avoid friction and ongoing breakage of the skin.

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