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This issue of the journal has paper that discusses issues related to infant feeding , surgical infection and sickle cell disease

Dorri et al., looked at the knowledge and infant feeding practices' Influence on Arab Immigrant Mothers' Initiation and Exclusive Breastfeeding.Breastfeeding is known to provide health benefits for newborns and breastfeeding mothers. The World Health Organization and Health Canada recommend exclusive breastfeeding for the first six months of an infant's life. However, the rates of exclusive breastfeeding practices among Arab immigrant mothers are lower when compared with rates for non-immigrant Canadian mothers and mothers in the immigrants' countries of origin.. An analysis of the qualitative narrative data indicated that knowledge and traditional infant feeding practices primarily influenced Arab immigrant mothers' initiation and exclusive breastfeeding practices. The findings from this study have the potential to facilitate supportive culturally safe and sensitive interventions that are tailored to address Arab mothers' breastfeeding concerns and needs, so that exclusive breastfeeding might be promoted within this population in Canada. Further, the research will provide information needed for addressing some key challenges relating to culture, religion, and the healthcare system.

Mohamed et al., did a review to gain a better understanding of the relationship between uncontrolled blood glucose and the odds of developing a Surgical Site Infection among cancer patients. A database search (which engaged PubMed, Medline, Cumulative Index to Nursing and Allied Health Literature and The Cochrane Database of Systematic Reviews) was completed using the keywords: 'surgical site infection' or 'surgical wound infection' OR 'SSI' AND cancer or neoplasms OR oncology OR tumor OR malignancy AND diabetes OR hyperglycemia AND risk factors. Twenty-seven studies met the inclusion criteria to be included in this review.

The odds ratio for history of diabetes or hyperglycemia and SSI following cancer surgery varied across studies. This is likely explained in part by the fact that some types of surgery are more invasive than others, are more lengthy and certain involve areas of the body that are more prone to infection. The study with the highest rate of SSI (62.1%) was among patients with oral cancer and the study with the lowest rate of SSI (3.1%) was among patients with spinal cancer. The literature review results suggested an association between SSI and patients with a history of diabetes mellitus or hyperglycemia.

Helvaci et al., did two studies related to sickle cell disease, in the first paper they tried to understand whether or not there is a significant association between avascular necrosis (AVN) and atherosclerosis in sickle cell diseases (SCD). The study included 434 patients. 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 hardened RBC into the tissues. Although the higher smoking and alcohol-like strong atherosclerotic risk factors and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like obvious atherosclerotic consequences in male gender, AVN was not higher in them, significantly. In another definition, AVN may not have an atherosclerotic background in the SCD. In the second paper they tried to understand whether or not there is a significant relationship between auto splenectomy and atherosclerosis in sickle cell diseases (SCD). The study included 434 patients. 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 hardened RBC into the tissues. Although the higher smoking and alcohol-like strong atherosclerotic risk factors and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like obvious atherosclerotic consequences in male gender, autosplenectomy was not higher in them, significantly. In another definition, autosplenectomy may not have an atherosclerotic background in the SCD.

KNOWLEDGE AND INFANT FEEDING PRACTICES' INFLUENCE ON ARAB IMMIGRANT MOTHERS' INITIATION AND EXCLUSIVE BREASTFEEDING

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Abstract

Breastfeeding is known to provide health benefits for newborns and breastfeeding mothers. The World Health Organization and Health Canada recommend exclusive breastfeeding for the first six months of an infant's life. However, the rates of exclusive breastfeeding practices among Arab immigrant mothers are lower when compared with rates for non-immigrant Canadian mothers and mothers in the immigrants' countries of origin. Critical ethnography was used to explore the contextual factors that influence the initiation and exclusive breastfeeding practices by Arab immigrant mothers in Canada. Critical ethnography, using individual in-depth interviews was employed to explore the breastfeeding practices among immigrant Arab mothers in Alberta, and factors influencing the mothers' decision or ability to breastfeed exclusively. Exploratory and open-ended questions were used. Face-to-face interviews were conducted with ten women for 1 and 1 and ½ hours . Participant selection criteria included Arab mothers who were within six months postpartum, aged 18–49 years, and who have resided in Canada for less than five years. An analysis of the qualitative narrative data indicated that knowledge and traditional infant feeding practices primarily influenced Arab immigrant mothers' initiation and exclusive breastfeeding practices. The findings from this study have the potential to facilitate supportive culturally safe and sensitive interventions that are tailored to address Arab mothers' breastfeeding concerns and needs, so that exclusive breastfeeding might be promoted within this population in Canada. Further, the research will provide information needed for addressing some key challenges relating to culture, religion, and the healthcare system.

Key words: Arab immigrant mothers, exclusive breastfeeding,

Introduction

Breastfeeding is universally recognized as the most appropriate method of infant feeding (1). It provides several health benefits for children, breastfeeding mothers, and for the community. WHO and Health Canada recommend that it be the only source of nutrition postpartum for healthy, full-term babies (2,3). This practice is known as exclusive breastfeeding and is defined as feeding infants human milk only, with no supplementation of any liquid or solids apart from vitamins, minerals, and medications for at least the first six months of an infant's life (4). Breastfeeding practices within Canadian society are considered a public health issue, due to the many associated health benefits and cost savings to health care (5,6,7).

Although breastfeeding initiation rates in Canada are high immediately after birth (90.3%), by 6 months of age, only 13.8 % of babies are breastfed exclusively (8). There is some evidence that new immigrants in Canada are more likely to initiate breastfeeding than their Canadian-born counterparts (9,10). However, by 16 weeks post-partum immigrant mothers are significantly less likely to opt for exclusive breastfeeding (50.7%) in comparison to non-immigrant Canadian mothers (70.9%) and mothers in the immigrants' countries of origin (11).

In Arab society, customs around childbearing are informed by the common language (12), the religion of Islam and family traditions. Fifty-five percent (55%) of Arabs who live in Canada are followers of Islam(13). Breastfeeding an infant is considered the child's God-given right, endorsed by the Qur'an (Islamic sacred book) and the Hadith (Islamic traditions), and is considered a spiritual act by Muslims (14, 15). These teachings influence individuals' breastfeeding perceptions and actions (14).

Overall, breastfeeding is a common practice among Middle Eastern mothers with high initiation rates in Kuwait (18), Lebanon (19), and Saudi Arabia (20). However, practicing exclusive breastfeeding for six months is less common among Arab mothers (21) with low exclusive breastfeeding rates. In the cultural context, Arab mothers seek to breastfeed their children for at least two years following birth (15). However, it is a common practice among Arab mothers to stop breastfeeding earlier. Experiencing breastfeeding problems is a key reason mothers quit breastfeeding early (22, 23, 24). Arab mothers' perceptions of insufficient breastmilk production or their uncertainty regarding the amount of milk the infant receives are significant factors contributing to the decision to continue or not continue with exclusive breastfeeding (21, 25). In various studies conducted in Arab countries, the mothers were found to be concerned about their inherited inability to produce milk, having "bad milk", and nutritional value or supposed health risks of colostrum (26, 27, 28).

Family traditions and beliefs may influence breastfeeding practices (14). The practice of introducing sweetened water and other non-milk supplementation early in an infant's life is especially common in Arab culture (29). Use of water or other supplementation within six months of childbirth has been associated with a reduction of frequency of breastfeeding, delay of lactation onset, rise in infant weight, and lower duration of breastfeeding (30). During breastfeeding, mothers are encouraged to take the herb black seed also known as blessed seed (Nigella Sativa) (31). Some Arab mothers, particularly in Egypt, are offered "mughaat" which is a combination of powdered fenugreek seeds and nuts fried in butter and sugar (31). Additionally, mothers are encouraged to take a lot of broth and soup to improve milk production (32).

Understanding cultural values, beliefs, and practice of breastfeeding among Arab mothers during the postpartum periods is necessary for the initiation and sustainment of successful exclusive breastfeeding. Therefore, the purpose of this qualitative research is to explore the social and cultural contexts that influence the initiation and exclusive breastfeeding practices among Arab immigrant mothers. In the current literature, few studies have examined breastfeeding among immigrants in Canada (i.e., the majority of studies reviewed were done in the United States and European countries). Secondly, an extensive search of the literature failed to identify an in-depth understanding of contextual factors by healthcare providers (HCPs) that influence Arab mothers' breastfeeding practices in Canada.

Critical ethnographic research is needed to provide in-depth information about Arab women's perceptions of breastfeeding which can then be used to develop health education programs and services that will support the initiation and sustainment of exclusive breastfeeding practices among Arab mothers. The following research questions guided this exploratory ethnographic research.

How do Arab mothers conceptualize exclusive breastfeeding practices, and utilize available health care services to support infant breastfeeding and exclusive breastfeeding? How do contextual factors influence Arab mothers' breastfeeding experiences and decisions regarding exclusively breastfeeding their infant and what services or strategies could promote Arab mothers' breastfeeding and exclusive breastfeeding? In this paper, Arab mothers' knowledge and infant care practices influence on their decisions regarding exclusive breastfeeding is described.

Methodology

Theoretical Framework: Critical Social Theory (CST)

The theoretical foundation for this qualitative study was based on CST. CST emphasizes language, power relations, and the social processes associated with knowledge. HCPs can use the communicative interpretations of CST to investigate and reduce communication failures that result from unconfirmed, unintentional, or erroneous assumptions and cultural misunderstandings between HCPs and patients (33). Inadequate communication may have serious negative consequences on the immigrant mothers, including increased psychological stress and misunderstanding of health information and medical advice (34). The language barrier was the most pervasive barrier to health care access and quality of care for Arab immigrants(34, 35). Adopting CST methodology empowers Arab mothers to have their voices heard and enhances their communication skills by freely sharing their experiences using the language of their choice.

In this study, Carspecken's critical ethnographic method (1996) is used as immigrant women of Arab origin who come from cultures that are significantly different from those in Canada. Further, due to their racial and cultural orientations, immigrant mothers are largely predisposed to discrimination which inhibits their level of access to opportunities (35). Findings from the various studies highlight the historical marginalization of visible minorities in Canada, immigration status, gender relation, and cultural values creating a background that influences infant feeding practices in recently immigrated mothers (9, 10). The critical ethnography, which has CST as its theoretical foundation, facilitates Arab mothers to have more authority to express their perspectives, challenges, and desires, address unequal power relations, and to gain a new understanding of factors that influence their health care practices through empowerment and critical thinking.

Participant selection criteria included Arab mothers living in a metropolitan city in western Canada; who were within six months postpartum; older than 18; thus able to provide informed consent; and residents of Canada for less than five years as the duration of immigration influences breastfeeding initiation and exclusive breastfeeding (36). Participants were excluded if their babies were born before 37 weeks of gestation or if they were caring for an infant with congenital abnormalities. As a significant place for attendance by members of the Arab community, key personnel in Postpartum Community Services (PCS) were identified. Detailed information about the study, its purpose, and eligibility criteria along with the first author (RD)'s contact information was shared with Arab mothers. A list of potential participants was shared with the RD after their permission was obtained. Purposive sampling and snowball sampling techniques were used for recruiting. Recruitment was ongoing until data saturation was reached after 10 interviews.

All mothers who enrolled in the study were interviewed face-to-face within six months of their infant's birth at their homes with minimal distractions. Participants were provided complete information about the research. They were given the choice to be interviewed in Arabic and English. All of them chose to be interviewed in Arabic. RD engaged in reflexive journaling during the research process to achieve reflexivity paying careful attention to her social, cultural, and professional positioning and how they influenced her actions and thoughts in the field and interpretation of the data.

Data Collection and Data Analysis

Carspecken's (37) five-stage process for doing critical ethnography was followed. Individual in-depth interviews, using a semi-structured questionnaire with open-ended questions such as "Tell me about the beliefs and values that influence your decision to participate in breastfeeding" and "what comes to your mind when I say "exclusive breastfeeding"? were used. Additional probing questions were used to explore, illuminate, and clarify Arab mothers' breastfeeding experiences in greater depth.

Prior to starting the recorded interviews, the participants' physical environment, behaviors, activities, social interactions, timing, tone of voice, gestures, body movements, and facial expressions were observed. The preliminary reconstructive analysis was used for analyzing the primary record and reconstructing meanings from the observations collected in the first-stage. When reviewing the primary record, RD identified relationships between meaning reconstruction, power, and roles that influence participants' breastfeeding experiences.

The interviews were conducted for approximately 60 to 90 minutes in duration in Arabic, the participants' primary language and, with permission from participants, were audio recorded. The recorded interviews were translated into English. Data analysis included three aspects: description, analysis, and interpretation of culture the Arab mothers shared. Data coding and categorization were undertaken using NVivo software. Data were coded into categories and themes using low-level coding to group initial data. High-level coding of abstraction was then generated by linking categories to provide coherence and meaning to themes. Throughout the research process, the data were revisited several times and reconceptualization in order to move beyond the categorisation of data to the more in-depth synthesis and construction of these meaning fields. To further achieve trustworthiness, credibility, transferability, dependability, and confirmability of meaning reconstructions, three participants were interviewed again for member checking. Additional information from these interviews was incorporated into the research results.

Results

Four primary components of support emerged from the analysis of the participant interviews: knowledge, family, religion, and infant feeding practices. Because a full discussion of all four themes would be very lengthy, this paper is limited to knowledge and infant feeding practices. Family and religion are presented in a separate paper. All participants' names used in this paper are pseudonyms.

Knowledge

The findings of the study indicated that all participants had some knowledge regarding breastfeeding. However, they did not have specific knowledge about exclusive breastfeeding, nor were they aware of the recommended number of months to exclusively breastfeed. Six out of ten Arab mothers breastfed their infants; none of them practiced exclusive breastfeeding for six months as recommended by the WHO and Health Canada. They provided fluids other than breastmilk to their baby without knowing the negative impact of these fluids on breastfeeding frequency and duration. When asked about exclusive breastfeeding, the participants had never heard of it or mistranslated and misunderstood the phrase as "only the mother feeding the baby". The participants of this study indicated that they were never told by their family members or HCPs back home or in Canada about the practice of exclusive breastfeeding. Lena put forth that the concept of exclusive breastfeeding was unfamiliar to Arab mothers: "This terminology does not really exist in the Arab world"

Five participants expressed their concern that the practice of exclusive breastfeeding would not be sufficient for a baby's growth. Rather, they supported the introduction of formula as a complement to breastmilk to meet the baby's demands and promote their growth. Eman voiced her thoughts on this subject: "I learned that breastmilk is better than formula feeding but not only breastmilk." Haneen feared that she may not have "enough milk" to fully feed the baby without supplements. "Based on my experience, I think it will be next to impossible to only breastfeed without formula feeding. Without the formula, my baby will lose weight and her health will deteriorate", she added.

Misinformation about the nutritional value of the formula in comparison to breastmilk may have influenced breastfeeding practices among Arab mothers. Rania voiced her opinion on breastmilk versus formula saying: "In general, I think that formula is also very good. I do not think there is any difference between the two." Some of the mothers conveyed the belief that formula milk contains more nutrients than breastmilk. This was evident in the statement by Shaima who said: "When they [mothers] look at the formula feeding label, they see all the vitamins and they think they do not have it in their milk." Consequently, their lack of knowledge and misinformation inhibited their ability to make informed decisions about optimal feeding options for their infants.

Four participants spoke about the possible negative impact of formula feeding on infants, for example, diarrhea, constipation, stomach gas and discomfort, and lack of immunity. Four of ten participants mentioned that formula supplementation was advised by the doctors and nurses to maintain the child's growth, weight, and hydration. Maya mentioned that she was sent to the hospital emergency room for the child's weight loss where the doctor advised her to formula feed. Maya said, "I think it is the doctor's decision, it is not the mother…if a mother cannot breastfeed for more than two days, they would immediately give formula feeding." These mothers seemed to believe that by combining breastmilk and infant formula, their babies had better outcomes in terms of weight gain and overall wellbeing.

The participants acquired knowledge through a variety of ways including handouts in clinics, doctors' offices, and the hospital, internet, DVDs, and incidental (non-scheduled) teaching by nurses, lactation consultants, and dietitians. However, the mothers asked for more information about aspects such as feeding, positioning the baby to facilitate latching, how often to feed, and whether to combine breastfeeding with formula feeding. They also had questions about what foods they should eat to stimulate milk production, how to care for engorged breasts and sore nipples, and whether lack of breast engorgement was an indicator of lack of milk. What they were advocating for, although they did not use the term, was an expansion of the nurse's role to include these components of care more completely. Receiving a brochure that included the information they needed was not sufficient since it did not give the nurses the opportunity to ensure that their clients understood the relevant information. For example, Fatima suggested: "It would be better to inform mothers about the benefits of breastfeeding… may be teaching mothers about the latching positions."

Even when knowledge was made available, a major barrier to its acquisition was language. Some of the mothers spoke about the language barrier as an obstacle to understanding the information given by the HCPs. Lena said: "I do not speak English, so it was hard for me to understand the nurses." Their lack of comprehension was compounded further by the use of medical terms by the HCPs preventing even those who could speak English from really understanding. For instance, Sara explained: "My English is very poor, and I could not understand the medical terms." This lack of ability to communicate can be frustrating and worrying, and indirectly inhibit mothers' ability to breastfeeding.

Infant Feeding Practices

The participants came from a variety of Middle Eastern countries with different cultural beliefs and practices pertaining to the production of breastmilk and its quality, and introduction of foods in addition to breastmilk.

Traditionally in Arab societies, water, herbs, formula milk, medicinal liquids, and supplements are given to babies at various stages of infancy. As Sara explained: "In our culture [in Iraq], we give our babies sugar dissolved in water in the first three days of the baby's life to clean their stomach from bacteria and the amniotic fluids that were swallowed inside the mother's womb." Maya, who is also from Iraq, cited the practice of giving herbs such as anise meant to alleviate gas pains. Maya chose not to give this herb, despite her grandmother's insistence, based on advice she received from Canadian doctors and nurses. This is an example of conflict, which can arise between cultures that have different beliefs and practices. Giving herbs is also the practice in Egypt although they are started after the first month. It is believed that products such as anise, licorice, fennel, etc. help to calm and relax the babies.

Giving water in addition to milk was also a practice among Arab mothers in this study, although the reasons were not always clear. In Canada, the participants reported that the nurses told them not to give water to their babies although Haneen was told she could begin giving water when her baby was six months old. The advice to withhold water created a conflict for Rania. While in Canada, she chose not to give water to her baby. However, when she visited Tunisia, she was reprimanded for not giving water to the baby. Most, but not all, of the participants said they were likely to hold to traditional beliefs and follow the traditional practice in their decision to give or not to give water. Other participants stated that they also gave their babies medicinal liquids and supplements. For example, Fatima and Asma started giving their children Gripe Water right after birth to treat colic or stomach discomfort.

Participants reported divergent practices related to the early introduction of solid foods in contradiction to the teachings in Canada where solid foods are not introduced until six months of age. Explaining the tradition she followed in Iraq, Eman said, "After turning three months old, I [normally] try to feed them things that we eat. I learned it from my family." Other participants, like Shaima and Fatima, mentioned that they start having their infants taste food within the first 40 days of the baby's life, so the infant can "get used to it". Also, right after birth, they start feeding infants boiled milk, dates, and some fruits in order to, as suggested by Shaima, provide extra nutrition and build up their immunity against food allergies. Fatima added that introducing solid foods can reduce picky eating habits in children.

All of the participants identified the quantity of milk they produced as a source of concern. In the absence of any method to measure the milk, some believed that the amount of milk was insufficient especially when their babies did not settle readily or slept only short periods between feedings. Factors that affected the production of breastmilk included infant sucking difficulties, mother's fatigue, stress, diet, bottle preference by the baby, and supplementation with formula. A number of interventions were initiated in response to these factors. Shaima, who practiced both breastfeeding and formula feeding due to low milk production, argued, "I tried to breastfeed her [the baby] for the first month; however, the milk secretion got lower slowly … so, I had to give her formula milk." Similarly, Rania struggled with getting her son to latch on properly, she also felt that her milk supply was inadequate for him. Although at first, Nadia was able to easily feed her baby, once her milk supply started to diminish, she chose to formula feed as well; now she just formula feeds. Lena contributed her baby's weight loss to the low milk supply which caused her to switch to formula feed.

Getting the baby to latch properly was one of the breastfeeding difficulties encountered by several of the mothers. Two reasons for this included nipple size (too large, too small) and incorrect positioning of the baby. Haneen said, "Due to my [big] nipple's size, the nurse gave me a nipple shield to make the sucking process easier for the infant." Eman emphasized: "A nurse actually helped and showed me how to put the baby in position for breastfeeding. Before that, I used to use only one position to breastfeed my baby." These mothers noted that the support provided by the nipple shield and the concurrent teaching by the nurses helped them to initiate breastfeeding.

Measures used to stimulate greater milk production included using a breast pump, feeding the baby on demand, medications, breast massage, application of warm cloth on the breast prior to feeding, and the mothers' diet. Asma explained: "I massaged my breast and put something warm on top of my breast to help increase the milk supply. It worked for a while, but I generally do not have enough milk." In relation to diet, Rania maintained that the amount of breastmilk she produced was dependent on the amount of milk that she drank. When these various interventions failed to achieve the desired result for at least eight of these mothers, they were advised by HCPs to supplement breastfeeding with formula feedings. Nadia described:

I breastfed her [the baby], but she always cried a lot and the nurse asked me to give her formula milk. The milk supply […] came out in such small doses. The nurse told me to give her the formula at night so that she sleeps, and I can rest too." However, some of the participants noted that supplementation with formula reduced the number of breastfeedings resulting in diminished milk production. Consequently, while some of the women continued with a combination of breast and formula feedings, others discontinued breastfeeding in favor of formula feedings only. None of the women continued with breastfeeding exclusively.

Other factors that influenced the participants' decision to breastfeed versus formula feed were convenience and finances. Breastmilk was readily available, free of contaminants, easy to store in the freezer without deteriorating, and inexpensive. Asma expressed her concern regarding the price of the formula: "Not everyone

can afford the financial status to provide formula milk." Haneen suggested: "It is better to breastfeed if a mother can, to save some money." On the other hand, Rania touched on the inconvenience of breastfeeding due to her inability to go out to work, or out to rest and relax.

Other potential negative outcomes of breastfeeding that were expressed by participants were related to body image. As Nadia stated: "It [breastfeeding] changes the breast's shape and makes it look saggy." Sara asserted: "Some mothers would rather choose style and clothes over their child's health because it is uncomfortable to wear stylish clothes while breastfeeding […] so the formula is the new trend." During the member checking, it was observed that there was general concern among some mothers with regards to the long-term effects of breastfeeding on their physique and social life. Lena confirmed: "I know that many women, including my sister, would not breastfeed because they do not want their breasts to sag."

Discussion

Knowledge

The level of knowledge among the Arab mothers with regards to exclusive breastfeeding influences delayed initiation and early cessation of breastfeeding. Emmanuel (38) reported that inadequate knowledge about exclusive breastfeeding may cause mothers to turn to a combination of breastfeeding and formula feeding or formula feeding alone. This is especially true when the mothers perceived that their milk supply was inadequate for their babies' needs. Studies related to the evaluation of the nature of breastfeeding decisions (39, 40, 41, 42) suggest that mothers are predisposed to make poor choices when there is a lack of adequate knowledge or family and spousal support. Moreover, mothers with lower education backgrounds often reported more misconceptions regarding breastfeeding and formula feeding (43). According to Wandel et al.(24) improving the level of maternal education is positively linked to the enhancement of infants' health outcomes. Despite several Arab mothers in this study having a post-secondary education, a significant number of them did not follow the six-month requirement for exclusive breastfeeding. Thus, Siggia and Rosenberg (44) suggested the need to adopt effective education strategies about the relative benefits of different breastfeeding methods.

In this study, Arab mothers with low milk supply as assessed by the HCPs in the hospital were advised to use formula milk to satisfy their infants. Such advice undermines the practice of exclusive breastfeeding especially if the mother does not know that giving formula negates exclusive breastfeeding (45, 46). One of the mothers in the study felt that the healthcare provider did not give her any option other than to introduce formula feeding to her baby. Others were reluctant to use formula supplementation but, after further discussion with the nurse, capitulated. De Almeida, De Araújo Barros Luz, and Da Veiga Ued (47) reported that many HCPs possessed theoretical expertise on breastfeeding, but they lacked the practical skills related to promoting breastfeeding. To better support exclusive breastfeeding, Chantry et al.(45) suggested that strategies should be sought to support breastfeeding and to avoid unnecessary formula supplementation. HCPs need to be better trained to implement strategies that promote exclusive breastfeeding.

Research has shown that mothers who have access to individualized breastfeeding support demonstrate more positive outcomes (48). Most of the Arab mothers in this study sought assistance from a range of sources including professionals in the health sector, lay people or both to increase their breastfeeding knowledge. A combination of these two approaches has been observed to deliver better outcomes in terms of exclusive breastfeeding achieving longer periods of exclusive breastfeeding as recommended by WHO and better health results for breastfed children(49).

The most used source of information pertaining to breastfeeding (except for their mothers) by the Arab mothers was the Internet which functioned as a complementary lay support system (49). Latcu et al.(48) reported the Internet's potential of offering personalized support to breastfeeding mothers during the early postnatal phase through professional websites that are linked to credible and verifiable health information and maintain accountability. The Internet helps mothers transcend the challenges of cost and isolation in access to health professional services (50, 51). In the context of exclusive breastfeeding, the Internet assists mothers to address breastfeeding problems, hence, increasing the potential to attain the six-month period. In this study, some mothers used Google search and YouTube to learn about breastfeeding practices, such as the positioning of the baby or evaluating the benefits of formula milk. Here again, the lack of English fluency can limit their ability to discern the validity of the information they access.

Issues relating to the poor quality of information from nurses or the lack of self-determination in breastfeeding practices were some of the key areas of concern. Professional education enhances the knowledge, skills, attitudes, and behaviors of the healthcare providers so as to value the significance of breastfeeding it should be implemented. HCPs involved in maternity care such as obstetrics, midwifery pediatrics and those in the family practice as well as lactation consultants, midwives, and nurses, etc. can highly impact the decision, desire, and ability of a breastfeeding mother to continue to breastfeed. Breastfeeding education programs that are provided online or in person, in-service presentations by trained health care professionals within the health care centers and clinical protocols developed by experts can be used to provide in-depth knowledge and skills pertaining to breastfeeding and lactation management among the health professionals. To address this problem, there is a need to undertake a collaborative approach involving both HCPs and immigrant mothers. Schools of nursing can promote breastfeeding by including its physiology,

benefits, challenges, cultural aspects, management, and evidence-based research outcomes in their curricula. An advanced practice nurse educator/instructor can provide experiential examples and demonstrations to nursing students that will enable them to provide more inclusive care.

Lack of English fluency among some of the participants created a communication barrier when explanations included unfamiliar medical and technical terms. This barrier needs to be addressed to effect progressive social change as identified in the CST. HCPs should, therefore, consider ways to appropriately communicate their knowledge to make it accessible to Arab women. Such a situation can be solved by providing more written information in the women's native language or having translators available. Furthermore, accessibility to trained bilingual (English and Arabic) staff with skills and knowledge covering all aspects of breastfeeding is needed. In addition, Arab mothers should be empowered to strengthen their English language skills to effectively access health care services and interpret breastfeeding-related information.

Infant Feeding Practices

The participants in this study displayed low adherence to the WHO and Health Canada's recommendation of exclusive breastfeeding infants for the first six months. Various studies by Jessri et al.(52), Millar and Maclean(25), as well as Oweis et al.(21) reported broad support in Arab cultures for use of supplementary feeding stemming from concerns about inadequate milk to meet the nutritional needs of their children. Although these feeding practices have been scientifically determined to inhibit the process of breastfeeding (53), they were carried out by some of the Arab mothers in this study. This implies a strong impact of cultural socialization on interpretations and perceptions held by the mothers with regards to milk supply and unquestioning acceptance of social norms. The CST emphasizes the need to challenge these basic assumptions in order to develop a true understanding and propose effective solutions.

The traditional breastfeeding practices are borrowed from and propagated by elders and mothers who are considered a source of authority due to their many years of experience with childrearing. As these customs are established and successfully practiced over the years, it becomes very difficult for individuals to depart from them without anything concrete to discredit them. The system and the lifeworld concepts of CST(54) are demonstrated herein that mothers have to immerse themselves in the lifeworld shared with others. There is little personal choice here as they must follow certain regular patterns to further the strategic interest of their environment. Interventions that introduce or reinforce the Baby-Friendly Initiative (BFI) practices which ... are needed to improve breastfeeding initiation, and to reinforce exclusive breastfeeding (55). Access to scientific information on milk secretion might have a positive impact on the exclusive breastfeeding practice of these mothers.

The Arab mothers in this study experienced some difficulty when adapting to new breastfeeding practices in Canada. For instance, the suggestion by the postpartum nurse to breastfeed the baby for half an hour and then waiting three hours before the next feed resulted in an inadvertent rejection of an "on-demand" schedule. Jessri et al.(52) argue that Arab women might be less knowledgeable and confident about issues of breastfeeding. These perceptions influence the extent to which these mothers are perceived to be open to new ideas on breastfeeding. Also, the cross-cultural differences might have contributed to a lack of confidence in HCPs by the Muslim Arab mothers in this study, some of whom turned to their cultural values and religion to inform their practices.

Arab culture forbids indecent exposure by women which further complicates the process of breastfeeding for Arab lactating mothers (56). The participants found the requirement of modesty a significant challenge because it imposed isolation. The interview data also suggests that mothers need help understanding what services, resources, groups, etc., are available to them. Prenatal Arab mothers need to be referred to, or encouraged to attend, such groups so that they can share their problems with other immigrant mothers and exchange advice with each other. This can be part of a wider socialization program to deal with the issue of isolation.

The lack of adequate facilities to support breastfeeding mothers in public spaces such as nursing rooms presents a significant barrier to the process (57). The CST school of thought advances the idea that change can only be realized by challenging the existing social and economic structures. This implies that in addition to establishing a debate geared towards advocacy and policy change on breastfeeding, more emphasis should be placed on socializing the public and HCPs on the need to create better social and economic support for breastfeeding mothers.

The intake of fluids other than breastmilk could have a negative impact on breastfeeding frequency and duration, which suggests a need for increased prenatal and postnatal breastfeeding education. In terms of health policy, new mothers need to be taught how to breastfeed, how to express and store breastmilk, alternative methods of offering expressed breastmilk, a list of foods that promote milk production, stress management techniques, and ways to deal with fatigue. This information could be provided in printed pamphlets, booklets, or in the form of audio-visual presentations. Further, the integration of scientific knowledge on breastfeeding will play a crucial role in influencing positive outcomes towards exclusive breastfeeding. More particularly, this will focus on challenging the practice of prelacteal feeding through providing factual information on its implications hence promoting better breastfeeding outcomes.

Conclusion

The initiation of breastfeeding by Arab mothers in Canada is high, but by six-months after birth, breastfeeding duration rates quickly drop below the desired international rates. Lack of knowledge and support available to immigrant Arab mothers contribute to the lack of successful breastfeeding, leading them to prematurely wean their infants. This critical ethnography study has provided insight into the breastfeeding experiences of Arab mothers and the contextual factors that influence their experiences. The findings from this qualitative study revealed influences of mother's knowledge and traditional infant feeding practices on initiation and exclusive breastfeeding practices by Arab immigrant mothers.

The findings show that women's lack of knowledge of exclusive breastfeeding and their tendency to carry out the religiously endorsed traditional customs against the recommendations of the HCPs influences the frequency and duration of exclusive breastfeeding. Mothers also actively sought information regarding breastfeeding from sources such as the Internet to assist them with problems they faced, rather than only going to HCPs, who they did not always understand due to the language barriers. A clearer understanding of the socio-cultural contexts that support and encourage exclusive breastfeeding is an important consideration by HCPs caring for Arab immigrant mothers in Canada. Culturally sensitive interventions that are tailored to the specific Arab mothers' breastfeeding concerns and needs are needed in order to have exclusive breastfeeding become the norm among this population in Canada.

For future research on the topic, participatory action research can be done with Arab mothers to develop educational programs and support regarding exclusive breastfeeding. Educational programs should be provided to these mothers in a culturally sensitive way. Since mothers voiced isolation and a need for support, it is important for researchers to involve mothers in program planning and evaluate the outcomes of their participation. Further research is needed to evaluate best ways to involve male Arab partners in supporting exclusive breastfeeding. Further critical ethnographic research can be conducted with nurses, lactation consultants, and physicians who provide care to mothers and their families to evaluate these practitioners' beliefs and practices that may affect exclusive breastfeeding among Arab mothers. Moreover, the spouses who are perceived to play a minor role in supporting breastfeeding practices may provide greater insight into understanding new perspectives towards exclusive breastfeeding.

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AVASCULAR NECROSIS MAY NOT HAVE AN ATHEROSCLEROTIC BACKGROUND IN SICKLE CELL DISEASES

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Abstract

Background: We tried to understand whether or not there is a significant association between avascular necrosis (AVN) and atherosclerosis in sickle cell diseases (SCD).

Methods: All patients with the SCD were included.
Results: The study included 434 patients (212 females) with similar mean ages in male and female genders (30.8 versus 30.3 years, respectively, p>0.05). Smoking (23.8% versus 6.1%, p<0.001) and alcohol (4.9% versus 0.4%, p<0.001) were higher in male gender, significantly. Transfused units of red blood cells (RBC) in their lives (48.1 versus 28.5, p=0.000) were also higher in male gender, significantly. Similarly, disseminated teeth losses (<20 teeth present) (5.4% versus 1.4%, p<0.001), chronic obstructive pulmonary disease (COPD) (25.2% versus 7.0%, 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), coronary heart disease (CHD) (18.0% versus 13.2%, p<0.05), chronic renal disease (CRD) (9.9% versus 6.1%, p<0.05), and stroke (12.1% versus 7.5%, p<0.05) were all higher in male gender but not AVN (24.3% versus 25.4%, p>0.05), significantly.

Conclusion: SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of hardened RBC into the tissues. Although the higher smoking and alcohol-like strong atherosclerotic risk factors and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like obvious atherosclerotic consequences in male gender, AVN was not higher in them, significantly. In another definition, AVN may not have an atherosclerotic background in the SCD.

Key words: Sickle cell diseases, chronic endothelial damage, atherosclerosis, avascular necrosis, male gender, smoking, alcohol

Introduction

Chronic endothelial damage may be the leading cause of aging and death by causing persistent tissue hypoxia in 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, arterial 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 atherosclerotic process are male gender, physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or infectious processes including sickle cell diseases (SCD), rheumatologic disorders, tuberculosis, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, stroke, benign prostatic hyperplasia (BPH), early aging, and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1-3). Although early withdrawal of the causative factors may delay terminal consequences, the endothelial changes can not be reversed completely after the development of obesity, HT, DM, PAD, COPD, CRD, CHD, stroke, or BPH due to their fibrotic nature (4, 5). Similarly, SCD are severe inflammatory processes on vascular endothelium mainly at the capillary level, terminating with an accelerated atherosclerotic process induced end-organ failures in early years of life (6). We tried to understand whether or not there is a significant association between avascular necrosis (AVN) and atherosclerosis in the SCD.

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 were included into the study. The SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, painful crises per year, transfused units of red blood cells (RBC) in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, priapism, and symptoms of BPH including urgency, weak stream, incomplete emptying, and nocturia 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, 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 AVN was diagnosed via MRI (7). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since the SCD patients with associated thalassemia minors show a milder clinic than the sickle cell anemia (SCA) alone (8). Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (PHT) (9). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (10). Acute chest syndrome is diagnosed clinically with the presence of new infiltrates on chest X-ray film, fever, cough, sputum production, dyspnea, or hypoxia (11). 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 male and 1.2 mg/dL or higher in female genders. 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 (12, 13). An exercise electrocardiogram is performed in patients with an abnormal electrocardiogram 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, smoking, alcohol, painful crises per year, transfused units of RBC in their lives, and consequences of the SCD were detected in both genders, and compared in between. Additionally, mean ages of the consequences were calculated. 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). The mean ages of the patients were similar in male and female genders (30.8 versus 30.3 years, respectively, p>0.05). Prevalence of associated thalassemia minor were similar in both genders, too (72.5% versus 67.9%, respectively, p>0.05). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were much higher in male gender, significantly (p<0.001 for both) (Table 1). Interestingly, transfused units of RBC in their lives (48.1 versus 28.5, p=0.000) were also much higher in male gender, significantly. Similarly, disseminated teeth losses (<20 teeth present) (5.4% versus 1.4%, p<0.001), COPD (25.2% versus 7.0%, 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), and stroke (12.1% versus 7.5%, p<0.05) were all higher in male gender but not AVN (24.3% versus 25.4%, p>0.05), significantly. There were 11 patients (4.9%) with the symptoms of BPH with a mean age of 41.5 (27-58) years. Additionally, there were 23 patients (10.3%) with priapism with a mean age of 33.4 (18-51) years. There were 31 mortality cases (17 males and 14 females) during the ten-year follow up period. The mean ages of mortality were 30.2 (19-50) in male and 33.3 (19-47) years in female genders (p>0.05) (Table 2). On the other hand, when we look at the mean ages of the consequences, stroke (33.5 years), COPD (33.6 years), PHT (34.0 years), leg ulcers (35.3 years), digital clubbing (35.4 years), CHD (35.7 years), DVT or varices or telangiectasias (37.0 years), cirrhosis (37.0 years), CRD (39.4 years), and BPH (41.5 years) may indicate advanced diseases in such patients due to the significantly shortened survival of the SCD in both genders (Table 3).

Table 1: Characteristic features of the study patients

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 patients

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**** or varices or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
AVN*****	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)
Acute chest syndrome	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

*****Avascular necrosis

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)
Acute chest syndrome	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)
AVN*	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¶ or varices or telangiectasias	*37.0 ± 8.4 (17-50)*
Cirrhosis	*37.0 ± 11.5 (19-56)*
*CRD***	*39.4 ± 9.7 (19-59)*
*BPH****	*41.5 ± 10.6 (27-58)*

*Avascular necrosis †Chronic obstructive pulmonary disease ‡Pulmonary hypertension §Coronary heart disease ¶Deep venous thrombosis **Chronic renal disease ***Benign prostatic hyperplasia

Discussion

SCD are chronic inflammatory processes on vascular endothelium terminating with accelerated atherosclerosis induced end-organ failures and a shortened survival in both genders (14, 15). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of RBC. Probably loss of elasticity instead of shape is the main pathology since sickling is rare in peripheric blood samples of the SCD patients with associated thalassemia minor, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated during inflammations, infections, 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 (16, 17). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level, since the capillary system is the main distributor of the abnormally hardened RBC into the tissues (18). The hardened cells induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages of the patients. As a result, the mean lifespans of the patients were 42 and 48 years in male and female genders in the literature, respectively (19), whereas they were 30.2 and 33.3 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 (20). Actually, RBC supports must be given immediately during all medical or surgical events in which there is an evidence of clinical deterioration in the SCD (11). RBC supports decrease sickle cell concentration in circulation and suppress bone marrow for the production of abnormal RBC. So it decreases sickling-induced endothelial damage, inflammation, edema, and tissue hypoxia all over the body.

Bone involvement is the most common clinical manifestation of the SCD both in the acute events including painful crises and in the chronic events including AVN, osteomyelitis, and septic arthritis (21, 22). For example, we detected AVN in 24.8% of the SCD patients in the present study. AVN is one of the most devastating musculoskeletal manifestations of the SCD (23). AVN or osteonecrosis or bone infarction or aseptic necrosis or ischemic bone necrosis is a disease where there is cellular death of bone components due to interruption of the blood supply. Without blood, the bone tissue dies and the bone collapses. If the AVN involves the bones of a joint, it often leads to destruction of the articular surface that is called osteochondritis dissecans. SCD, decompression sickness, vascular compression, and vasculitis including rheumatoid arthritis and systemic lupus erythematosus

are the common causes of the AVN. Experimental evidence suggests that the bone cells (osteocytes, osteoclasts, osteoblasts, etc.) die within 12-48 hours, and the fat cells of the bone marrow die within 5 days after reduction of the blood supply. After reperfusion, repair of ischemic bone occurs in two phases. First, there is angiogenesis and migration of undifferentiated mesenchymal cells from the adjacent living bone tissue into the dead marrow spaces, as well as entry of macrophages that degrade dead cellular and fat debris. Second, there is cellular differentiation of mesenchymal cells into osteoblasts or fibroblasts. Normally, bone is broken down and rebuilt up, continuously. Whereas in the AVN, the healing process is usually ineffective and the bone tissue is broken down faster than the body can rebuild it up again. Thus some clinicians also prescribe biphosphonates to reduce the osteoclastic activity in the early phases of the AVN. If the process is left untreated, the bone collapses, and the articular surface is broken down, leading to pain and arthritis. In the earlier stages of the disease (stage I and II of the Ficat and Arlet classification), the articular surface is preserved, and X-ray images are normal (24, 25). Therefore MRI is the chief method both for the diagnosis and staging of AVN, and should be performed in unexplained bone pain in young patients with normal X-rays. In the more advanced stages (stage III and IV), the articular surface collapses (25). AVN can affect any bone in the body, and half of the cases show multiple sites of involvement in the SCD. Clinical AVN most commonly affects the ends (epiphysis) of long bones. It primarily affects the femoral head in more than 75% of cases, followed by the humeral head, knee, and small bones of the wrist and foot (25, 26). Although the exact pathophysiology is unknown, an acute-onset capillary endothelial damage, inflammation, and edema caused by the hardened RBC around the bone tissues may be the major underlying cause in the SCD. Since although the higher prevalences of smoking and alcohol-like strong atherosclerotic risk factors and disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like obvious atherosclerotic consequences in male gender in the SCD, the prevalence of AVN was not higher in them, significantly (24.3% versus 25.4%, respectively, $p>0.05$). On the other hand, AVN frequently affects young patients, and is usually seen between the ages of 30 and 50 years that may also indicate a nonatherosclerotic background of the AVN. Similarly, the mean age of AVN was 32.8 years in the SCD patients in the present study.

COPD is the third leading cause of death with various causes in the world (27). It is an inflammatory disorder that mainly affects the pulmonary vasculature. Although aging, smoking, and excess weight may be the major underlying risk factors, regular alcohol consumption may also be important in the inflammatory process. For example, COPD was one of the most common diagnoses in alcohol dependence (28). Furthermore, 30-day readmission rates were higher in COPD with alcoholism (29). Probably an accelerated atherosclerotic process is the main structural background of functional changes of the COPD. The inflammatory process on the vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and 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 (30, 31). For example, there may be close relationships between COPD, CHD, PAD, and stroke (32). Furthermore, two-thirds of mortality 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 (33). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (33). In another study, 27% of mortality was due to the cardiovascular diseases in the moderate and severe COPD (34). As a result, COPD is one of the terminal consequences of the SCD due to the higher prevalence of priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the SCD patients with COPD (35).

Digital clubbing is characterized by an increased normal angle of 165° between the nail bed and nail fold, increased convexity of the nail fold, and thickening of the whole distal finger (36). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (37). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (13). But according to our experiences, digital clubbing is frequently associated with pulmonary, cardiac, renal, and hepatic disorders and smoking which are characterized by chronic tissue hypoxia (4). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect each others' functions in a short period of time. On the other hand, digital clubbing is also common in the SCD, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD. Beside effects of the SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in male gender (14.8% versus 6.6%, $p<0.001$) may also indicate some additional role of male sex on clubbing.

Leg ulcers are seen in 10-20% of patients with the SCD (38), and the ratio was 13.5% in the present study. The prevalence increases with age, male gender, and SCA (39). Similarly, the prevalence was higher in male gender (19.8% versus 7.0%, $p<0.001$), and the mean age of the patients with leg ulcers was significantly higher than the others (35.3 versus 29.8 years, $p<0.000$) in the present study. These results may indicate some effects of systemic atherosclerotic process on leg ulcers. Similarly, the leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (38). As another evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (38). 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 (39). Prolonged exposure to the hardened cells due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened cells induced venous insufficiencies may also accelerate the process by pooling of causative RBC in the legs, and vice versa. Similarly, pooling of blood may also have some effects on higher prevalences of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, the pooling may be the cause of delayed wound and fracture healings in the lower extremities. Beside the hardened RBC, the higher prevalences of smoking and alcohol may also have some additional effects on the leg ulcers by accelerating the atherosclerotic process in male gender. Hydroxyurea is the first drug that was approved by Food and Drug Administration for the treatment of SCD (18). 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 (20). Its main action may be the suppression of hyperproliferative white blood cells (WBC) and platelets (PLT) in the SCD (40). Although the presence of a continuous damage by 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 (41). According to our ten-year experiences, prolonged resolution of leg ulcers in most but not all of the SCD patients with hydroxyurea may also suggest that the leg ulcers may be secondary to the increased WBC and PLT counts induced prolonged vascular endothelial inflammation and edema at the capillary level. Probably due to the irreversible fibrotic process on vascular endothelium, the drug is not so effective in terminal patients.

The prevalence of 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 (5). Despite the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being and increased prevalence of excess weight all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it has become the most common cause of chronic liver disease even at childhood at the moment (42). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation that results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerotic process (42). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased cardiovascular diseases (43). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (44). NAFLD may be considered as the hepatic consequence of the metabolic syndrome and SCD (14, 45). Smoking may also take a role in the endothelial inflammation in the liver since the inflammatory effects of smoking on vascular endothelium is well-known with Buerger's disease and COPD (46). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with an accelerated atherosclerosis in smokers. Atherosclerotic effects of alcohol are much more prominent on hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Chronic infectious or inflammatory processes may also terminate with an accelerated atherosclerosis all over the body (47). For instance, chronic hepatitis C virus (HCV) infection raised CIMT, and hepatic functions were normalized with the clearance of HCV (47). As a result, beside COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may also be one of the atherosclerotic consequences of the metabolic syndrome and SCD.

CRD is increasing all over the world, too (48). The increased prevalence of CRD may be explained by aging of the societies and increased prevalence of excess weight since CRD may also be one of the atherosclerotic consequences of the metabolic syndrome (49). Aging, physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or infectious processes may be the major causes of the vascular endothelial inflammation in the kidneys. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged renal tissues, particularly endothelial cells of the renal arteriols. Due to the prolonged irritations of the vascular endothelium, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, renal hypoxia and infarcts, and fibrosis. Excess weight induced metabolic abnormalities such as hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause various cellular stresses by means of acceleration of tissue inflammation and immune cell activation (50). For instance, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) showed significant correlations with the CIMT (49). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to 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 (51). Excess weight also causes renal vasodilation and glomerular hyperfiltration, initially serving as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (51). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys by causing chronic endothelial damage in long term (52). With prolonged excess weight, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in the overweight and obese individuals, CRD progresses more rapidly (51). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in CRD (53). 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 CRD (53), it is not logical, since 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 disorders may also terminate with an accelerated atherosclerosis on renal vascular endothelium (47). Although CRD is mainly thought to be an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other consequences of the metabolic syndrome and SCD including CHD, COPD, PAD, cirrhosis, and stroke (54). For example, the most common cause of death was the cardiovascular diseases in the CRD again (55). In another definition, CRD may also be one of the atherosclerotic consequences of the metabolic syndrome and SCD (56).

Stroke is an important cause of death in human beings, and thromboembolism in the background of atherosclerosis is the most common cause of stroke. Aging, male gender, smoking, alcohol, hyperglycemia, dyslipidemia, elevated BP, excess weight, and chronic inflammatory or infectious processes may be the major triggering factors of the stroke. Stroke is also a frequent complication of the SCD (57, 58). Similar to the leg ulcers, stroke is higher in the SCA cases (59). Additionally, a higher WBC count is associated with a greater incidence of stroke (40). Sickling induced vascular endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic endothelial inflammation, edema, remodeling, and fibrosis (60). Probably, stroke is a complex and terminal event, and it may not have a macrovascular origin in the SCD. Instead disseminated capillary endothelial inflammation and edema may be much more important in the process. Associated inflammatory or infectious disorders or stressful conditions of the human body may precipitate stroke in the SCD, since increased metabolic rate during such episodes may accelerate sickling. On the other hand, a significant reduction of stroke with hydroxyurea therapy may also suggest that a significant proportion of strokes is secondary to the increased WBC and PLT counts induced disseminated capillary endothelial inflammation and edema (61).

Although the accelerated atherosclerotic process, the venous endothelium is also involved in the SCD (62). For example, varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Risk factors include aging, excess weight, menopause, pregnancy, and heredity. Normally, leg muscles pump veins to return blood against gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, DVT or varices or telangiectasias develop. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus the physical examination must be performed in upright position. Although the younger mean ages of the patients in the present study (30.8 and 30.3 years in male and female genders, respectively) and significantly lower mean body mass index of the SCD patients in the literature (17), DVT or varices or telangiectasias of the lower limbs were higher in the study cases (9.0% versus 6.6% in male and female genders, respectively, $p>0.05$) indicating an additional venous endothelial involvement in the SCD (62). Similarly, priapism is the painful erection of penis that cannot return to its flaccid state within four hours in the absence of any stimulation (63). 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 (63). It is seen with hematological and neurologic disorders including the SCD, leukemia, thalassemia, Fabry's disease, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (15, 64, 65). Ischemic (veno-occlusive, low-flow), stuttering (recurrent ischemic), and nonischemic priapisms (arterial, high-flow) are the three types of priapism (66). Ninety-five percent of clinically presented priapisms are the ischemic (low-flow) type in which blood cannot return adequately from the penis into the body as in the SCD, and these cases are very painful (63, 66). The other 5% are nonischemic (high-flow) type usually caused by a blunt perineal trauma in which there is a short circuit of the vascular system of the penis (63). Treatment of high-flow type is not as urgent as the low-flow type due to the absence of risk of ischemia (63). RBC support is the treatment of choice in acute phase in the SCD (67), whereas in chronic phase, hydroxyurea therapy should be the treatment of choice. According to our ten-year experiences, hydroxyurea is an effective drug for prevention of attacks and consequences if iniatiated early, but the success rate is low due to the excessive fibrosis around the capillaries if initiated later.

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 hardened RBC into the tissues. Although the higher smoking and alcohol-like strong atherosclerotic risk factors and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like obvious atherosclerotic consequences in male gender, AVN was not higher in them, significantly. In another definition, AVN may not have an atherosclerotic background in the SCD. Instead, an acute-onset capillary endothelial damage, inflammation, and edema caused by the hardened RBC around the bone tissues may be the major cause of AVN in the SCD.

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AUTOSPLENECTOMY MAY NOT HAVE AN ATHEROSCLEROTIC BACKGROUND IN SICKLE CELL DISEASES

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Abstract

Background: We tried to understand whether or not there is a significant relationship between autosplenectomy and atherosclerosis in sickle cell diseases (SCD).

Methods: All patients with the SCD were included.

Results: The study included 434 patients (222 males and 212 females) with similar mean ages in male and female genders (30.8 versus 30.3 years, respectively, p>0.05). Smoking (23.8% versus 6.1%, p<0.001) and alcohol (4.9% versus 0.4%, p<0.001) were higher in males, significantly. Transfused units of red blood cells (RBC) in their lives (48.1 versus 28.5, p=0.000) were also higher in males, significantly. Similarly, disseminated teeth losses (<20 teeth present) (5.4% versus 1.4%, p<0.001), chronic obstructive pulmonary disease (COPD) (25.2% versus 7.0%, 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), coronary heart disease (CHD) (18.0% versus 13.2%, p<0.05), chronic renal disease (CRD) (9.9% versus 6.1%, p<0.05), and stroke (12.1% versus 7.5%, p<0.05) were all higher in males but not autosplenectomy (50.4% versus 53.3%, p>0.05) in the SCD.

Conclusion: SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of hardened RBC into the tissues. Although the higher smoking and alcohol-like strong atherosclerotic risk factors and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like obvious atherosclerotic consequences in male gender, autosplenectomy was not higher in them, significantly. In another definition, autosplenectomy may not have an atherosclerotic background in the SCD.

Key words: Sickle cell diseases, chronic endothelial damage, atherosclerosis, autosplenectomy, male gender, smoking, alcohol

Introduction

Chronic endothelial damage may be the leading cause of aging and death by causing tissue infarcts 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 vessels 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, arterial 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 atherosclerotic process are male gender, physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or infectious processes including sickle cell diseases (SCD), rheumatologic disorders, tuberculosis, and cancers for the development of irreversible consequences including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, stroke, and benign prostatic hyperplasia (BPH) which terminate with early aging and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1-3). Although the early withdrawal of the causative factors may delay terminal consequences, the endothelial changes cannot be reversed completely after the development of obesity, HT, DM, PAD, COPD, CRD, CHD, stroke, or BPH due to their fibrotic natures (4-6). Similarly, SCD are severe inflammatory processes on vascular endothelium mainly at the capillary level, terminating with an accelerated atherosclerotic process induced end-organ failure in early years of life (7). We tried to understand whether or not there is a significant relationship between autosplenectomy and atherosclerosis in the SCD.

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 were included into the study. The SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, painful crises per year, transfused units of red blood cells (RBC) in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, priapism, and symptoms of BPH including urgency, weak stream, incomplete emptying, and nocturia 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 or infectious or traumatic 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, 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 (AVN) were scanned according to the patients' complaints. So AVN was diagnosed via MRI (8). Autosplenectomy is diagnosed in the absence of any history of surgical splenectomy, ultrasonographically. Associated thalassemia minor was detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via the HPLC. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (PHT) (9). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (10). Acute chest syndrome is diagnosed with the presence of new infiltrates on chest X-ray film, fever, cough, sputum, dyspnea, or hypoxia, clinically (11). 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 the 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, laboratory parameters, and ultrasonographic results. 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 (12, 13). An exercise electrocardiogram is performed in patients with an abnormal electrocardiogram or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive patients. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders of 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 in patients with visual complaints. Eventually, the mean age, associated thalassemia minors, smoking, alcohol, painful crises per year, transfused units of RBC in their lives, autosplenectomy, and other consequences of the SCD and mean ages of the consequences 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). Their mean ages were similar in males and females (30.8 versus 30.3 years, respectively, p>0.05). Prevalence of associated thalassemia minor was similar in males and females, too (72.5% versus 67.9%, respectively, p>0.05). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were much higher in males, significantly (p<0.001 for both) (Table 1). Transfused units of RBC in their lives (48.1 versus 28.5, p=0.000) were also higher in males, significantly. Similarly, disseminated teeth losses (<20 teeth present) (5.4% versus 1.4%, p<0.001), COPD (25.2% versus 7.0%, 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), and stroke (12.1% versus 7.5%, p<0.05) were all higher in males but not autosplenectomy (50.4% versus 53.3%, p>0.05), significantly. There were 11 patients (4.9%) with the symptoms of BPH with a mean age of 41.5 (27-58) years. Additionally, there were 23 patients (10.3%) with priapism with a mean age of 33.4 (18-51) years. There were 31 mortality cases (17 males and 14 females) during the ten-year follow up period. The mean ages of mortality were 30.2 (19-50) in males and 33.3 (19-47) years in females (p>0.05) (Table 2). On the other hand, when we look at the mean ages of the irreversible consequences, stroke (33.5 years), COPD (33.6 years), PHT (34.0 years), leg ulcers (35.3 years), digital clubbing (35.4 years), CHD (35.7 years), DVT or varices or telangiectasias (37.0 years), cirrhosis (37.0 years), CRD (39.4 years), and BPH (41.5 years) may indicate advanced diseases in such patients due to the significantly shortened survival of the SCD in both genders (Table 3).

Table 1: Characteristic features of the study patients

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 patients

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**** or varices or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
AVN*****	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)
Acute chest syndrome	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 *****Avascular necrosis

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)
Acute chest syndrome	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)
AVN*	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¶ or varices or telangiectasias	*37.0 ± 8.4 (17-50)*
Cirrhosis	*37.0 ± 11.5 (19-56)*
*CRD***	*39.4 ± 9.7 (19-59)*
*BPH****	*41.5 ± 10.6 (27-58)*

*Avascular necrosis †Chronic obstructive pulmonary disease ‡Pulmonary hypertension §Coronary heart disease ¶Deep venous thrombosis **Chronic renal disease ***Benign prostatic hyperplasia

Discussion

SCD are chronic inflammatory processes on vascular endothelium terminating with an accelerated atherosclerosis induced end-organ failures and a shortened survival in both genders (14, 15). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of RBC. Probably loss of elasticity instead of shape is the main pathology since sickling is very rare in peripheric blood samples of the SCD with associated thalassemia minors, and overall survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated during 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 and infarcts all over the body (16, 17). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level, since the capillary system is the main distributor of the abnormally hardened RBC into the tissues (18). The hardened cells induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages of the patients. As a result, the mean lifespans of the patients were 42 and 48 years in males and females in the literature whereas they were 30.2 and 33.3 years in the present study, respectively (19). The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during emergencies in Turkey (20). Actually, RBC supports must be given during all medical or surgical events in which there is an evidence of clinical deterioration in the SCD, immediately (11). RBC supports decrease sickle cell concentration in the circulation, and suppress bone marrow for the production of abnormal RBC. So it decreases sickling-induced endothelial damage, inflammation, edema, and tissue ischemia and infarcts all over the body.

Spleen is the major lymphatic organ in the body, and found in all vertebrates with a similar structure to the lymph nodes. Like the thymus, spleen has only the efferent lymphatic vessels. It has a central role in the reticuloendothelial system, and retains the ability to produce lymphocytes after birth. It primarily acts as a blood filter, and removes old and abnormal RBC, and recycles the iron. It synthesizes antibodies, and removes antibody-coated bacteria and blood cells from the circulation. It acts as a pool of peripheral blood cells that are released into the circulation in case of requirement.

For example, it stores half of the monocytes in mice (21). In case of an injury, they can migrate to the injured tissues, and transform into the dendritic cells and macrophages to assist the tissue healing (22). On the other hand, autosplenectomy is a common pathology in the SCD. Increased deoxygenation causes sickling of RBC which adhere to the splenic wall and macrophages, and cause ischemia and infarcts (23). Splenic injury is generally silent and progressive in the SCD in which the spleen suffers from multiple occlusions of its microvasculature. In other words, splenic infarcts are usually small and repetitive, leading ultimately to autosplenectomy, whereas massive splenic infarcts are extremely rare in the SCD (24). Repeated vaso-occlusions lead to fibrosis and splenic atrophy in a progressive manner. The autosplenectomy is the first major organ failure in the SCD (25). Similarly, the prevalence of autosplenectomy was the highest among all of the affected tissues of the body with the ratios of 50.4% versus 53.3% in males and females in the present study, respectively ($p>0.05$). On the other hand, asplenia can increase susceptibility to infections, particularly due to the polysaccharide encapsulated bacteria and organisms that invade RBC. Thus asplenia patients are recommended to be vaccinated against Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae. A 28-year follow-up study of 740 veterans of World War II with surgical removal of spleen on the battlefield found that they showed increased mortality due to pneumonia and CHD (26). Parallel to the increased frequency of infections, painful crises were also increased in patients with autosplenectomy (27). The increased frequency of painful crises may be due to the loss of filtering capability of the spleen for the abnormal RBC which induce vaso-occlusions in bone tissues. On the other hand, splenic functions can be measured by filtering capabilities for Howell-Jolly bodies and pitted RBC in the peripheral blood. Howell-Jolly bodies are remnants of RBC nuclei that are normally removed by the spleen. A high number of Howell-Jolly bodies in the circulation is indicative of splenic hypofunction and autosplenectomy. Similarly, RBC with membrane pits in the peripheral blood can also be an indicator of splenic hypofunction since they are normally cleaned by the spleen. Humans with a healthy spleen have less than 2% of their RBC with pits on them. However, asplenia cases may have up to 50% of their RBC with pits in the circulation.

COPD is the third leading cause of death in the world (28). It is an inflammatory disorder that mainly affects the pulmonary vasculature. Although aging, smoking, and excess weight may be the major underlying risk factors, regular alcohol consumption may also be important in the inflammatory process. For instance, COPD was one of the most common diagnoses in alcohol dependence (29). Furthermore, 30-day readmission rates were higher in the COPD with alcoholism (30). Probably an accelerated atherosclerotic process is the main structural background of the COPD. The inflammatory process of the vascular endothelium is enhanced by the release of various chemicals by inflammatory cells, and terminates with an advanced atherosclerosis 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 (31, 32). For example, there may be close relationships between COPD, CHD, PAD, and stroke (33). Furthermore, two-thirds of mortality 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 (34). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (34). In another study, 27% of mortality were due to the cardiovascular diseases in the moderate and severe COPD (35). As a result, COPD is one of the terminal consequences of the SCD due to the higher prevalence of priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the SCD with COPD (36).

Digital clubbing is characterized by an increased normal angle of 165° between the nail bed and nail fold, increased convexity of the nail fold, and thickening of the whole distal finger or toes (37). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (38). In the previous study, only 40% of clubbing cases turned out to have significant diseases while 60% remained well over the subsequent years (13). But according to our experiences, digital clubbing is frequently associated with pulmonary, cardiac, renal, or hepatic disorders or smoking which are characterized by chronic tissue hypoxia (4). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect each others' functions in a short period of time. On the other hand, digital clubbing is also common in the SCD, and its prevalence was 10.8% in the present study. 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 digital clubbing in males (14.8% versus 6.6%, $p<0.001$) may also indicate some additional role of male sex on clubbing.

Leg ulcers are seen in 10-20% of patients with SCD (39), and the ratio was 13.5% in the present study. The prevalence of leg ulcers increases with age, male gender, and sickle cell anemia (SCA) (40). It is shown that SCA shows a more severe clinic than SCD with associated thalassemia minors (41). Similarly, the prevalence was higher in males (19.8% versus 7.0%, $p<0.001$), and the mean age of the patients with leg ulcers was significantly higher than the others in the present study (35.3 versus 29.8 years, $p<0.000$). These results may indicate effects of systemic atherosclerosis on the leg ulcers. Similarly, the leg ulcers have an intractable nature, and around 97% of ulcers relapse in a period of one year (39). As another evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (39). The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the main cause in the SCD (40). Prolonged exposure to the hardened cells

due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened cells induced venous insufficiencies may also accelerate the process by pooling of causative RBC in the legs, and vice versa. Similarly, pooling of blood may also have some effects on higher prevalence of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, the pooling may be the cause of delayed wound and fracture healings in the lower extremities. Beside the hardened RBC, the higher prevalences of smoking and alcohol may also have some effects on the leg ulcers by accelerating the atherosclerotic process in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration for the SCD (18). 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 (20). Its main action may be the suppression of hyperproliferative white blood cells (WBC) and platelets (PLT) in the SCD (42). Although the presence of continuous damage by hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the higher numbers of WBC and PLT. 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 (43). According to our ten-year experiences, prolonged resolution of leg ulcers with hydroxyurea in most patients may also suggest that the leg ulcers may be secondary to the increased WBC and PLT counts induced prolonged vascular endothelial inflammation and edema at the capillary level. Probably due to the irreversible fibrotic process on the vascular endothelium, hydroxyurea is not so effective in terminal patients with the leg ulcers.

Cirrhosis is increasing in the world, and is the 11th leading cause of death globally (5). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being and increased prevalence of excess weight all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it has become the most common cause of chronic liver disease even at childhood at the moment (44). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation that results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (44). Besides terminating with cirrhosis, NAFLD is associated with higher cardiovascular diseases and overall mortality rates (45). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (46). NAFLD may be considered as a hepatic consequence of the metabolic syndrome and SCD (14, 47). Smoking may also take a role in the endothelial inflammation in the liver since the inflammatory effects of smoking on vascular endothelium are well-known with Buerger's disease and COPD (48). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with an accelerated atherosclerosis in smokers. Atherosclerotic effects of alcohol are much more prominent on hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Chronic infectious or inflammatory processes may also terminate with an accelerated atherosclerosis all over the body. For instance, chronic hepatitis C virus (HCV) infection raised CIMT, and hepatic functions were normalized with the clearance of HCV (49). As a result, beside COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may just be one of the consequences of the metabolic syndrome and SCD.

CRD is increasing all over the world, too (50). The increased prevalence of CRD may be explained by aging of the human being and increased prevalence of excess weight, since CRD may also be one of the consequences of the metabolic syndrome (51). Aging, physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or infectious processes may be the major underlying causes of the vascular endothelial inflammation in the kidneys. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged renal tissues, particularly endothelial cells of the renal arteriols. Due to the prolonged irritations of the vascular endothelium, prominent changes develop in the architecture of the renal tissues with an advanced atherosclerosis and subsequent ischemia and infarcts. Excess weight induced metabolic abnormalities such as hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause various cellular stresses by means of acceleration of tissue inflammation and immune cell activation (52). For instance, 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 (51). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to activations of sympathetic nervous and renin-angiotensin systems, and physical compression of kidneys by visceral fat tissue may just be some of the mechanisms of the increased BP with excess weight (53). Excess weight also causes renal vasodilation and glomerular hyperfiltration, initially serving as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (53). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys by causing chronic endothelial damage in long term (54). With prolonged excess weight, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in the overweight and obese individuals, CRD progresses more rapidly (53). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (55). 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 is not related with the CRD (55), it is not logical, since various metabolites of alcohol circulate even in the renal vasculature, and cause harm to the vascular endothelium. Chronic inflammatory or infectious disorders

may also terminate with an accelerated atherosclerosis in the kidneys (49). Although the CRD is mainly thought of as an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other consequences of the metabolic syndrome and SCD (56). For instance, the most common causes of death were the stroke and CHD in the CRD again (57). In another definition, CRD may just be one of the consequences of the metabolic syndrome and SCD, again (58).

Stroke is an important cause of death in human beings, and thromboembolism on an atherosclerotic background is the most common mechanism of the stroke. Aging, male gender, smoking, alcohol, excess weight and its consequences, and chronic inflammatory or infectious processes may just be some of the triggering factors of the stroke. Stroke is also a frequent complication in the SCD (59, 60). Similar to the leg ulcers, stroke is higher in the SCA cases (61). Additionally, a higher WBC count is associated with a higher risk of stroke (42). Sickling induced vascular endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic vascular endothelial inflammation, edema, remodeling, and scarring (62). Probably, stroke is a complex and terminal event, and it may not have a macrovascular origin in the SCD. Instead disseminated capillary endothelial inflammation and edema may be much more important in the process. Associated inflammatory or infectious disorders or stressful conditions may precipitate the stroke, since increased metabolic rate during such episodes may accelerate the sickling. On the other hand, a significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of strokes is secondary to the increased WBC and PLT counts induced disseminated capillary endothelial inflammation and edema in the brain (63).

Although the accelerated atherosclerotic process, the venous endothelium is also involved in the SCD (64). For instance, varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Risk factors include aging, excess weight, menopause, pregnancy, and heredity. Normally, leg muscles pump veins to return blood against the gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, DVT or varices or telangiectasias develop. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus the physical examination must be performed in upright position. Although the younger mean ages of the patients in the present study (30.8 and 30.3 years in males and females, respectively), and significantly lower mean body mass index of the SCD patients in the literature (17), DVT or varices or telangiectasias of the lower limbs were higher in the study cases (9.0% versus 6.6% in males and females, respectively, $p>0.05$), indicating an additional venous endothelial involvement in the SCD (64). 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 (65). 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 (65). It is seen with hematological and neurological disorders, including the SCD, leukemia, thalassemia, Fabry's disease, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (15, 66, 67). Ischemic (veno-occlusive, low-flow), stuttering (recurrent ischemic), and nonischemic priapisms (arterial, high-flow) are the three types of the pathology (68). Ninety-five percent of the clinical cases are the ischemic (low-flow) type in which blood cannot return adequately from the penis into the systemic circulation as in the SCD, and these cases are very painful (65, 68). The other 5% are nonischemic (high-flow) type, usually caused by a blunt perineal trauma in which there is a short circuit of the vascular system of the penis (65). Treatment of high-flow type is not as urgent as the low-flow type due to the absence of risk of ischemia (65). RBC support is the treatment of choice in acute phase in the SCD (69). Whereas in chronic phase, hydroxyurea therapy should be the treatment of choice. According to our ten-year experiences, hydroxyurea is an effective drug for prevention of the attacks and consequences if iniatiated early in the course of the disease, but the success rate is low due to the excessive fibrosis around the capillaries if initiated later.

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 hardened RBC into the tissues. Although the higher smoking and alcohol-like strong atherosclerotic risk factors and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like obvious atherosclerotic consequences in male gender, autosplenectomy was not higher in them, significantly. In another definition, autosplenectomy may not have an atherosclerotic background in the SCD.

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delirium vs dementia

Dr. Ebtisam Elghblawi

Confused, fearful and frail
Can't concentrate can't recognize
Life on a bleak
Hard to dialogue
Struggle to communicate
Difficult to concentrate
Interruptions and distractions
Imposing and restricting
Invading personal space
Seeing through others eyes
Healing the deeply triggered emotions
Watchful with tears in eyes
I am sorry I wiped down
Unexpectedly experience
Ending the momentous
Deteriorating and dying
For good and bad
Reversed image
Mirroring our life paths
All walks of life
No day lasts forever
Reflecting can be cathartic

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BLOOD GLUCOSE CONTROL AND SURGICAL SITE INFECTIONS IN CANCER PATIENTS: A LITERATURE REVIEW

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Abstract

Background: Surgical site infections (SSI) are the most common acquired infection during hospitalization and a major cause of morbidity, mortality, increased health care costs and delays in treatments for cancer patients.

Objective: The objective of this literature review was to gain a better understanding of the relationship between uncontrolled blood glucose and the odds of developing a SSI among cancer patients.

Interventions/Methods: A database search (which engaged PubMed, Medline, Cumulative Index to Nursing and Allied Health Literature and The Cochrane Database of Systematic Reviews) was completed using the key words: 'surgical site infection' or 'surgical wound infection' OR 'SSI' AND cancer or neoplasms OR oncology OR tumor OR malignancy AND diabetes OR hyperglycemia AND risk factors. Twenty-seven studies met the inclusion criteria to be included in this review.

Results: The odds ratio for history of diabetes or hyperglycemia and SSI following cancer surgery varied across studies. This is likely explained in part by the fact that some types of surgery are more invasive than others, are more lengthy, and involve areas of the body that are more prone to infection. The study with the highest rate of SSI (62.1%) was among patients with oral cancer and the study with the lowest rate of SSI (3.1%) was among patients with spinal cancer.

Conclusion: The literature review results suggested an association between SSI and patients with a history of diabetes mellitus or hyperglycemia.

Key Words:
Diabetes, cancer, literature review, surgical site infections, surgery, glucose

Introduction

Surgical site infection (SSI) following surgery can be devastating for patients, families and the entire health care team. In patients who experience surgery as a treatment for cancer, especially those who also have issues with diabetes or hyperglycemia, SSI can result in substantial morbidity and increased health care costs from longer hospital stays and consequent poor clinical outcomes. This is particularly important for cancer patients, as SSI can cause delays in chemotherapy and other treatments (Al-Naimi et al., 2015).

While SSI is known to be associated with uncontrolled blood glucose levels following surgery among cancer patients (Ambiru et al., 2007), and is the most common acquired infection during hospitalization (Badia et al., 2017), very little evidence had been available looking at the collective literature on risk of SSIs for cancer, as it related to the patients' blood glucose levels.

Observational studies suggest that postoperative hyperglycemia increases the rates of SSI and likely worsens patient's outcomes (Jeon et al., 2012; Jenks et al., 2014; Kalalla, et al., 2015). Several risk factors for the development of SSI have been reported, such as age, poor nutritional status, diabetes mellitus, smoking, and altered immune response (Atkinson et al., 2017). Ma et al., (2019) reported that elevated blood glucose was an independent factor influencing the occurrence of SSI. Another study reported a greater risk of SSI among patients with advanced breast cancer who had higher blood glucose levels during or immediately after surgery (Vilar-Compte et al., 2008). Therefore, proper management of blood glucose, regardless of whether patients have diabetes mellitus or not, is effective in decreasing the rates of SSI in cancer patients undergoing surgery, which in turn will likely decrease the length of hospital stay and health care costs (Ma et al. 2019).

Background

SSI and Patients with Diabetes, Cancer, and Surgeries

As early as the 1950s, researchers reported that people with uncontrolled diabetes were more likely to become infected during surgery compared to those without diabetes (Bortz & Burraughs, 1954). Today, there is considerable evidence to support the notion that patients with diabetes are more prone to infections than patients without diabetes. However, questions remain about the practical implications of reducing infections in patients with hyperglycemia before and during surgery (Pozzilli, et al., 2016). SSI may have negative outcomes for patients, nurses, and health care organizations. One study reported a significant decrease in patients' quality of life in relation to SSI occurrence, (Anderson et al., 2010), while another study reported that the relative health care cost for patients with SSIs were 1.43 times greater compared to patients without SSIs (Schweizer, 2014). Lastly, when comparing length of hospital stay among patients with or without an SSI, results reported a decrease in length of hospital stay from 14.2 (SD 10.9) to 8.1 (SD 2.4) days among patients without SSIs (Ozdemir, 2016).

Chronic hyperglycemia is associated with poor surgical outcomes and is a risk factor for SSI (Underwood et al., 2013). Patients with chronic hyperglycemia may also face longer hospital stays, repeat surgeries, pain, and an increased risk of death (Harrop et al., 2012). Although SSIs are a worldwide health concern, patients in the Gulf region may be at greater risk partly due to the high incidence of diabetes and certain types of cancers in this area (Hague et al., 2019). One study in Saudi Arabia found that 20 out of 228 patients (i.e., 8.7%) experienced SSIs after a variety of surgeries (Al-Naami, 2009).

Patients undergoing cancer surgeries have higher rates of SSI than non-cancer patients undergoing surgery partly due to a weakened immune system. Cancer can upset the body's ability to manufacture immune cells if there is organ involvement (Cancer Research UK, 2016). Furthermore, cancer treatments (e. g. radiotherapy) may indirectly reduce the body's ability to defend against disease (Iversen, 2013).

Some cancer surgeries pose a greater risk of developing an SSI. For example, one study reported that patients with malignant musculoskeletal tumors developed SSIs in 12.2% of cases (Satoshi et al., 2014), while another study reported that patients with oral cancer developed SSIs 40.6% of the time (Karakida, et al., 2010). In contrast, the incidence of SS1 among patients undergoing orthopedic surgery (0.83%) or surgery for spinal canal stenosis (0.28%) was low.

Although chemotherapy and radiation are the most useful and common treatments for cancer, surgery remains the primary treatment for solid tumors and provides the highest opportunity for cure (Bird et al., 2021). High success rates can be realized when the cancer is in its early stage and the surgery is combined with radiotherapy and chemotherapy. Other treatment options that may be necessary during this time include such options as the creation of an ostomy in order to improve patients' quality of life (Bird et al., 2021).

The aim of this literature review is to explore the relationship between the risk of SSI and uncontrolled blood glucose levels in adult patients with cancer. The primary research question was "Is there a relationship between SSI and uncontrolled blood glucose before, during and after surgery in adult patients with cancer?" A better understanding of this relationship is important because this knowledge can be used to inform clinical practice and health policy.

Methods

This review was guided by the work of Long (2002) because this method is clinically focused and provides a framework that allowed the research question (described above) to be answered. This method includes major sections such as the study's general properties, settings, sample, ethics, group comparability, outcome measurements, as well as a section on analysis of policy and practice implications.

Literature Search Strategy

A database search of PubMed, Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Cochrane was completed in 2016. Keywords used were 'surgical site infection' OR 'surgical wound infection' OR 'SSI' AND cancer or neoplasms OR oncology OR tumor OR malignancy AND diabetes OR hyperglycemia AND risk factors. Table 1 below illustrates the inclusion/ exclusion criteria for this review.

This initial search generated 532 citations (CINHAL (27 articles), Medline (128), PubMed (157) and the Cochrane database (220). After reading the title and abstract 501 articles were excluded because they were not relevant to the topic. Thirty-one studies met the inclusion criteria. and a further three were discarded as they did not contain relevant information, yielding 31 articles. Review of the reference section of the retained articles resulted in the addition of six articles (n=31). The first and second author reviewed these articles and met to reach consensus as to what articles to include or to exclude. Next, four more articles were discarded. Hence, 27 articles were included in this review. Figure 1 (below) illustrates the search strategy and outcome.

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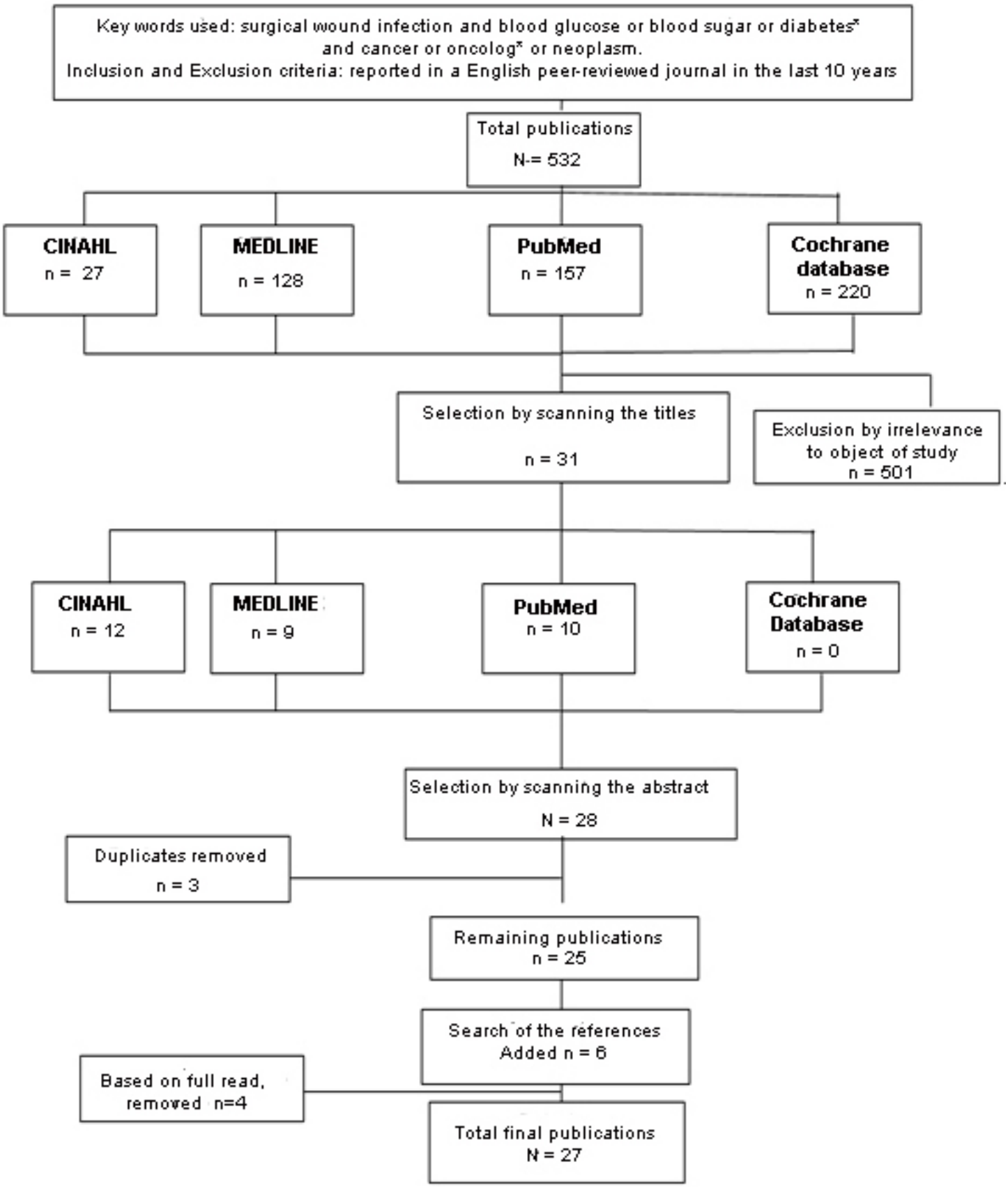
Table 1: Inclusion and exclusion criteria

Inclusion	Exclusion
Adult patients (18 years and older) with cancer who underwent surgery for cancer	Not an adult patient with cancer who did not undergo surgery
Adult patients with or without diabetes	Not an adult patient with or without diabetes
Article published in English or Arabic from 2006 to 2016	Article not published in English or Arabic between 2006-2016
Article is original research	Not original research (secondary source such as literature review)
Article focused on the rate of SSI among cancer patients	Article did not focus on rate of SSI among cancer patients

Figure 1: Search Strategy and Outcome



Assessment of the Methodological Quality of the Articles

The Johns Hopkins Nursing Evidence-Based Practice Research Evidence Appraisal Tool (Dearholt & Dang, 2012) was used to assess the methodological quality of the 27 articles. This appraisal tool ranks the evidence level and quality according to the methodology of the study and the completeness of the report of that study. Methodologies are ranked from 1 to 6, based on the strength of evidence, and quality is ranked from A to C based on the overall rating of the quality appraisal. A is high quality, B is good quality and C is low quality (or the study has major flaws). Most of the studies were assessed to be level III for level of evidence with the exception of the experimental studies and all, but one study was ranked as A or B for quality. The study that ranked a "C" was excluded from this review.

Data Extraction and Data Analyses

Based on the work of Long (2002), data extraction tables were developed. These tables included the following data: citation, year, country; purpose statement, number of participants, type of cancer; guideline or criteria used to measure SSI; and results (overall rate of SSI and OR). The data in these tables were critically analyzed and presented in the results section below.

Results

Characteristics of the Studies

Twenty-one studies were retrospective and chart reviews were the most common method for data collection. The remaining six studies could be classified as prospective designs and included the following types of studies (i.e., cohort (n=2), nested case control (n=1), cross sectional (n =1), RCT (n=1) and case control (n=1).

The studies included a range of different types of cancer such as gynecological, hepatic biliary-pancreatic, breast, head and neck, oral/oropharyngeal, spinal, colon rectal, brain, and esophageal cancer. Two studies focused on the relationship between high blood glucose levels and SSI (Vilar-Compte et al., 2008; Jackson et al., 2012), while the other studies focused on diabetes as a possible risk factor for SSI.

Most of the studies were from Asian countries (i.e., Japan, South Korea, China, Singapore, Taiwan, and India). Fewer studies were from the USA and Latin America and none of the studies were conducted in Middle Eastern countries. There was a total of 66,043 participants across all 27 studies and the sample size ranged from 53 to 9,638. Studies included patients undergoing surgery for hepatic-biliary-pancreatic (n=1) gynecologic (n=4), breast (n=4), head and neck (n=4), oral (n=3), spinal (n=2), colorectal (n=5), brain (n=4).

Studies used different definitions to confirm the presence of SSI (e. g. Centers for Disease Control and prevention (CDC), and the National Nosocomial Infections Surveillance System (NNIS). The most common guideline used was CDC. Some studies measured SSI daily for at least 30 days after surgery and one study measured the outcome every two weeks for one year.

Results: Literature Review

Due to the variety of cancers measured and surgeries assessed, there was a range of different results related to the outcome of interest (i.e., SSI). Some types of cancer surgery are more invasive than others and some areas of the body are more prone to infection. The study with the highest prevalence of SSI (i.e., 62%) was a study of 111 patients with oral cancer in Croatia (Belusic-Gobic et al., 2006) and the study with the lowest SSI rate (3.1%) was among patients with spinal cancer in Japan (Demura et al., 2009).

One of the measures that is commonly used to examine at the relationship between a variable and its outcome is odds ratio (OR) (Szumilas, 2010). All ORs that were not reported in the article were calculated by the researchers based on the data provided in the literature. Table 2 presents the ORs (next page).

Discussion

Most of the studies showed a relationship between SSI and uncontrolled glucose levels among diabetic and non-diabetic adult patients undergoing surgery. Overall, patients who have diabetes or hyperglycemia are more likely to have SSIs than those who do not have diabetes or high glucose levels. Notably, one study found that the presence of diabetes worked as a protective mechanism toward SSI (Jackson et al., 2012). This is surprising given that patients with cancer carry a greater risk for a SSI, even in the absence of diabetes or high blood glucose. Most hospital protocols aim to maintain a blood glucose levels less than 200 d/L in patients, regardless of the reason for admission (Shi et al., 2017). It is still unclear whether this is the correct cut point to aim for, to achieve the most positive outcomes. Therefore, it is important to test the blood glucose of patients and respond in order to keep them within a reasonable range as directed by the diabetes specialist.

It would be reasonable to question whether monitoring and controlling blood glucose levels might have deleterious effects on patients and patient care. For example, it could be hypothesized that lowering the blood glucose levels before surgery may cause negative outcomes. However, in those studies that measured blood glucose in order to control blood sugar levels during surgery, none of the patients suffered from hypoglycemia. Rather, patients on insulin drips whose blood glucose was continuously measured to maintain glucose levels at less than 150 d/L or 200 d/L. experienced less hypoglycemia.

Table 2: Odds Ratios of having an SSI among cancer patients with uncontrolled blood glucose levels undergoing surgery

Study	OR (C1) (95%) (p value)	Study	OR (C1) (95%) (p value)
Al-Naimi et al. (2015) USA	0.5 (0.28-0.9) p=0.001	Liu et al. (2007) Taiwan	2.51(0.92-10.44) p=0.002
Ambiru et al. (2008) Japan	6.6 (3.5-12.5) p<0.001	Lotfi et al. (2007) Brazil	p=0.129
Angrita et al. (2011) Colombia	10.9 (4.5-26.3) p<0.0001	Ma et al. (2016) China	6.07(3.95-8.5) p<.0001
Bakkum-Gamez et al. (2011) USA	2.2 (1.1-4.5) p=0.03	Mahdi et al. (2014) USA	p=0.001
Barreto et al. (2015) India	0.22 (0.07-0.63) p=0.01	Nakamoura et al. (2006) Japan	2.45(1.02-5.8) p=0.252
Belusic-Gobic et al. (2006) Croatia	p=0.13	Nakamoura et al. (2008) Japan	p=0.03
Bianchini et al. (2016) Italy	1.04 (0.41-2.60) p=0.930	Ogihara et al. (2008) Japan	p=0.38
Chaichana et al. (2015) USA	6.09 (1.38-9.354) p=0.02	Okabayashi et al. (2009) Japan	9.6(1.14-80.5) ***p=0.030
Chapman et al. (2015) USA	1.8 (0.85-3.85) p=0.032	Park et al. (2015) Korea	2.15(1.108-4.19) p=0.02
Davis et al. (2013) USA	0.0036 (1.10-1.59) p<0.0001	Serra-Aracil et al. (2011) Spain	9.43(1.04-85.9) p=0.047
Demura et al. (2009) Japan	17.1(3.64-43.6) p=0.011	Tuomi et al. (2015) USA	3.1(1.1-8.4) p<0.0001
Edwards et al. (2014) USA	1.24 (0.49-3.14)	Vilar-Comte et al. (2008) Mexico	2.9(1.2-6.8) p=0.04
Jackson et al. (2012) USA	1.44 (1.1-1.87)* 1.21 (0.97-1.52)**		
Lee et al. (2011) South Korea	33 (11-98) p<0.0001 p=0.0001		
Li et al. (2013) China	3.9 (0.92-10.44) p=0.077		
Vilar-Comte et al. (2008) Mexico	2.9 (1.2-6.8) p=0.004		

Legend: * = OR for Mild hyperglycemia:**= OR for moderate hyperglycemia, *** = unadjusted OR, OR= odds ratio, CI= confidence interval,

Another important question is whether or not the statistical significance found in many of the studies was also clinically significant. For example, continuous blood glucose monitoring and control may be expensive and time-consuming. None of the studies in this review looked at cost-effectiveness or time commitment that nurses spend doing these activities. However, it would be reasonable to assume that an overall time saving for hospital staff is likely when SSI are prevented.

According to Franciosi et al. (2001), although continuous blood glucose monitoring is very useful in metabolic control, frequent blood glucose monitoring for diabetic patients could increase patients' stress, worries and lead to depressive mood. Therefore, nurses and physicians should be aware of this possible stress and if present they should intervene with tailored strategies. Many risk factors for SSI were identified in this review. Overall, most studies indicated a significant association between SSI and diabetic patients with cancer or those with uncontrolled blood glucose with cancer. However, there were some differences among studies related to contributing factors and SSI. In some studies, SSI was rare. For instance, a study that included patients with spinal cancer showed a SSI rate of only 3.1% (Demura et al., 2009), while another study among patients with brain cancer found a SSI rate of 5% (Chaichana, 2015). In some cases, variation in the rate of SSI among patients with similar types of cancer was found. For example, one study reported a 19.1% rate of SSI among women with breast cancer (Angarita et al., 2011), while another study reported a much lower rate (i.e., 7.3%) among breast cancer patients (Edwards et al., 2014). Other contributing factors include patient adherence to treatment, patient's nutrition status, stage of disease, length of stay in the hospital, hygiene, and health care practices and skills.

Okabayashi et al. (2009) described the amount of insulin required by patients undergoing hepatic resection. This RCT assessed the use of continuous glucose monitoring and an artificial pancreas (i.e., continuous insulin drip). The group that had a continuous insulin drip required on average 175 units plus another 93 units of insulin during the first 18 hours post-surgery while the group receiving usual care (sliding scale) used less than 24 units in total, for the first 18 hours after surgery. Patients whose blood glucose was monitored and treated through a sliding-scale had a significantly higher infection rate and, also received significantly lower amounts of insulin during the perioperative and postoperative period compared to the group that were on a continuous insulin drip.

Conclusion

Most of the studies in this review showed a relationship between uncontrolled blood glucose and SSI rates among cancer patients undergoing surgery. There were higher odds of having SSI in patients who were diagnosed with diabetes compared to those without the disease. Results of studies that measured blood glucose regardless of diabetic status found a higher incidence of SSI in patients with hyperglycemia. Therefore, close monitoring should be done for those patients with a history of diabetes or hyperglycemia during pre, intra, and postoperative periods. More research continues to be carried out, contributing to the evidence on the relationship between SSI and blood glucose control in patients with cancer (Belluse et al., 2020). Integrating monitoring and control as a part of the operative experience is likely to reduce costs and improve outcomes for surgical cancer patients.

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