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FROM THE EDITOR

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This is the second issue of the journal this year with papers from Saudi Arabia, Turkey, Lebanon and Australia.

Aboshaiqah et al., did a systematic review was performed to assess cultural competence among nurses in Saudi Arabia. Nursing staffs are typically multi-national, especially in Saudi Arabia, and Saudi nurses deal with multicultural patients, which creates a culturally diverse atmosphere. As a result, cultural competence is essential. The study provides in-depth summaries of 11 papers included in this review. No studies published before 2014 investigated the cultural competence of Saudi Arabian nurses. However, the authors noted a sharp rise from 2020 in the number of studies dealing with this issue. Sample sizes ranged from 11 to 650 participants. The authors concluded that Healthcare systems should be structured to encourage the empowerment of nurses from different nationalities and build effective communication policies to improve cultural competency among nurses. Future research should look at the relationship between individual training programs designed to increase cultural competence and their effect on the quality

Dr. Mujallad, reviewed the Nursing Profession in the New Era of Saudi Arabia. People unfamiliar with Saudi Arabia will never realize the change the country is experiencing today. Women have become empowered over a short period. Change is happening now and is happening quickly. Women who have never even considered being engaged in higher positions are taking managerial and leadership positions. Along with the change that is taking place, the healthcare sector is one priority for the newly crowned prince Mohammed bin Salman in his 2030 vision to the nation; the Minister of Health addresses that nursing is the top priority to achieve the vision of the Kingdom of Saudi Arabia, pointing out that 50% of the total workforce in the health sector are nurses. The researcher used secondary data from the Ministry of Health in Saudi Arabia to do a Descriptive Comparative Research Design to compare the number of nursing students to medical students in the major public universities in Saudi Arabia to see if there is a big difference between choosing nursing and medicine in the light of the high demand for the nursing profession.

Helvaci*, et al., looked whether autosplenectomy which is higher in females in sickle cell diseases is a good prognostic sign. The authors studied 222 males and 212 females with similar ages (30.8 vs 30.3 years, p>0.05, respectively). Although the higher prevalence of autosplenectomy (50.4% vs 53.3%, p<0.05), transfused units of red blood cells (RBCs) in their lives (48.1 vs 28.5, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), clubbing (14.8% vs 6.6%, p<0.001), coronary heart disease (CHD). The authors concluded that the sickled or just hardened RBCs-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood. Although RBCs suspensions and corticosteroids in acute, and aspirin with an anti-inflammatory dose plus low-dose warfarin plus hydroxyurea both in acute and chronic phases decrease severity, survivals are still shortened in both genders, dramatically. Although the higher prevalence of autosplenectomy, transfused units of RBCs in their lives disseminated teeth losses, ileus, cirrhosis, leg ulcers, clubbing, CHD, CRD, COPD, and stroke were all lower in females. So there may be an inverse relationship between autosplenectomy and severity of SCDs, and spleen may act as a chronic inflammatory focus as a filter of blood for these sickled or just hardened RBCs.

Helvaci*, et al., looked whether Male gender alone may be a bad prognostic feature in sickle cell diseases. Patients with RBCs transfusions of less than 50 units in their lives were put into the first and 50 units or higher were put into the second groups. There were 224 and 92 patients in the first and second groups, respectively. Mean ages were similar in them (28.9 vs 30.0 years, respectively, p>0.05). Although the lower prevalence of autosplenectomy (56.2% vs 45.6%, p<0.05), male ratio (45.5% vs 64.1%, p<0.001), white blood cells (WBCs) (14.931 vs 15.346/μL, p<0.05) and platelets (PLTs) (435.670 vs 498.310/μL, p= 0.005) counts, painful crises per year (3.8 vs 8.4, p= 0.000), smoking (12.0% vs 17.3%, p<0.05), clubbing (7.1% vs 15.2%, p<0.01), chronic obstructive pulmonary disease (COPD) (6.6% vs 20.6%, p<0.001), leg ulcers (11.6% vs 21.7%, p<0.01), stroke (5.8% vs 11.9%, p<0.05), chronic renal disease (CRD) (4.9% vs 14.1%, p<0.001), and coronary heart disease (CHD) (4.0% vs 8.6%, p<0.05) were higher in the second group, and mean age of mortality was lower in males (29.7 vs 33.3 years, p<0.05). The author conclude that although the lower prevalence of autosplenectomy, male ratio, WBCs and PLTs counts, painful crises per year, smoking, clubbing, COPD, leg ulcers, stroke, CRD, and CHD were higher in the second group, and mean age of mortality was lower in males. So male gender alone may be a bad prognostic feature that can not be explained by smoking alone at the younger age.

Helvaci*, et al., looked whether Red blood cell supports prolong the survival in sickle cell diseases. Patients with red blood cells (RBCs) transfusions of less than 50 units in their lives were put into the first and 50 units or higher were put into the second groups. There were 224 cases in the first and 92 cases in the second groups. Mean ages were similar in them (28.9 vs 30.0 years, respectively, p>0.05). Although the lower prevalence of autosplenectomy (56.2% vs 45.6%, p<0.05), male ratio (45.5% vs 64.1%, p<0.001), white blood cells (WBCs) (14.931 vs 15.346/μL, p<0.05) and platelets (PLTs) (435.670 vs 498.310/μL, p= 0.005) counts, painful crises per year (3.8 vs 8.4, p= 0.000), smoking (12.0% vs 17.3%, p<0.05), clubbing (7.1% vs 15.2%, p<0.01), chronic obstructive pulmonary disease (COPD) (6.6% vs 20.6%, p<0.001), leg ulcers (11.6% vs 21.7%, p<0.01), stroke (5.8% vs 11.9%, p<0.05), chronic renal disease (CRD) (4.9% vs 14.1%, p<0.001), coronary heart disease (CHD) (4.0% vs 8.6%, p<0.05), and mean age of mortality (29.5 vs 34.6 years, p<0.05) were all higher in the second group. The authors concluded that although the lower prevalence of autosplenectomy, male ratio, WBCs and PLTs counts, painful crises per year, smoking, clubbing, COPD, leg ulcers, stroke, CRD, CHD, and mean age of mortality were higher in the second group. So autosplenectomy may be a good, and male gender alone may be a bad prognostic feature that can not be explained by smoking alone at the younger age, and RBCs supports prolong the survival.

CULTURAL COMPETENCE IN NURSES IN SAUDI ARABIA: A SYSTEMATIC REVIEW

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Abstract

Background. Nursing staff are typically multi-national, especially in Saudi Arabia, and Saudi nurses deal with multicultural patients, which creates a culturally diverse atmosphere. As a result, cultural competence is essential.

Aim. To assess cultural competence among nurses in Saudi Arabia

Methods. A systematic review was performed to assess cultural competence among nurses in Saudi Arabia.

Findings. The study provides in-depth summaries of 11 papers included in this review. No studies published before 2014 investigated the cultural competence of Saudi Arabian nurses. However, the authors noted a sharp rise from 2020 in the number of studies dealing with this issue. Sample sizes ranged from 11 to 650 participants. Three studies were qualitative compared to eight quantitative studies. Seven studies focused on staff nurses, one on academic nurses, two on nursing students, and one on nurse leaders. Three concentrated on the academic setting, seven on clinical settings, and one on community settings. Most studies collected data from surveys, while a few used interviews and cross-sectional methodologies.

Conclusion. Healthcare systems should be structured to encourage the empowerment of nurses from different nationalities and build effective communication policies to improve cultural competency among nurses. Future research should look at the relationship between individual training programs designed to increase cultural competence and their effect on the quality of patient care. Also, further research should incorporate a more diverse range of cultures.

Keywords: Cultural competence, nurses, Saudi Arabia, patient outcome, knowledge, skills, attitude.

Introduction

The Kingdom of Saudi Arabia recently reformed its healthcare system to meet the general public's requirements and the objectives outlined in Saudi Vision 2030 (Albargawi et al., 2022). Vision 2030 for the Kingdom of Saudi Arabia is based on three pillars that represent distinct competitive advantages to create the best future for the nation. The Kingdom's position will allow it to strengthen its dominant position as the center of the Arab and Islamic worlds. Moreover, the domain will capitalize on its advantageous location to reinforce its position as a critical facilitator of global trade and to connect the three continents of Africa, Asia, and Europe (Vision 2030, 2022). Saudi Arabia has risen to prominence and earned a reputation for warmth and friendliness toward all Muslims. As a result, it occupies a specific place in the hearts of believers and pilgrims worldwide. Eight million people have visited the nation for Umrah in the past 10 years, a threefold increase. Thus, to fulfill the responsibility to show visitors proper hospitality, accepting cultural diversity is a moral duty (Vision 2030, 2022).

These accelerated changes impact nursing education and practice because Saudi Vision 2030 emphasizes the importance of high-quality healthcare. As a result, nurses must possess the necessary knowledge and skills to care for their patients to achieve the program's objectives (Albargawi et al., 2022). The nursing profession is multi-national, especially in Saudi Arabia, and Saudi nurses deal with multicultural patients, which creates a culturally diverse atmosphere. As a result, cultural competence is essential (Falatah et al., 2022). It is a range of skills and behaviors that allow a nurse to function well within the cultural environment of a patient from a different cultural background (Falatah et al., 2022). According to the Chicago School (2020), in nursing, it is the capacity to provide patients with the best medical treatment while exhibiting cultural knowledge of their beliefs, race, and values. It requires being aware of the cultural diversity of patients and treating them accordingly.

Madeline Leininger noted that in the 1950s, the significance of addressing cultural differences to facilitate efficient nursing interventions was already recognized (Leininger & McFarland, 2002). She postulated that it was essential for nurses to understand and address individual differences, which led to her theory of cultural care diversity and the universality of nursing. Leininger and McFarland (2002) described culture as "learned, shared, and transmitted values, beliefs, norms, and life practices of a particular group that guides thinking, decision, and actions in patterned ways" (Curtis et al., 2016; Leininger & McFarland, 2002). The language has changed over the ensuing decades to better convey this crucial part of care, but nevertheless, the emphasis on offering treatment that considers patients' preferences and beliefs has not changed. Leininger's goal to improve the standard of cultural competence and to aid healthcare workers in this endeavor led to the founding of the Transcultural Nursing Society (Curtis et al., 2016; Leininger & McFarland, 2002).

According to Falatah et al. (2022), cultural competence makes nurses more conscious of their culture's impact on their work. Culturally competent nurses know that everyone has a different way of classifying health and illness based on their beliefs. Therefore, nurses must be attentive to and knowledgeable about the various cultures represented in their workplaces. Nursing leaders must be aware that while cultural diversity can increase workplace performance, it can also result in less effective workplaces. Ineffective treatment of cultural differences may cause communication problems and compromise patient safety (The Chicago School, 2020).

Improving cultural competence can considerably reduce working under pressure and stereotyping among nurses. Therefore, it is strongly advised that cultural competence education be initiated at an early stage to equip nurses with the necessary training to offer culturally acceptable patient-centered care (Falatah et al., 2022). According to Curtis et al. (2016), several strategies or procedures have been employed by nurse educators to assist students in learning how to deliver culturally competent care, according to the nursing literature. However, disagreement exists regarding how to incorporate this into a nursing curriculum. Some of these initiatives include weaving cultural education into existing courses' curricula, service-learning approaches, and courses concentrating on culture. Healthcare executives and administrators should establish a tool for incorporating culturally competent nursing care in Saudi Arabia since the Kingdom is a critical facilitator of global trade and connects the three continents of Africa, Asia, and Europe (Curtis et al., 2016; Vision 2030, 2022).

This study aims to assess cultural competence among nurses in Saudi Arabia, since no systematic review has been done to address the issue. Accordingly, our objectives were to assess cultural competence among nurses in Saudi Arabia in the selected studies and to identify existing effects of cultural competence on knowledge, skills, attitudes, and patient outcomes. Therefore, the review centered on answering the question: What is the effect of cultural competence on knowledge, skills, attitude, and patient outcomes in Saudi Arabia?

Methods

Study Selection

The authors systematically reviewed the literature pertaining to cultural competence among nurses in Saudi Arabia and used four healthcare-focused databases: MEDLINE (via PubMed), CINHAL (via EBSCOhost), Embase, and Google Scholar. The authors performed the review using the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines and guidelines for conducting systematic reviews in medical education (Sharma et al., 2014).

Inclusion and Exclusion Criteria

Specific criteria were used to minimize bias. Studies met our inclusion criteria if they (a) had participants who were Saudi or non-Saudi nurses, undergraduate nursing students, staff nurses, and nurse leaders working in Saudi Arabia, (b) were published in indexed journals between January 2015 and January 2023, and (c) were written in English. Free full texts examined consisted of quantitative and qualitative studies, projects, a thesis, and a dissertation. The authors excluded studies that were non-refereed.

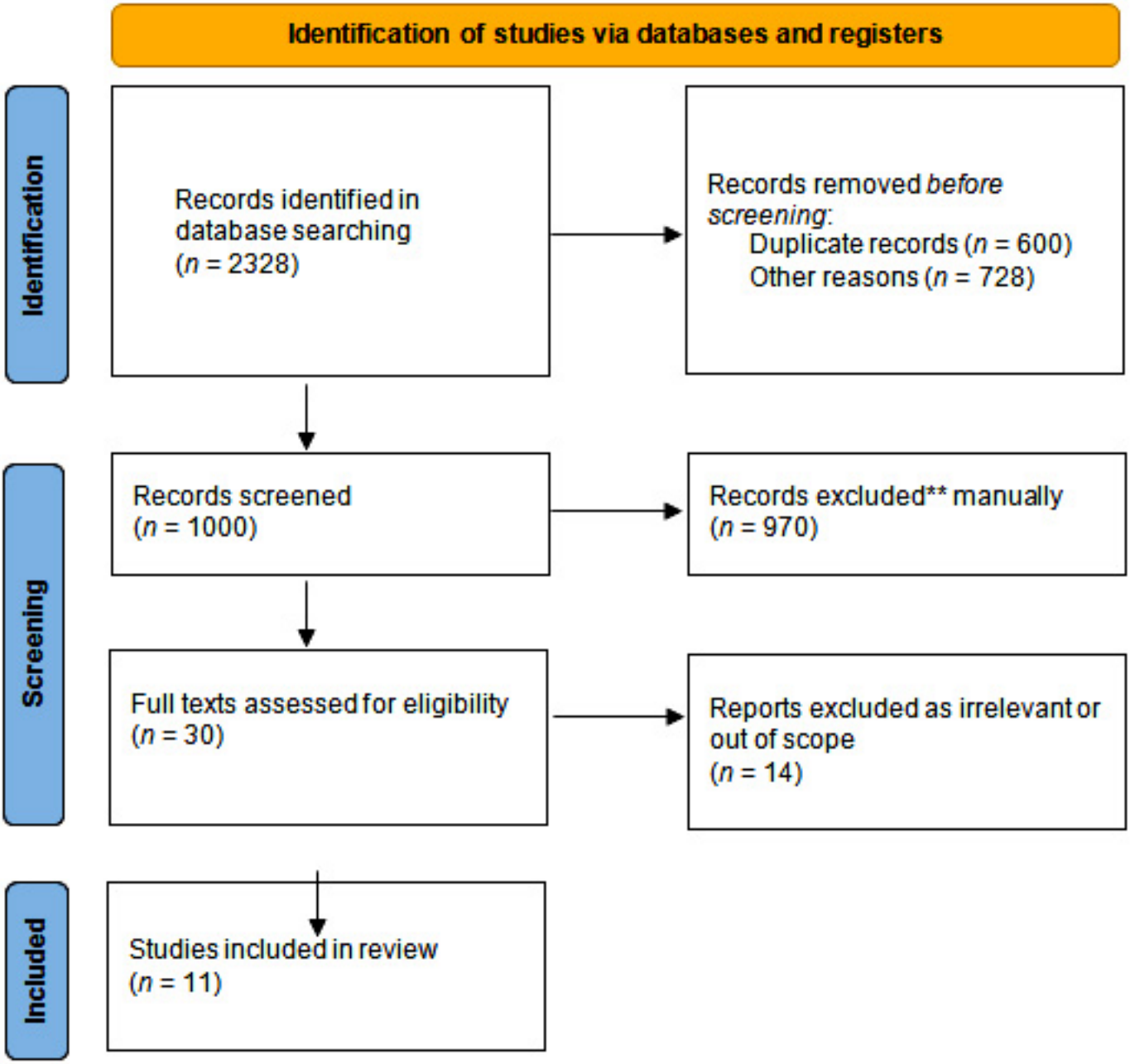
Search Terms

For this study, the researchers used a range of keywords in the literature search, such as “nurse,” “nurses,” “nursing,” Saudi nurses,” “cultural competence,” “culturally competent care,” “cultural competence in nursing,” “culture awareness,” and their MeSH terms, as well as Boolean operators (i.e., “AND” and “OR”). A manual search was performed based on the references in the retrieved articles. After removing duplicate articles, the authors evaluated the eligibility of the studies.

Search Strategy

Data collection was done in two stages by two reviewers. The two reviewers initially evaluated the papers individually and considered the titles, keywords, and abstract. The reviewers retrieved and assessed the full texts of articles in which the information given by the titles and abstracts was insufficient to determine inclusion, exclusion, and relevance to the research issue. The authors prepared tables to organize included and excluded items and the exclusion justification. Similarities and discrepancies between studies were incorporated into the analytic structure.

Figure 1. PRISMA flow diagram of the systematic review



Source: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Data Analysis

The team aggregated the results from the chosen studies and identified and listed the most frequently reported results in the table.

Results

The publications that were identified, screened, and excluded are summarized in the PRISMA flowchart (Fig. 1). Table 1 presents comprehensive summaries of each of the 11 papers included in the assessment. Before 2014, no research had examined cultural competence among Saudi Arabian nurses. However, in 2020, the authors saw a rapid increase in the number of studies addressing this topic (Table 1). The sample sizes ranged from 11 to 650 participants. Eight studies were quantitative, whereas three were qualitative.

While three studies concentrated on the academic setting, seven on clinical settings, and one on community settings, seven focused on staff nurses, one on academic nurses, two on nursing students, and one on nurse leaders. Most studies used surveys to collect data and the others used interviews. Most used a cross-sectional methodology.

Effect of Cultural Competence on Nurse's Knowledge, Skills, and Attitude

The nurses in one study by Falatah et al. (2020) reported difficulties and obstacles with language because pilgrims had come from a variety of backgrounds, and many of them were unfamiliar with English. Additionally, some participants noted a lack of professionalism in some staff members' commitment to patients.

According to the study outcomes of Hashish et al. (2020), most academic nursing educators have a moderate level of general cultural competence. They are committed to transcultural teaching behaviors as an indicator and predictor of seeking cultural competence. More culturally competent nurse educators were those who had greater professional experience, were fluent in another language, and incorporated culture into the courses they teach.

The first quantitative study that examined the relationship between cultural competence, conditions for work effectiveness, and effective communication in Saudi Arabia was conducted by Falatah et al. in 2022. The results of this study revealed a statistically significant relationship between cultural competence and effective communication ($r = 0.747$, $p < 0.001$) and between structural empowerment and cultural competence ($r = -0.123$, $p = 0.014$).

Notably, the total model that accounts for nurses' nationality while controlling for effective communication and structural empowerment significantly explains 56% of the variation in cultural competence.

Manlangit et al.'s (2022) study, performed at a university hospital in Saudi Arabia, found a substantial relationship between Middle Eastern racial characteristics and cultural sensitivity. Furthermore, leadership roles and years of experience in Saudi Arabia strongly correlated with culturally competent behaviors. In Saudi Arabia, the quality of the decision-making process is strongly correlated with experience levels. Effective decision-making is strongly correlated with cultural understanding, sensitivity, and culturally competent behavior.

However, there was no correlation between the quality of decision making and age, leadership experience, total nursing experience, diversity experience with different racial/ethnic groups, diversity experience with special populations, educational attainment, cultural diversity training, or being from a different race/ethnic group.

Another study showed that a multicultural nursing workforce in this setting was culturally competent. This may be due to a number of factors—prior exposure to a similar population, pre-departure orientation, and the nurses' extensive experience in this setting, as most nurses included had one or more years of experience. Additionally, nurses expressed an increased desire to learn about their patients' cultural traditions, worldviews, and practices in regard to health, spirituality, and religion, as well as attitudes toward people with disabilities. Nurses can frequently engage with and learn about different cultures by participating in educational programs, learning independently, and interacting with colleagues from many cultural backgrounds (Aboshaiqah et al., 2017).

According to Cruz et al. (2017), nursing students who had received diversity training in the past, who had experience caring for patients from a variety of cultural backgrounds or patients belonging to specific population groups, and those who had lived in an environment with a diverse population were more culturally competent than those who had not had these experiences. Regarding the effect of cultural competence on skill, the results also suggest that bridging program participants had a greater level of cultural competence than regular program participants (Cruz et al., 2017).

In Cruz et al.'s (2017) study, male students were more culturally competent than female students . These results might be explained by the gender-related cultural influences present in the Kingdom. Saudi Arabia is renowned for its strict laws and regulations, which have a significant cultural impact on many facets of Saudi life. As a result, Saudi women are less likely than Saudi men to interact with people from other cultures. Additionally, BSN nursing students in their last year had higher levels of cultural competence than their counterparts at lower levels (Cruz et al., 2017). Participation in training and education on cultural diversity has been found to improve cultural knowledge, skills, and attitudes. This study showed that Saudi nursing students have a respectable level of cultural competence (Cruz et al., 2017).

In a qualitative study by Almutairi et al. (2014) in a culturally varied setting, nurses found it difficult to be culturally competent in light of their cultural standards and those of Saudi culture. Regarding the effect of cultural competence on knowledge, none of the participants discussed these Saudi healthcare issues. The participants also needed to understand the philosophical principles guiding Saudi cultural norms about health and illness. Three participants acknowledged their knowledge of various customs, such as using ZamZam water and customary burning, but expressed doubts about their efficacy.

Furthermore, the nurses' experiences varied, and they had different opinions about how effective the general nursing orientation and the required post-orientation workshop had been. Orientation for one participant appeared to address only a small portion of cultural requirements; it concentrated mostly on introducing the hospital, which she felt was important. Most participants agreed with the statements presented (Almutairi et al., 2014).

Regarding the effect of cultural competence on nurses' skills, the participants' experiences suggested that some attempted to utilize their cultural knowledge and critical thinking abilities when examining their patients. For instance, they noted that certain Saudi citizens, particularly the elderly, tend to hide their discomfort due to cultural beliefs about suffering (Almutairi et al., 2014).

In a study by Halabi and de Beer (2018), most participants were able to interact with people from various cultures and were culturally conscious. A third of the respondents preferred to receive ongoing cultural training. Half of the students favored a specialized course on working with individuals from diverse cultures. Although students were exposed to some cultural knowledge content during their training, cultural desire reported the highest mean and cultural knowledge the lowest among the cultural competence subscales. "There was a negative correlation (−0.016) but no statistical significance between age and cultural knowledge" (Halabi & de Beer, 2018).

Another factor that affects cultural competence is educational level, which directly affects nurses' knowledge and skills. Regarding educational level categories and CCA, there were statistically significant differences between nurses at the .05 level, particularly for the bachelor's degree, compared to the diploma degree groups (Alharbi et al., 2020).

Effect of Cultural Competence on Patient Outcomes

According to Falatah et al. (2020), nurses were satisfied with their ability to offer patients quality care. In their study titled "Cultural Competence among Nursing Students in Saudi Arabia," the nursing students demonstrated a reasonable degree of cultural competence, as shown by the CCS's overall mean score of 73.35. This suggests that responders can offer nursing care suited to the culture of patients from various cultural backgrounds (Cruz et al., 2017). This is the first study on this subject in Saudi Arabia, making it useful for developing plans for Saudi Arabia's enhancement of cultural competence (Cruz et al., 2017).

The results of the interviews in a study titled "Understanding Cultural Competence in a Multicultural Nursing Workforce" showed that when language barriers exist, both parties' capacity for productive communication is greatly reduced. The participants' capability to communicate in Arabic was either weak or absent, which they frequently mentioned as being detrimental to the effectiveness of their interactions and, as a result, the care they could deliver (Almutairi et al., 2014).

In a qualitative study titled "The Challenges of Cultural Competence among Expatriate Nurses Working in Kingdom of Saudi Arabia," several themes emerged from the nurses' experiences caring for Muslims, such as the inability to perform nursing tasks due to cultural, religious, and linguistic limitations. Most nurses offered comparable illustrations and addressed related topics from their perspective, such as how patients' families, fasting, and prayer can negatively affect care (Alosaimi & Ahmad, 2016).

According to the study by Inocian et al. (2015), 53% of respondents were Indians and 39% were Filipinos, making up most of the respondents. They had experience providing nursing care in their respective cultures. There were noticeable differences in their cultural competence when they were categorized based on age, gender, level of education, nationality, and duration of service.

Title	Authors	Type (Method) Approach	Purpose	Sample and Sample size	Setting	Results
Transcultural Nurses Caring for Pilgrims for the First Time during Hajj Season in Saudi Arabia, 2020	Rawaih Falatah · Lamees Almansour· Aishah Alsolami· Arwa Aljehani· Ebtisam Al Dhubayban Rachel K. Walker	Qualitative descriptive phenomenology	To explore the lived experiences of transcultural Muslim nurses providing medical care to diverse pilgrims for the first time during the 2018 Hajj season	11 transcultural nurses; purposive sampling technique	Staff housing complex at Makkah, Al Noor Specialist Hospital, and Mona Hospitals	Their lived experiences are described in five themes: serving with satisfaction, a supportive and fair system; professional and personal values; differences; and difficulties and problems. The results highlight transcultural nurses' perceptions of the benefits and challenges of providing care during the Hajj and potential strategies to improve preparation and care quality. The study makes a unique contribution to understanding the lived experience of transcultural Muslim nurses who participated in Hajj services for the first time.
Assessment of Cultural Competence Level among Academic Nursing Educators and Associated Factors, Jeddah- Saudi Arabia, 2020	Ebtsam Aly Abou Hashish, Hadeel Abdul Rahman AlJohani, Ranin Ahmed Bahawi	Quantitative descriptive correlational	To assess the cultural competence levels of academic nursing educators and to identify the factors associated with the overall cultural competence score of nurse educators	45 Convenience sampling	College of Nursing – Jeddah	The majority of academic nursing educators had a moderate level of overall cultural competence. They are committed to transcultural teaching behaviors as motivators and predictors toward pursuing cultural competence. Nurse educators with more work experience, fluency in other languages, and integrating culture into their courses were more culturally competent. Nationality did not affect cultural competence. This study could be considered the first national study that assessed the cultural competence of nursing faculty teaching in BSN programs in the KSA. It may provide a deeper understanding of the factors affecting the cultural

						competence level of BSN faculty, provide suggestions for nursing education, and recognize the training needs of nursing faculty in the area of cultural competence.
The Association between Cultural Competence, Structural Empowerment, and Effective Communication among Nurses in Saudi Arabia: A Cross-Sectional Correlational Study, 2022	Rawaih Falatah, Lina Al-Harbi, and Eman Alhalal	Quantitative cross-sectional correlational study	To examine the association between cultural competence, structural empowerment, and effective communication among nurses in Saudi Arabia	396 Non-probability convenience sampling	Three hospitals in Jeddah City, Saudi Arabia	The findings showed statistically significant association between cultural competence and effective communication ($r = 0.747$, $p < 0.001$) and between structural empowerment and cultural competence ($r = -0.123$, $p = 0.014$). Moreover, the overall model with effective communication and structural empowerment as predictors, controlling for nurses' nationalities, significantly explains 56% of the variance in cultural competence. Structural empowerment did not significantly predict cultural competence ($b = -0.052$, $\beta = -0.069$, $p < 0.052$, 95% CI = [−0.104, −0.001]), while effective communication was found to be a significant positive independent predictor of cultural competence ($b = 0.745$, $\beta = 0.741$, $p < 0.001$, 95% CI = [0.677, 0.811]). This study is the first to examine the relationship between cultural competence, conditions for work effectiveness, and effective communication in Saudi Arabia.
Cultural Competence and Decision-Making of Nurse Leaders in a University Hospital in Saudi Arabia: A Descriptive Correlational Study, 2022	Arsenic T. Manlangit Fritz Gerald V. Jabonete Queenie Roxas-Ridulme	Descriptive correlational quantitative	To determine the quality of decision-making and cultural competence in terms of culturally competent	122 Nurse leaders in a university hospital in the Kingdom of Saudi Arabia	A 300-bed general teaching hospital on a university campus	Cultural awareness and sensitivity are significantly related to the Middle Eastern race. Culturally competent behavior is significantly related to years of experience in the KSA and leadership positions. The quality of decision-making is significantly related to years of experience in Saudi Arabia. Cultural awareness, sensitivity, and culturally competent behavior significantly

			behavior, cultural awareness, and sensitivity of nurse leaders			affect the quality of decision-making. There was no significant relationship between the quality of decision-making and age, years of experience in a leadership position, total years of nursing experience, diversity experience with different racial/ethnic groups, diversity experience with special populations, educational attainment, cultural diversity training, and being from a different race/ethnic group.
Enhancing Culturally Competent Nursing Care in Saudi Arabia, 2017	Ahmad E. Aboshaiqah Regie B. Tumala Ergie P. Inocian Adel F. Almutairi Mohammed Atallah	Cross-sectional descriptive quantitative	To examine self-reported individual assessment of cultural competence among expatriate nurses and to evaluate whether educational training led to improvement	584 Non-Saudi nurses	A large municipal university hospital in Riyadh, Saudi Arabia.	Multicultural nursing workforce in this setting was culturally competent in both pre and post-tests. Nurse participants reflected improvement in self-reflection and examination of one's own cultural background, biases, and prejudices related to race, culture, and sexual orientation that may influence their behaviors during care delivery. Such improvement indicated the effectiveness of the training program, which enabled nurses to engage in self-reflection and realize that their own cultural perspective is only one way of understanding the world around them. After the program, nurses showed more desire to learn about their patients' culture—cultural traditions, beliefs, health, spiritual, and religious practices, and attitudes toward disability. There was also improvement in engaging patients and family in decision making. Recognizing the significant role of family members in healthcare decisions, regardless of potential differences in professional values and beliefs, enabled the

						nurses to score higher on the post-training test. Nurses reflected improvement in their willingness to intervene if they observed other staff engaging in behaviors that appeared culturally insensitive, indicating that they were more culturally competent, sensitive to, and non-judgmental of patients' cultural backgrounds. The nurses increased their cultural competence by learning and using key Arabic words and colloquialisms used by their patients and families. This reflected their intention to provide culturally competent nursing care to Saudi patients by learning how to speak the Arabic language. Nurses can engage and learn about different cultures through education and learning activities, self-learning, and interaction with colleagues from other cultures. This process can refine their understandings and perceptions of other cultures.
Understanding Cultural Competence in a Multicultural Nursing Workforce: Registered Nurses' Experience in Saudi Arabia, 2014	Adel F. Almutairi, Alexandra McCarthy, Glenn E. Gardner	Qualitative, semi-structured interviews	To explore beliefs of cultural competence among non-Saudi nurses working in Saudi Arabia	24 Non-Saudi registered nurses working in various healthcare settings	An 800-bed teaching hospital for KSA National Guard employees and their families	The concept of cultural competence was difficult for nurses to understand in this atmosphere because of the cultural expectations of others and those of the prevailing Saudi culture. The use of a descriptive approach allowed the researchers to gain in-depth insights into the lived experiences of nurses related to cultural competence, providing a rich understanding of the phenomenon.

Exploring the Cultural Competence of Undergraduate Nursing Students in Saudi Arabia, 2017	Jehad O. Halabi, Jennifer de Beer	Descriptive quantitative	To explore the cultural competence of undergraduate nursing students in Saudi Arabia	205 Convenience sample	College of nursing at a health science university in Jeddah, Saudi Arabia.	The majority of students were able to interact with persons from various cultures and were culturally conscious. A third of respondents desired ongoing cultural training. Studying a specialized course on working with individuals from diverse cultures was favored by half of the students. Despite students being exposed to some cultural knowledge content throughout their training, cultural desire ranked highest and cultural knowledge ranked lowest on cultural competence subscales. The use of a quantitative method allowed researchers to objectively measure the cultural competence of undergraduate nursing students and identify factors influencing their competence.
Cultural Competence among Pediatric Registered Nurses in Saudi Arabia: A Cross Sectional Design, 2022	Manal Hamlan Alhamlan	Cross-sectional descriptive correlational quantitative	To investigate the level of cultural competence among pediatric registered nurses in Saudi Arabia	394 Non-probability sampling	Five hospitals in Riyadh, Saudi Arabia.	Analysis calculated a mean cultural competence score of 4.88 and mean self-reported competence of 4.13, suggesting a high level of cultural competence among pediatric registered nurses in Saudi Arabia. The use of non-probability sampling may introduce bias and a sample that is not representative of all pediatric registered nurses in Saudi Arabia.
The Challenges of Cultural Competence among Expatriate Nurses Working in the Kingdom of Saudi Arabia 2018	Dalyal N. Alosaimi	Qualitative hermeneutic phenomenology Interviews and focus groups	To examine the perspective of non-Muslim nurses caring for Muslim patients and of Muslim patients being cared for	20 Muslim patients, 20 non-Muslim nurses	Not specified	The study found that language barriers were a significant challenge for expatriate nurses in developing cultural competence. Moreover, non-Muslim nurses mix Islam as a religion and as a local culture. Nurses were not subjected to sufficient training and orientation either in their own countries or when they joined Saudi

			by non -Muslim nurses			hospitals. The use of a qualitative approach allowed the researchers to explore the challenges of cultural competence among expatriate nurses in depth and gain a deeper understanding of their experiences and perspectives.
Cultural Competence among Expatriate Nurses in Saudi Arabia 2015	Ergie Inocian	Descriptive baseline assessment survey	To establish a baseline understanding of cultural competence levels and identify areas needing improvement or potential gaps in their cultural competence	584 Expatriate nurses, random sampling	University hospital in the Kingdom of Saudi Arabia	The majority of the respondents were Indians and Filipinos (53% and 39%, respectively), who were culturally competent in providing nursing care. There were significant differences in their cultural competence based on age, gender, educational status, nationality, and length of service. The study serves as a baseline assessment survey, providing an initial understanding of the level of cultural competence among expatriate nurses and as a foundation for future research and interventions in the field.
Cultural Competence among Nursing Students in Saudi Arabia: A Cross-sectional Study, 2017	J.P. Cruz N. Alquwez C.P. Cruz Felicilda-Reynaldo L.M. Vitorino S.M.S. Islam	Descriptive cross-sectional quantitative	To assess the cultural competence of nursing students in a Saudi University	272 Nursing (BSN) students Convenience sample	The nursing depart-ment of a Saudi university in Riyadh province	In terms of cultural background, nursing students who had prior diversity training, experience caring for patients from diverse cultural backgrounds and in special population groups, and who had lived in a culturally diverse environment were more culturally competent than those without those experiences. The students manifested a fairly good level of cultural competence, as evidenced by the overall mean score of the CCS. This implies that the respondents possess the ability to provide culturally appropriate nursing care to patients with diverse

						cultural backgrounds. The findings suggest that students in the bridging program had a higher level of cultural competence than students in the regular program. Furthermore, male students were more culturally competent than females in this study, These results might be explained by the gender-related cultural influences present in the Kingdom. Saudi Arabia is renowned for its strict laws and regulations, which have a significant cultural impact on many facets of Saudi life. As a result, Saudi women are less likely than Saudi men to interact with people from other cultures. This study also reported that nursing students in the final year of the BSN program had better cultural competence than students in the lower levels. Cultural knowledge, skills, and attitude were shown to improve through training in cultural diversity. This study contributes to the existing knowledge about the cultural competence of Saudi nursing students. This is the first study conducted on this topic in Saudi Arabia, which makes it valuable in planning specific strategies for developing cultural competence among Saudi nursing students.

Discussion

Being culturally competent enables nurses to be aware of how their culture affects their profession. Culturally competent nurses know that everyone categorizes health and illness differently depending on their beliefs. As a result, nurses must be aware of and knowledgeable about the different cultures represented at work (Falatah et al., 2022).

Abundant evidence supports the idea that cultural competence training affects outcomes, including nursing knowledge, attitudes, and abilities. Although this comprehensive review found that cultural competence affects nurses' knowledge, attitudes, and abilities, drawing conclusions from the available research about which training programs have the greatest effects on outcomes is challenging. There were no studies that compared various training methodologies or course materials, although our study discovered that a desire for cultural competence was a predictor and indicator of commitment to transcultural teaching behaviors, a finding in line with results reported by Chen et al. (2020).

A study we looked at generally showed that a multicultural nursing staff is culturally competent; this finding concurs with the results reported by Rittle (2015). Another study found that language barriers and lack of professionalism impacted Saudi Arabian nurses' cultural competence, in line with results reported by Grandpierre et al. (2018), and another factor—educational level—impacts nurses' knowledge and skills, thus influencing cultural competence (Alharbi et al., 2020). This finding is congruent with the results reported by Filej et al. (2016).

By engaging in educational programs, learning on their own, and interacting with coworkers from various cultural backgrounds, nurses can regularly engage with and learn about different cultures (Aboshaiqah et al., 2017). This finding is in agreement with the results of Kula et al. (2021), who showed that intervention effectively increased the participants' culturally competent knowledge.

The authors recommend that universities, organizations, providers, and policymakers implement educational initiatives to advance cultural competence. More research is required to confirm the effect of cultural competence on Saudi nurses.

Conclusion

Research in cultural competence is increasing. In this systematic review, eleven studies were selected to assess the effectiveness of cultural competency of nurses' knowledge, skills, attitude, and patient outcome in Saudi Arabia. Findings show that ANP diploma trainees are able to increase their cultural competency when they are properly oriented and guided by experts in education and allied health professionals and when they acquire the required clinical knowledge, skill, and the required attitude through various training strategies, which in turn improves patient outcomes. Professional cultural programs for faculties must be mandated and inclusive of the major constructs of cultural competence, specifically cultural encounters in clinical skills and interactions with individuals from culturally diverse backgrounds. Healthcare systems should be structured to encourage the empowerment of nurses from different nationalities and build effective communication policies to improve cultural competency among nurses. Future research should look at the relationship between individual training programs designed to increase cultural competence and their effect on the quality of patient care. Also, further research should incorporate a more diverse range of cultures.

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THE NURSING PROFESSION IN THE NEW ERA OF SAUDI ARABIA

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Abstract

People unfamiliar with Saudi Arabia will never realize the change the country is experiencing today. Women have become empowered over a short period. Change is happening now and is happening quickly. Women who have never even considered being engaged in higher positions are taking managerial and leadership positions. Along with the change that is taking place, the healthcare sector is one priority for the newly crowned prince Mohammed bin Salman in his 2030 vision to the nation. The Minister of Health addresses that nursing is the top priority to achieve the vision of the Kingdom of Saudi Arabia, pointing out that 50% of the total workforce in the health sector are nurses. The researcher used secondary data from the Ministry of Health in Saudi Arabia to do a Descriptive Comparative Research Design to compare the number of nursing students to medical students in the major public universities in Saudi Arabia to see if there is a big difference between choosing nursing and medicine in the light of the high demand for the nursing profession.

Key Words: Nursing, Saudi Arabia, Nursing Shortage, Vision 2030

Introduction

The Nursing Profession in the New Era of Saudi Arabia

Many Saudi women have been wondering and thinking in the quietness of their heart and looking around us and seeing how amazing women are doing many remarkable things. It has left us thinking, when is our turn. The Crown Prince Mohammed bin Salman stated in an interview on the television show 60 Minutes, "That Islam does not prohibit mixing between genders, and women are half of our society, so we have to give them the right to participate equally" (M. Salman, 60 Minutes, March 19, 2018). This was a correction of the entire Saudi path dealing with half of the society, "women" and a strong indication of how important the Saudi women are, and the is the most important message of Prophet Mohammed is to have a society that respects all people no matter their gender, race, and colour (Sahih al-Bukhari).

People unfamiliar with Saudi Arabia will never realize the change the country is experiencing today. Women have become empowered over a short period of time. Change is happening now and is happening quickly. Women who have never even considered being engaged in higher positions are taking managerial and leadership positions.

Now the Saudi Arabian ambassador to the United States is a woman (Alsoraihi, 2022). Along with the change that is taking place, the healthcare sector is one priority for the newly crowned prince Mohammed bin Salman. In his 2030 vision to the nation (Rahman & Al-Borie, 2021); the Minister of Health addresses that nursing is the top priority to achieve the vision of the Kingdom of Saudi Arabia, pointing out that 50% of the total workforce in the health sector are nurses (Ministry of Health, 2019).

Purpose

The aim is to compare the number of nursing students to the medicine students in the major public universities in Saudi Arabia to see if there is a big difference between choosing nursing and medicine in the light of the high demand for the nursing profession.

Review of the Literature

Universal Nursing Shortage

The country of Saudi Arabia is experiencing issues with its health care system due to the insufficient number of Saudi nurses to meet the country's needs. This nursing shortage is related to many factors, including the life expectancy of the Saudi population, which has increased from age 69 in 1990 to age 76 in 2012. Also, the annual population growth rate in Saudi Arabia has increased by 2.5% each year from 1990 to 2012, and that will lead to a growing demand for healthcare (Alghamdi & Urden, 2016). Furthermore, although the overall number of nurses who are working in Saudi Arabia is 140,389, only 51,350 are Saudi nurses. Thus, the representation of Saudi nurses among all the other registered nurses in Saudi Arabia is only 36.6% (Aboshaiqah, 2016).

The poor image of nurses as maids who must follow the physician's orders is still prominent and influences the decision-making of parents and children (Aboshaiqah, 2016). Some nursing students left their schools because they got married, and their husbands did not agree to let them continue studying to be nurses in the future. Moreover, many families did not like the idea that their daughters would work night shifts, long hours, and weekends (Lamadah & Sayed, 2014). Together, these issues led to a nursing shortage in Saudi Arabia. The public needs to be educated about nursing to be able to attract more Saudi citizens (Aboshaiqah, 2016).

Cultural beliefs have a big impact on the nursing profession in Saudi Arabia. Many Saudi families believe that nursing is an inappropriate profession for their daughters because they will be exposed to male patients. Such interaction between males and females is inappropriate in many Saudi families, given the importance of preserving modesty and gender segregation in Islam. Some nursing practices, such as taking care of the private (e.g. genital) areas, create a negative perception among conservative Muslims (Aboshaiqah, 2016). The necessity of separation of men and women in society is a debatable issue in Islam. Many scholars agree that the interaction of genders is acceptable in Islam as long as the female modesty requirement is met through modest dress and the interactions with unrelated men are limited to only conversations that discuss professional and educational issues. There are some considerations and limitations that should be considered when males and females interact. They should discuss only their joint work, and this necessitates maintaining respect and having limits between each other to prevent any prohibited relationship (e.g., sex outside marriage) that could occur between them (Smerecnik, 2010).

Improving the quality of patient care has become one of the major priorities for all healthcare providers, and making it happen in the hospital is mainly the responsibility of the nursing staff. Due to the fact that nurses are the largest group in the hospital who are delivering direct patient care, the quality of care for patients is strongly connected to the performance of the nursing staff. Many studies have shown that a shortage of nurses has a direct impact on patient care by correlating to longer lengths of stay and increased incidence of urinary tract infections, pneumonia, and cardiac arrest (Zarea et al, 2009).

The nursing shortage is a universal problem even in industrialized countries such as the United States of America. Joyce Murray, a nursing professor in the United States, said "As a faculty, we also have a very important role to play. We must communicate how the faculty shortage stands in the way of increasing the number of nurses who are available to provide healthcare in the United States" (Murray, 2005, p.2). The International Council of Nurses warned that there could be a shortage of 13 million nurses in the US by 2030 (International Council of Nurses, March 2023). Nurses and all other healthcare providers need to work together now more than ever to increase the size of

the nursing workforce and to design alternative ways to maintain the quality of care during nursing shortages.

Why do we need part-time nurses?

To overcome the nursing shortages or at least to increase the number of nurses around the globe, there have been many agencies to support hospitals with part-time nurses to fill the shortages that they are experiencing. Part-time nurses are not only beneficial to reduce the nursing shortages, but are also cost-effective because the nurses are paid hourly or by shift without the incentives that are given to the permanent nurses (Seo & Spetz, 2014).

There are some social issues that impact the nursing shortages too, as we discussed earlier, about the Saudi culture in Saudi Arabia and how the majority of the nursing profession are women. Part-time work will give them more flexibility to take care of their children, and allow gradual exposure to the workload stressors. Moreover, as healthcare providers are always at risk of getting sick while dealing with patients, part-time work will give them more time to recover from work. Finally, the culture of Saudi Arabia is family centered, so working too many night shifts will not allow the nurses to be engaged in many family occasions. That is why part-time nurses allow for a better adjustment to the considerations of family and friends (Halger, Maarten, Steffen & Hans, 2013).

Theoretical Framework

Theory of Reasoned Action

A theoretical model is an important component in research because it is the foundation that can guide scholars to identify which concepts are important, what these concepts are like, and how they may be related to each other. They shape what research questions are asked, and then influence how the findings are interpreted. The Theory of Reasoned Action (TRA) is a very common model that is used in vaccination behaviour literature and will guide this study (Dunn et al., 2015).

Concepts of the Theory

The components of the theory include the constructs of attitude toward the behaviour, subjective norms, behavioural intention, and outcome behaviour. How these four concepts are related is depicted in the following diagram (see Figure 1).

Applying the TRA to the Present Study

The author examined how the concepts used in the TRA can guide the study of how attitudes and subjective norms would influence intentions of Saudi students to choose the nursing major and will lead to improved quality care and reduced cost. The attitudes (which include reflection or are influenced by behavioural beliefs) and subjective norms will predict the behavioural intentions, which will lead to the behaviour. The attitudes toward the nursing profession in this study will be assessed by secondary data of the number of nursing students compared to medical students in Saudi Arabia. It is assumed that if nurses have positive attitudes toward the profession of nursing, they will work as nurses, and be effective. Subjective norms are important factors that affect decisions regarding any health issue. These norms include behavioural and cultural trends that affect personal decision-making when the students choose nursing as a profession. It will be measured through all the literature reviews regarding the Saudi families' opinions toward the nursing profession.

In this study, there are several subjective norms to consider. Subjective norms in this theory means the opinions of the surrounding people and beliefs about the behaviour. In the context of this study, some Saudi Arabian families see that nursing is not a prestigious profession for their daughter because in their opinion nurses are the assistants of the doctors. These subjective norms are expected to influence their intention to work as registered nurses when they graduate.

The diagram (see Figure 1) below summarizes the application of the TRC to the present study. It shows how the attitudes and the subjective norms are expected to affect intention to work as nurses. This, in turn, will lead to the desired behavioural outcomes. Future behaviour, the last element of the theory, will not be included during this study. If the results show that nurses have the intention to promote cervical cancer prevention methods then it will likely lead to the implementation of those methods in the future.

Ethics

No ethical approval was needed because the data was secondary data from the website of the Ministry of Health of Saudi Arabia (MOH).

Sampling Selection

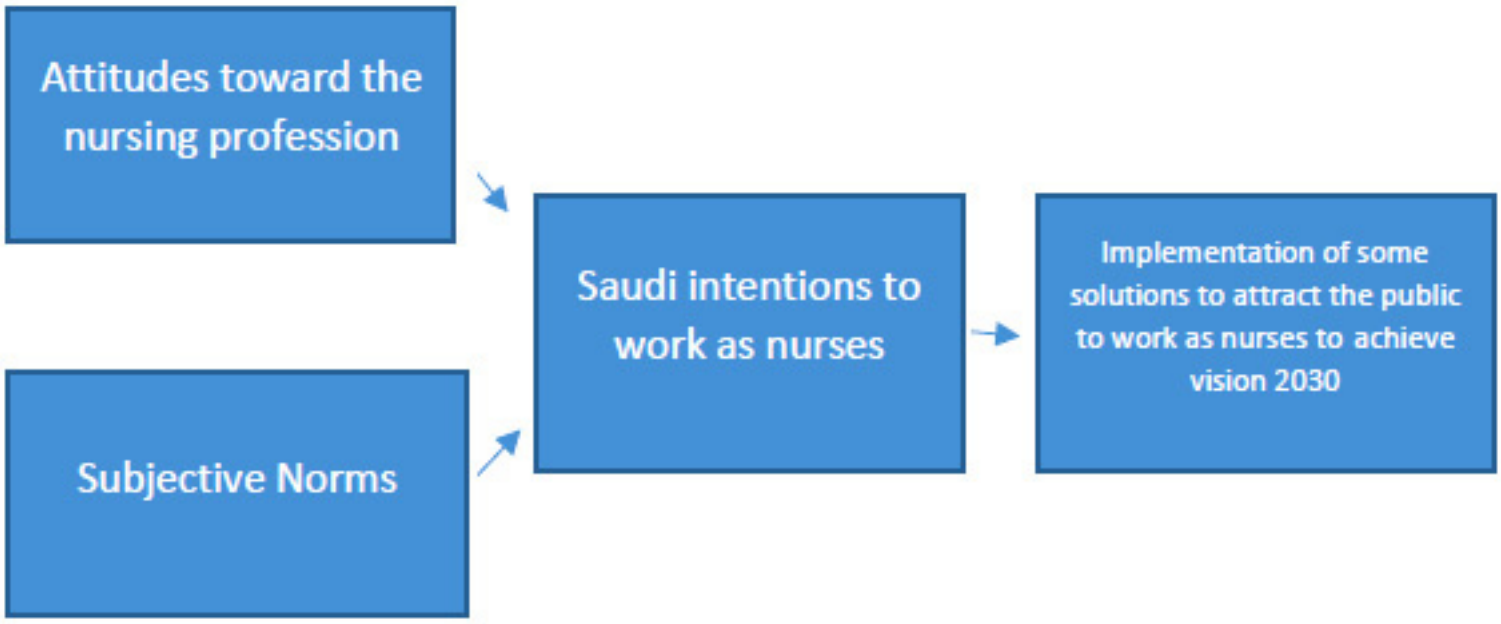
All the nursing and medicine student graduates who are studying in the major public universities in the year.

Design and Method

The data that has been used in this study was secondary data which is the use of existing data to answer new research questions. It is a proven methodology in many specialties. The use of this method in the nursing field has been very popular (Dunn et al., 2015).

The researchers used this data to do a Descriptive Comparative Research Design to show the intention of Saudi students to be nurses. The aim is to compare the number of nursing students to the medical students in the major public universities in Saudi Arabia to see if there is a big difference between choosing nursing and medicine in the light of the high demand for nursing profession.

Figure 1. Application of Theory of Reasoned Action to the Present Study



Results

Examination of Table 1 reveals that the majority of students have chosen a medicine major over the nursing major in most the universities that provided nursing and medicine majors. The results show that only in one university which is Hail University, the demand on nursing major is more than medicine. The number of the nursing students is (607). Thus, these data indicate the demand on nursing major is less than medicine.

Table 1: Comparison between the number of nursing and medical students in the Saudi Universities

	University	Medicine Students	Nursing Students
1	King Abdulaziz University	2941	624
2	Umm Al Qura University	2015	714
3	Taibah University	840	593
4	King Saud University	1754	1226
5	King Saud bin Abdulaziz University for Health Sciences	2518	1381
6	King Khalid University	1196	898
7	Imam Abdulrahman bin Faisal University	1236	440
8	Jazan University	917	759
9	Najran University	376	353
10	Al Qussaim University	704	191
11	Hail University	418	607
12	Northern Border University	769	343

Statistical Year Book 2021, Ministry of Health (MOH), Saudi Arabia

Discussion

Despite the fact that the majority of healthcare providers are nurses, and they make up around 60% of the health-care providers that are working at the hospitals, still the demand on nursing is low compared to medicine. After the COVID-19 pandemic, the World Health Organization (WHO) named the year of the pandemic as Nursing and Midwifery year to shed light of the importance of these professions, and they discovered the severe nursing shortage all over the world.

Saudi Arabia is one of the countries that has a nursing shortage and especially among the Saudi nurses. The Saudi nurses make up only 40% among the other nationalities in their country. The Saudi government is working hard to fill the gaps of the nursing shortage. During the pandemic, the crowned prince Mohammed bin Salman initiated an internal scholarship for the nursing profession to increase the number of nursing students. Moreover, the Ministry of Education (MOE) encouraged all the schools to find ways to attract students to the nursing profession. The Vision 2030 has a huge impact on the nursing profession and that has led to an increase of nursing students. This study showed the number of students on 2021, and it is really important to do another comparison after at least 3 to 5 years to see if there is any difference.

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AS A GOOD PROGNOSTIC SIGN, AUTOSPLENECTOMY IS HIGHER IN FEMALES IN SICKLE CELL DISEASES

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Abstract

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

Methods: All patients with the SCDs were included.

Results: We studied 222 males and 212 females with similar ages (30.8 vs 30.3 years, p>0.05, respectively). Although the higher prevalence of autosplenectomy (50.4% vs 53.3%, p<0.05), transfused units of red blood cells (RBCs) in their lives (48.1 vs 28.5, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), clubbing (14.8% vs 6.6%, p<0.001), coronary heart disease (CHD) (18.0% vs 13.2%, p<0.05), chronic renal disease (CRD) (9.9% vs 6.1%, p<0.05), chronic obstructive pulmonary disease (COPD) (25.2% vs 7.0%, p<0.001), and stroke (12.1% vs 7.5%, p<0.05) were all lower in females.

Conclusion: The sickled or just hardened RBCs-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood. Although RBCs suspensions and corticosteroids in acute, and aspirin with an anti-inflammatory dose plus low-dose warfarin plus hydroxyurea both in acute and chronic phases decrease severity, survivals are still shortened in both genders, dramatically. Although the higher prevalence of autosplenectomy, transfused units of RBCs in their lives disseminated teeth losses, ileus, cirrhosis, leg ulcers, clubbing, CHD, CRD, COPD, and stroke were all lower in females. So there may be an inverse relationship between autosplenectomy and severity of SCDs, and spleen may act as a chronic inflammatory focus as a filter of blood for these sickled or just hardened RBCs.

Key words: Sickled or just hardened red blood cells, capillary endothelial edema, myocardial infarction, stroke, sudden deaths, autosplenectomy, female gender

Introduction

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

Material and methods

The clinical study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients of the SCDs were included. The SCDs are diagnosed with the hemoglobin electrophoresis performed by means of high performance liquid chromatography (HPLC). Smoking and alcohol habits, acute painful crises per year, transfused units of RBCs in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. Cases 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. Patients with an acute painful crisis or any other inflammatory process were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C, marker of 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 BPs 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 was performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (12). Associated TMs were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC, becuase the SCDs with associated TMs show a milder clinic than the sickle cell anemia (SCA) (Hb SS) alone (13). Systolic BPs of the pulmonary artery of 40 mmHg or higher are accepted as pulmonary hypertension (PHT) (14). The criterion for diagnosis of COPD is a post-bronchodilator forced expiratory volume in one second/forced vital capacity of lower than 70% (15). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum, dyspnea, or hypoxia (16). An x-ray film of abdomen in upright position was taken 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. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or greater in males and 1.2 mg/dL or greater in females. Cirrhosis is diagnosed with physical examination, laboratory parameters, and ultrasonographic findings. Clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of greater than 1.0, and with the presence of Schamroth's sign (17, 18). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is performed for the cases with exercise electrocardiogram positivity. So CHD is diagnosed either angiographically or with the Doppler

echocardiographic findings as movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT. Sickle cell retinopathy is diagnosed with ophthalmologic examination in cases with visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were the methods of statistical analyses.

Results

The study included 222 males and 212 females with similar ages (30.8 vs 30.3 years, p>0.05, respectively). Prevalences of associated TMs were similar in both genders, too (72.5% vs 67.9%, p>0.05, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were higher in males (p<0.001 for both) (Table 1). Although the higher prevalence of autosplenectomy (50.4% vs 53.3%, p<0.05), transfused units of RBCs in their lives (48.1 vs 28.5, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), CRD (9.9% vs 6.1%, p<0.05), COPD (25.2% vs 7.0%, p<0.001), and stroke (12.1% vs 7.5%, p<0.05) were all lower in females but not ACS (2.7% vs 3.7%), PHT (12.6% vs 11.7), DVT and/or varices and/or telangiectasias (9.0% vs 6.6%), or mean age of mortality (30.2 vs 33.3 years) (p>0.05 for all) (Table 2). Beside that the mean ages of terminal consequences were shown in Table 3.

Table 1: Characteristic features of the study patients

Variables	Males with SCDs*	*p*-value	Females with SCDs
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 TMs‡	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) ‡Thalassemia minor

Table 2: Associated pathologies of the study patients

Variables	Males with SCDs*	*p*-value	Females with SCDs
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBCs‡	***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)***	***<0.05***	***53.3% (113)***
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
ACS*****	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ± 8.4 (19-50)	Ns	33.3 ± 9.2 (19-47)

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

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

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

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

Discussion

Acute painful crises are the most disabling symptoms of the SCDs. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stress are the most common precipitating factors of the crises (19). Although the sickled or just hardened RBCs-induced capillary endothelial damage, inflammation, and edema are present even at birth, the increased basal metabolic rate during such stresses aggravates the sickling and capillary endothelial damage, inflammation, and edema, and may terminate with disseminated tissue hypoxia and multiorgan failures-induced sudden deaths in the SCDs (20). So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with the following crises by leaving some sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with sudden end-organ failures and death during a final acute painful crisis that may even be silent, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCDs. Unfortunately, most of the deaths develop just after the hospital admission, and majority of such cases are without hydroxyurea therapy (21). Rapid RBCs supports are usually life-saving for such patients, although preparation of RBCs units for transfusion usually takes time. Beside that RBCs supports in emergencies become much more difficult in such terminal patients due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBCs complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBCs transfusions should be kept just for acute events and emergencies in the SCDs (22). According to our experiences, simple and repeated transfusions are superior to RBCs exchange in the SCDs (23). First of all, preparation of one or two units of RBCs suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk cases. Secondly, transfusions of one or two units of RBCs suspensions in each time decrease the severity of pain and relax anxiety of the patients and their relatives because RBCs transfusions probably have the strongest analgesic effects during such crises. Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation in whole body. Thirdly, transfusions of lesser units of RBCs suspensions in each time by means of the simple transfusions decrease transfusions-related complications including infections, iron overload, and blood group mismatch. Fourthly, transfusions of RBCs suspensions in the secondary health centers prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices. On the other

hand, pain is the result of complex and poorly understood interactions between RBCs, white blood cells (WBCs), platelets (PLTs), and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes is unknown. The adverse actions of WBCs on the capillary endothelium are of particular interest with regard to the cerebrovascular diseases in the SCDs. For instance, leukocytosis even in the absence of an infection was an independent predictor of the severity of the SCDs, and it was associated with the higher risk of stroke (24). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Because of the severity of pain, narcotic analgesics are usually required to control them (25), but according to our long term experience, simple and repeated RBCs transfusions are much more effective than the narcotics to control the intolerable pain in the SCDs.

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

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

low dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction (37). According to the medical literature, aspirin may also be effective in prevention of colorectal cancers (38). On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Reye syndrome is a rapidly worsening brain disease (39). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (40). The syndrome mostly affects children, but it can only affect fewer than one in a million children a year (40). It usually starts just after recovery from a viral infection, such as influenza or chicken pox (40). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (39). Although the liver toxicity typically occurs in the syndrome and the liver is enlarged in most cases, jaundice is usually not seen with it (39). Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling (40). Although the death occurs in 20-40% of patients, about one third of survivors get a significant degree of brain damage (39). Interestingly, about 90% of cases in children are associated with an aspirin use (41). Due to the risk of Reye syndrome, the US Food and Drug Administration recommends that aspirin or aspirin-containing products should not be prescribed for febrile patients under the age of 16 years (42). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (39). When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% of Reye syndrome was seen (40). Due to the higher side effects of corticosteroids in long term, and due to the very low risk of Reye syndrome but much higher risk of death due to the SCDs even in children, aspirin should be added with an anti-inflammatory dose even in childhood into the acute and chronic phase treatments of the SCDs (43).

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

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

induced mechanical stress and inflammatory reaction, and the toxic effects of cigarette smoke (53). On the other hand, PHT is also a common consequence, and its prevalence was detected between 20% and 40% in the SCDs (54, 55). Whereas we detected the ratio as 12.2% in the present study. The relatively younger mean ages of the study cases (30.8 years of males and 30.3 years of females) may be the cause of the lower prevalence of PHT in the present study. Although the higher prevalences of smoking and alcohol-like atherosclerotic risk factors in male gender, and although the higher prevalences of disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CRD, COPD, and stroke-like atherosclerotic consequences in male gender, and the male gender alone is being a risk factor for the systemic atherosclerosis, the similar prevalences of PHT and ACS in both genders also support nonatherosclerotic backgrounds of them in the SCDs in the present study. Similar to our result, women have up to four times of the risk of men for development of idiopathic PHT, and generally develop symptoms 10 years earlier than men in the literature with the unknown reasons, yet (56). Although COPD and CHD are the most common causes of PHT in the society (52, 57), and although COPD (25.2% vs 7.0%, $p<0.001$) and CHD (18.0% vs 13.2%, $p<0.05$) were higher in male gender in the present study, PHT was not higher in males, again. In another definition, PHT may have a sickled or just hardened RBCs-induced chronic thromboembolic whereas ACS may have an acute thromboembolic backgrounds in the SCDs (58, 59), because the mean age of ACS was lower than PHT (30.3 and 34.0 years, $p<0.05$), but its mortality was much higher than PHT in the literature (44, 45, 50).

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

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (69). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (70). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, or hepatic diseases or smoking which are characterized by chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect each other's functions in a short period of time. Similarly, digital clubbing is also common in the SCDs, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillaries in the SCDs. Beside the effects of SCDs, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, $p<0.001$) may also show some additional risks of male gender in the systemic atherosclerosis.

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

with lower crises rates, and if a tissue infarct occurs, lower WBCs counts may decrease severity of pain and tissue damage (32). Because the main action of hydroxyurea may be the suppression of hyperproliferative WBCs and PLTs in the SCDs (31), prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBCs and PLTs counts-induced exaggerated capillary endothelial inflammation and edema.

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

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

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

45 to 64 years, and 1.3% of those between 18 and 45 years of age, and the rates were higher among men (93). On average, women experience symptoms 10 years later than men, and women are less likely to recognize symptoms and seek treatment (91). Women who are free of stress from work life show an increase in the diameter of their blood vessels, leading to decreased progression of atherosclerosis (94). Similarly, CHD was detected as 18.0% vs 13.2% in men and women in the present study , respectively ($p<0.05$).

Stroke is an important cause of death, and usually develops as an acute thromboembolic event on the chronic atherosclerotic background. Aging, male gender, smoking, alcohol, and excess weight may be the major underlying causes. Stroke is a common complication of the SCDs, too (95, 96). We detected prevalences of stroke as 12.1% vs 7.5% in males and females in the present study, respectively ($p<0.05$). Similar to the leg ulcers, stroke is particularly higher with the SCA and higher WBCs counts (97). Sickling-induced capillary endothelial damage, activations of WBCs, PLTs, and coagulation system, and hemolysis may cause inborn and severe capillary endothelial inflammation, edema, and fibrosis in the SCDs (98). Probably, stroke may not have a macrovascular origin in the SCDs, and diffuse capillary endothelial edema may be much more important (99). Infections, inflammations, medical or surgical emergencies, and emotional stress may precipitate stroke by increasing basal metabolic rate, sickling, and capillary endothelial edema. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed secondary to the increased WBCs and PLTs-induced exaggerated capillary endothelial inflammation and edema in the absence of prominent fibrosis, yet (46).

The venous capillary endothelium may also be involved in the SCDs (100). Normally, leg muscles pump veins against the gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and telangiectasias develop. DVT may also cause varicose veins and telangiectasias. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus physical examination must be performed in the upright position. Although the relatively younger mean ages and significantly lower body mass index of the SCDs cases in the literature (10), the prevalences of DVT and/or varices and/or telangiectasias of the lower limbs were relatively higher in the present study (9.0% vs 6.6% in males and females, $p>0.05$, respectively), indicating an additional venous involvement of the SCDs. Similarly, priapism is the painful erection of penis that can not return to its flaccid state within four hours in the absence of any stimulation (101). It is an emergency because repeated damaging of the blood vessels may terminate with fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, and non-erectile penis (101). It is mainly seen with SCDs, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (102, 103). Ischemic (veno-occlusive), stuttering (recurrent ischemic), and nonischemic priapisms (arterial) are the three types (104). Ninety-five percent of clinically presented priapisms are the ischemic (veno-occlusive) disorders in which blood can not return adequately from the penis as in the SCDs, and they are very painful (101, 104). RBCs support is the treatment of choice in acute whereas hydroxyurea should be the treatment of choice in chronic phases (105). According to our experiences, hydroxyurea is highly effective for prevention of attacks and consequences of priapism if iniatiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillaries if initiated later in life.

Warfarin is an anticoagulant, and first came into large-scale commercial use in 1948 as a rat poison. It was formally approved as a medication to treat blood clots in human being by the U.S. Food and Drug Administration in 1954. In 1955, warfarin's reputation as a safe and acceptable treatment was bolstred when President Dwight David Eisenhower was treated with warfarin following a massive and highly publicized heart attack. Eisenhower's treatment kickstarted a transformation in medicine whereby CHD, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. Warfarin is found in the List of Essential Medicines of WHO. In 2020, it was the 58th most commonly prescribed medication in the United States. It does not reduce blood viscosity but inhibits blood coagulation. Warfarin is used to decrease the tendency for thrombosis, and it can prevent formation of future blood clots and reduce the risk of embolism. Warfarin is the best suited for anticoagulation in areas of slowly running blood such as in veins and the pooled blood behind artificial and natural valves, and in blood pooled in dysfunctional cardiac atria. It is commonly used to prevent blood clots in the circulatory system such as DVT and pulmonary embolism, and to protect against stroke in people who have atrial fibrillation (AF), valvular heart disease, or artificial heart valves. Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery. The warfarin initiation regimens are simple, safe, and suitable to be used in ambulatory and in patient settings (106). Warfarin should be initiated with a 5 mg dose, or 2 to 4 mg in the very elderly. In the protocol of low-dose warfarin, the target INR value is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR value is between 2.5 and 3.5 (107). When warfarin is used and international normalised ratio (INR) is in therapeutic range, simple discontinuation of the drug for five days is usually enough to reverse the effect, and causes INR to drop below 1.5 (108). Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Blood products should not be routinely used to reverse warfarin overdose, when vitamin K1 could work alone. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticlotting protein C and protein S are also inhibited, but

to a lesser degree. A few days are required for full effect to occur, and these effects can last for up to five days. The consensus agrees that patient self-testing and patient self-management are effective methods of monitoring oral anticoagulation therapy, providing outcomes at least as good as, and possibly better than, those achieved with an anticoagulation clinic. Currently available self-testing/self-management devices give INR results that are comparable with those obtained in laboratory testing. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is low with a yearly rate of 1-3% (109). All types of bleeding may occur, but the most severe ones are those involving the brain and spinal cord (109). The risk is particularly increased once the INR exceeds 4.5 (109). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (110). But thirteen publications from 11 cohorts including more than 48.500 total patients with more than 11.600 warfarin users were included in the meta-analysis (111). In patients with AF and non-end-stage CRD, warfarin resulted in a lower risk of ischemic stroke (p= 0.004) and mortality (p<0.00001), but had no effect on major bleeding (p>0.05) (111). Similarly, warfarin resumption is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (112). Death occured in 18.7% of patients who resumed warfarin and 32.3% who did not resume warfarin (p= 0.009) (112). Ischemic stroke occured in 3.5% of patients who resumed warfarin and 7.0% of patients who did not resume warfarin (p= 0.002) (112). Whereas recurrent ICH occured in 6.7% of patients who resumed warfarin and 7.7% of patients who did not resume warfarin without any significant difference in between (p>0.05) (112). On the other hand, patients with cerebral venous thrombosis (CVT) those were anticoagulated either with warfarin or dabigatran had low risk of recurrent venous thrombotic events (VTEs), and the risk of bleeding was similar in both regimens, suggesting that both warfarin and dabigatran are safe and effective for preventing recurrent VTEs in patients with CVT (113). Additionally, an INR value of about 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted in no increase in the number of men ever reporting minor bleeding episodes, although rectal bleeding occurs more frequently in those men who report this symptom (114). Non-rheumatic AF increases the risk of stroke, presumably from atrial thromboemboli, and long-term low-dose warfarin therapy is highly effective and safe in preventing stroke in such patients (115). There were just two strokes in the warfarin group (0.41% per year) as compared with 13 strokes in the control group (2.98% per year) with a reduction of 86% in the risk of stroke (p= 0.0022) (115). The mortality was markedly lower in the warfarin group, too (p= 0.005) (115). The warfarin group had a higher rate of minor hemorrhage (38 vs 21 patients) but the frequency of bleedings that required hospitalization or transfusion was the same in both group (p>0.05) (115). Additionally, very-low-dose warfarin was a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer (116). The warfarin dose was 1 mg daily for 6 weeks, and was adjusted to maintain the INR value of 1.3 to 1.9 (116). The average daily dose was 2.6 mg, and the mean INR was 1.5 (116). On the other hand, new oral anticoagulants had a favourable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding (117). Interestingly, rivaroxaban and low dose apixaban were associated with increased risks of all cause mortality compared with warfarin (118). The mortality rate was 4.1% per year in the warfarin group, as compared with 3.7% per year with 110 mg of dabigatran and 3.6% per year with 150 mg of dabigatran (p>0.05 for both) in patients with AF in another study (119). On the other hand, infections, medical or surgical emergencies, or emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths in the SCDs. So lifelong aspirin with an anti-inflammatory dose plus low-dose warfarin may be a life-saving treatment regimen even at childhood both to decrease severity of capillary endothelial inflammation and to prevent thromboembolic complications in the SCDs (120).

The spleen is found in all vertebrates with a similar structure to the lymph nodes. It acts primarily as a blood filter, and removes old and abnormal RBCs and recycles the iron. Additionally, it synthesizes antibodies and removes antibody-coated bacteria and blood cells from the circulation. Like the thymus, the spleen has only efferent lymphatic vessels, and it is the major lymphatic organ of the body. It has a central role in the reticuloendothelial system, and retains the ability to produce lymphocytes after birth. The spleen acts as a pool of peripheral blood cells which are released in case of a need. For example, it stores half of the body's monocytes in mice (121). In case of an injury, the monocytes migrate to the injured tissues and transform into dendritic cells and macrophages, and assist tissue healing (122). It was detected in the present study that 56.2% of cases of the first and 45.6% of cases of the second groups (p<0.05) had autosplenectomy, and these ratios were the highest ones among all other affected tissues of the body. So the spleen is probably the primarily affected organ in the SCDs, and it may act as a chronic inflammatory focus, particularly due to the high WBCs content. Although, a 28-year follow-up study of 740 veterans of World War II with surgical removal of spleen on the battlefield found that they showed significant excesses of mortality from pneumonia and CHD (123), the prevalence of CHD was lower in females with the higher prevalence of autosplenectomy in the present study.

As a conclusion, the sickled or just hardened RBCs-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood. Although RBCs suspensions and corticosteroids in acute, and aspirin with an anti-inflammatory dose plus low-dose warfarin plus hydroxyurea both in acute and chronic phases decrease severity, survivals are still shortened in both genders, dramatically. Although the higher prevalence of autosplenectomy, transfused units of RBCs in their lives

disseminated teeth losses, ileus, cirrhosis, leg ulcers, clubbing, CHD, CRD, COPD, and stroke were all lower in females. So there may be an inverse relationship between autosplenectomy and severity of SCDs, and spleen may act as a chronic inflammatory focus as a filter of blood for these sickled or just hardened RBCs.

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MALE GENDER ALONE MAY BE A BAD PROGNOSTIC FACTOR IN SICKLE CELL DISEASES

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Abstract

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

Methods: All patients were included.

Results: We studied 222 males and 212 females with similar ages (30.8 vs 30.3 years, p>0.05, respectively). Smoking (23.8% vs 6.1%, p<0.001), alcohol (4.9% vs 0.4%, p<0.001), transfused red blood cells (RBCs) in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), chronic obstructive pulmonary disease (COPD) (25.2% vs 7.0%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), clubbing (14.8% vs 6.6%, p<0.001), coronary heart disease (CHD) (18.0% vs 13.2%, p<0.05), chronic renal disease (CRD) (9.9% vs 6.1%, p<0.05), and stroke (12.1% vs 7.5%, p<0.05) were all higher, and autosplenectomy (50.4% vs 53.3%, p<0.05) and mean age of mortality were lower in males (30.2 vs 33.3 years, p<0.05).

Conclusion: The sickled or just hardened RBCs-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood. Although RBCs suspensions and corticosteroids in acute, and aspirin with an anti-inflammatory dose plus low-dose warfarin plus hydroxyurea both in acute and chronic phases decrease severity, survivals are still shortened in both genders, dramatically. Transfused units of RBCs in their lives, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, clubbing, CHD, CRD, and stroke were all higher, and autosplenectomy and mean age of mortality were lower in males which can not be explained by effects of smoking and alcohol alone at these younger mean ages, relatively.

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

Introduction

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

Material and methods

The clinical study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients of the SCDs were included. The SCDs are diagnosed with the hemoglobin electrophoresis performed by means of high performance liquid chromatography (HPLC). Smoking and alcohol habits, acute painful crises per year, transfused units of RBCs in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. Cases 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. Patients with an acute painful crisis or any other inflammatory process were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C, marker of 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 BPs 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 was performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (12). Associated TMs were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC, becuase the SCDs with associated TMs show a milder clinic than the sickle cell anemia (SCA) (Hb SS) alone (13). Systolic BPs of the pulmonary artery of 40 mmHg or higher are accepted as pulmonary hypertension (PHT) (14). The criterion for diagnosis of COPD is a post-bronchodilator forced expiratory volume in one second/forced vital capacity of lower than 70% (15). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum, dyspnea, or hypoxia (16). An x-ray film of abdomen in upright position was taken 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. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or greater in males and 1.2 mg/dL or greater in females. Cirrhosis is diagnosed with physical examination, laboratory parameters, and ultrasonographic findings. Clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of greater than 1.0, and with the presence of Schamroth's sign (17, 18). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is performed for the cases with exercise electrocardiogram positivity. So CHD is diagnosed either angiographically or with the Doppler echocardiographic findings as movement

disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT. Sickle cell retinopathy is diagnosed with ophthalmologic examination in cases with visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were the methods of statistical analyses.

Results

The study included 222 males and 212 females with similar ages (30.8 vs 30.3 years, p>0.05, respectively). Prevalences of associated TMs were similar in both genders, too (72.5% vs 67.9%, p>0.05, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were higher in males (p<0.001 for both) (Table 1). On the other hand, transfused RBCs in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), COPD (25.2% vs 7.0%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), CRD (9.9% vs 6.1%, p<0.05), and stroke (12.1% vs 7.5%, p<0.05) were all higher, and autosplenectomy (50.4% vs 53.3%, p<0.05) and mean age of mortality were lower in males (30.2 vs 33.3 years, p<0.05) (Table 2). Beside that the mean ages of terminal consequences were shown in Table 3.

Table 1: Characteristic features of the patients with sickle cell diseases

Variables	Males	*p*-value	Females
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 TMs†	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)***

*Nonsignificant (p>0.05) †Thalassemia minors

Table 2: Associated pathologies of the patients with sickle cell diseases

Variables	Males with SCDs*	*p*-value	Females with SCDs
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBCs‡	***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)***	***<0.05***	***53.3% (113)***
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
ACS*****	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ± 8.4 (19-50)	Ns	33.3 ± 9.2 (19-47)

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

Discussion

Acute painful crises are the most disabling symptoms of the SCDs. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stress are the most common precipitating factors of the crises (19). Although the sickled or just hardened RBCs-induced capillary endothelial damage, inflammation, and edema are present even at birth, the increased basal metabolic rate during such stresses aggravates the sickling and capillary endothelial damage, inflammation, and edema, and may terminate with disseminated tissue hypoxia and multiorgan failures-induced sudden deaths in the SCDs (20). So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with the following crises by leaving some sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with sudden end-organ failures and death during a final acute painful crisis that may even be silent, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCDs. Unfortunately, most of the deaths develop just after the hospital admission, and majority of such cases are without hydroxyurea therapy (21). Rapid RBCs supports are usually life-saving for such patients, although preparation of RBCs units for transfusion usually takes time. Beside that RBCs supports in emergencies become much more difficult in such terminal patients due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBCs complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBCs transfusions should be kept just for acute events and emergencies in the SCDs (22). According to our experiences, simple and repeated transfusions are superior to RBCs exchange in the SCDs (23). First of all, preparation of one or two units of RBCs suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk cases. Secondly, transfusions of one or two units of RBCs suspensions in each time decrease the severity of pain and relax anxiety of the patients and their relatives because RBCs transfusions probably have the strongest analgesic effects during such crises. Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation in whole body. Thirdly, transfusions of lesser units of RBCs suspensions in each time by means of the simple transfusions decrease transfusions-related complications including infections, iron overload, and blood group mismatch. Fourthly, transfusions of RBCs suspensions in the secondary health centers prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices. On the other hand, pain is the result of complex and poorly understood interactions between RBCs, white blood cells (WBCs), platelets (PLTs), and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes is unknown. The adverse actions of WBCs on the capillary endothelium are of particular interest with regard to the cerebrovascular diseases in the SCDs. For instance, leukocytosis even in the absence of an infection was an independent predictor of the severity of the SCDs, and it was associated with the higher risk of stroke (24). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Because of the severity of pain, narcotic analgesics are usually required to control them (25), but according to our long term experience, simple and repeated RBCs transfusions are much more effective than the narcotics to control the intolerable pain in the SCDs.

Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCDs (26). It is an orally-administered, cheap, safe, and effective drug, and it may be the only life-saving drug in the treatment of the SCDs (27, 28). It interferes with the cell division by blocking the formation of deoxyribonucleotides via inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the prevention of leukocytosis and thrombocytosis by blocking the DNA synthesis (29, 30). By this way, the inborn inflammatory and destructive process of the SCDs is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As also seen in the viral hepatitis cases, although presence of a continuous damage of sickled or just hardened RBCs on the capillary endothelium, the severity of destructive process may be exaggerated by the patients' own WBCs and PLTs. So suppression of proliferation of the WBCs and PLTs may limit the capillary endothelial damage, inflammation, edema, tissue ischemia, and end-organ failures in the body (31). Similarly, final Hb F levels in the hydroxyurea users did not differ from their pretreatment levels (32). The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with the SCA, and compared the results of patients treated with hydroxyurea or placebo (33). The study particularly researched effects of hydroxyurea on the painful crises, ACS, and requirement of RBCs transfusion. The outcomes were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was started for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations (33). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (33). But this study was performed just in severe SCA cases alone, and the rate of painful crises was decreased from 4.5 to 2.5 per year (33). Whereas we used all subtypes of the SCDs with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7 per year ($p<0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p<0.000$) (28). Parallel to our results, adults using hydroxyurea therapy for frequent

painful crises appear to have a reduced mortality rate after a 9-year follow-up period (34). The complications start to be seen even in infancy in the SCDs. For instance, infants with lower hemoglobin values were more likely to have higher incidences of clinical events such as ACS, acute painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them (35). Hydroxyurea therapy in early years of life may improve growth, and prevent end-organ failures. Transfusion programmes can also reduce all of the complications, but transfusions carry many risks including infections, iron overload, and development of allo-antibodies causing subsequent transfusions difficult. On the other hand, elevations of liver enzymes during some acute painful crises can not be reversed by withdrawing of the hydroxyurea therapy alone, instead withdrawal of all of the medications were highy effective in such cases during the 20-year experience on such patients. After normalization of the liver enzymes, the essential medications must be started one by one, instead of all of them at the same time, again. Thus hydroxyurea must even be used during the acute painful crises. Additionally, we observed mild, moderate, or even severe bone marrow suppressions and pancytopenia in some patients using high-dose hydroxyurea (35 mg/kg/day). Interestingly, such cases were completely silent other than some signs and symptoms of anemia, and all of them were resolved completely just by giving a few-day break for the hydroxyurea therapy and starting with smaller doses again.

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) used to reduce inflammation and acute thromboembolic events. Although aspirin has similar anti-inflammatory effects with the other NSAIDs, it also suppresses the normal functions of PLTs, irreversibly. This property causes aspirin being different from other NSAIDs, which are reversible inhibitors. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin's ability to suppress the production of prostaglandins (PGs) and thromboxanes (TXs) is due to its irreversible inactivation of the COX enzyme required for PGs and TXs synthesis. PGs are the locally produced hormones with some diverse effects, including the transmission of pain into the brain and modulation of the hypothalamic thermostat and inflammation. TXs are responsible for the aggregation of PLTs to form blood clots. In another definition, low-dose aspirin use irreversibly blocks the formation of TXA2 in the PLTs, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLTs (8-9 days). Since PLTs do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin inhibited the enzyme. The antithrombotic property of aspirin is useful to reduce the incidences of myocardial infarction, transient ischemic attack, and stroke (36). Heart attacks are caused primarily by blood clots, and low dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction (37). According to the medical literature, aspirin may also be effective in prevention of colorectal cancers (38). On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Reye syndrome is a rapidly worsening brain disease (39). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (40). The syndrome mostly affects children, but it can only affect fewer than one in a million children a year (40). It usually starts just after recovery from a viral infection, such as influenza or chicken pox (40). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (39). Although the liver toxicity typically occurs in the syndrome and the liver is enlarged in most cases, jaundice is usually not seen with it (39). Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling (40). Although the death occurs in 20-40% of patients, about one third of survivors get a significant degree of brain damage (39). Interestingly, about 90% of cases in children are associated with an aspirin use (41). Due to the risk of Reye syndrome, the US Food and Drug Administration recommends that aspirin or aspirin-containing products should not be prescribed for febrile patients under the age of 16 years (42). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (39). When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% of Reye syndrome was seen (40). Due to the higher side effects of corticosteroids in long term, and due to the very low risk of Reye syndrome but much higher risk of death due to the SCDs even in children, aspirin should be added with an anti-inflammatory dose even in childhood into the acute and chronic phase treatments of the SCDs (43).

ACS is a significant cause of mortality in the SCDs (44). It occurs most often as a single episode, and a past history is associated with a higher mortality rate (44). Similarly, all of 14 patients with ACS had just a single episode, and two of them were fatal in spite of the immediate RBCs and ventilation supports and antibiotic therapy in the present study. The remaining 12 patients are still alive without a recurrence at the end of the 10-year follow up period. ACS is the most common between two to four years of age, and its incidence decreases with aging (45). As a difference from atherosclerotic consequences, the incidence of ACS did not show an increase with aging in the present study, and the mean ages of the patients with ACS and SCDs were similar (30.3 vs 30.5 years, $p>0.05$, respectively). The decreased incidence with aging may be due to the high mortality rate during the first episode and/or an acquired immunity against various antigens, and/or decreased strength of immune response by aging. Probably, ACS shows an inborn severity of the SCDs, and the incidence of ACS is higher in severe patients such as patients with the SCA and higher WBCs counts (44, 45). According to our long term experiences on the SCDs, the increased metabolic rate during infections accelerates sickling, thrombocytosis, leukocytosis, and capillary endothelial damage and edema, and terminates

with end-organ failures-induced sudden deaths. ACS may also be a collapse of the pulmonary vasculature during such infections, and the exaggerated immune response against the sickled or just hardened RBCs-induced diffuse capillary endothelial damage may be important in the high mortality rate. A preliminary result from the Multi-Institutional Study of Hydroxyurea in the SCDs indicating a significant reduction of episodes of ACS with hydroxyurea therapy suggests that a considerable number of episodes are exaggerated with the increased numbers of WBCs and PLTs (46). Similarly, we strongly recommend hydroxyurea for all patients that may also be the cause of low incidence of ACS in our follow up cases (2.7% in males and 3.7% in females). Additionally, ACS did not show an infectious etiology in 66% (44, 45), and 12 of 27 cases with ACS had evidence of fat embolism in the other study (47). Beside that some authors indicated that antibiotics did not shorten the clinical course (48). RBCs support must be given as earliest as possible. RBCs support has the obvious benefits of decreasing sickle cell concentration directly, and suppressing bone marrow for the production of abnormal RBCs and excessive WBCs and PLTs. So they prevent further sickling-induced exaggerated capillary endothelial edema, disseminated tissue hypoxia, and end-organ failures-induced sudden deaths in the SCDs.

PHT is a condition of increased BPs within the arteries of the lungs. Shortness of breath, fatigue, chest pain, palpitation, swelling of legs and ankles, and cyanosis are common symptoms of PHT. Actually, it is not a diagnosis itself, instead solely a hemodynamic state characterized by resting mean pulmonary artery pressure of 25 mmHg or higher. An increase in pulmonary artery systolic pressure, estimated noninvasively by the echocardiography, helps to identify patients with PHT (49). The cause is often unknown. The underlying mechanism typically involves inflammation, fibrosis, and subsequent remodelling of the arteries. According to World Health Organization (WHO), there are five groups of PHT including pulmonary arterial hypertension, PHT secondary to left heart diseases, PHT secondary to lung diseases, chronic thromboembolic PHT, and PHT with unknown mechanisms (50). PHT affects about 1% of the world population, and its prevalence may reach 10% above the age of 65 years (51). Onset is typically seen between 20 and 60 years of age (50). The most common causes are CHD and COPD (50, 52). The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy (53). But the pulmonary vascular remodeling in the COPD may have a much more complex mechanism than just being the medial hypertrophy secondary to the long-lasting hypoxic vasoconstriction alone (53). In fact, all layers of the vessel wall appear to be involved with prominent intimal changes (53). The specific pathological picture could be explained by the combined effects of hypoxia, prolonged stretching of hyperinflated lungs-induced mechanical stress and inflammatory reaction, and the toxic effects of cigarette smoke (53). On the other hand, PHT is also a common consequence, and its prevalence was detected between 20% and 40% in the SCDs (54, 55). Whereas we detected the ratio as 12.2% in the present study. The relatively younger mean ages of the study cases (30.8 years of males and 30.3 years of females) may be the cause of the lower prevalence of PHT in the present study. Although the higher prevalences of smoking and alcohol-like atherosclerotic risk factors in male gender, and although the higher prevalences of disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CRD, COPD, and stroke-like atherosclerotic consequences in male gender, and the male gender alone is being a risk factor for the systemic atherosclerosis, the similar prevalences of PHT and ACS in both genders also support nonatherosclerotic backgrounds of them in the SCDs in the present study. Similar to our result, women have up to four times of the risk of men for development of idiopathic PHT, and generally develop symptoms 10 years earlier than men in the literature with the unknown reasons, yet (56). Although COPD and CHD are the most common causes of PHT in the society (52, 57), and although COPD (25.2% vs 7.0%, $p<0.001$) and CHD (18.0% vs 13.2%, $p<0.05$) were higher in male gender in the present study, PHT was not higher in males, again. In another definition, PHT may have a sickled or just hardened RBCs-induced chronic thromboembolic whereas ACS may have an acute thromboembolic backgrounds in the SCDs (58, 59), because the mean age of ACS was lower than PHT (30.3 and 34.0 years, $p<0.05$), but its mortality was much higher than PHT in the literature (44, 45, 50).

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

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (69). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (70). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, or hepatic diseases or smoking which are characterized by chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect each other's functions in a short period of time. Similarly, digital clubbing is also common in the SCDs, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillaries in the SCDs. Beside the effects of SCDs, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, p<0.001) may also show some additional risks of male gender in the systemic atherosclerosis.

Leg ulcers are seen in 10% to 20% of the SCDs, and the ratio was 13.5% in the present study (71). Its prevalence increases with aging, male gender, and SCA (72). Similarly, its ratio was higher in males (19.8% vs 7.0%, p<0.001), and mean age of the leg ulcer patients was higher than the remaining ones in the present study (35.3 vs 29.8 years, p<0.000). The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (71). As an evidence of their atherosclerotic background, the leg ulcers occur in the distal segments of the body with a lesser collateral blood supply (71). The sickled or just hardened RBCs-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes, again (72). Prolonged exposure to the sickled or just hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCDs. The sickled or just hardened RBCs-induced venous insufficiencies may also accelerate the highly destructive process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood may be the main cause of delayed wound and fracture healings in the lower extremities. Smoking and alcohol may also have some additional atherosclerotic effects on the leg ulcers in males. Although presence of a continuous damage of hardened RBCs on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBCs counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBCs counts may decrease severity of pain and tissue damage (32). Because the main action of hydroxyurea may be the suppression of hyperproliferative WBCs and PLTs in the SCDs (31), prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBCs and PLTs counts-induced exaggerated capillary endothelial inflammation and edema.

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

The increased frequency of CRD can also be explained by aging of the human being, and increased prevalence of excess weight all over the world (80, 81). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, smoking, alcohol, inflammatory or infectious processes, and cancers may be the main underlying causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts. Excess weight-induced hyperglycemia, dyslipidemia, elevated BPs, and insulin resistance may cause tissue inflammation and immune cell activation (82). For example, age (p= 0.04), high-sensitivity C-reactive protein (p= 0.01), mean

arterial BPs (p= 0.003), and DM (p= 0.02) had significant correlations with the CIMT (81). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BPs with excess weight (83). Excess weight also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (83). However, along with the increased BPs, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (84). With prolonged weight excess, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in cases with excess weight, CRD progresses much faster (83). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (85). Although some authors reported that alcohol was not related with the CRD (85), various metabolites of alcohol circulate even in the renal capillaries, and give harm to the renal capillary endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature (78). Although CRD is due to the atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (86), and the most common cause of death was the cardiovascular diseases in the CRD again (87). The sickled or just hardened RBCs-induced capillary endothelial damage may be the main cause of CRD in the SCDs, again (88).

CHD is the most common of the cardiovascular diseases (89). In adults who go to the emergency department with an unclear cause of pain, about 30% have pain due to CHD (90). Although half of cases are linked to genetics, physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, high BP, high blood glucose, dyslipidemia, smoking, alcohol, chronic inflammations, prolonged infections, and cancers may be the most common causes (91). It is the reduction of blood flow to the heart muscle due to build-up of atherosclerotic plaques secondary to the chronic inflammation of the arteries. It can present with stable angina, unstable angina, myocardial infarction, and sudden cardiac death (89). It is usually symptomatic with increased basal metabolic rate and emotional stress (92). It is the cause of deaths in 15.6% of all deaths, globally (92). So it is the most common cause of death in the world, nowadays (92). In the United States in 2010, about 20% of those over the age of 65 years had CHD, while it was present in 7% of those between the ages of 45 to 64 years, and 1.3% of those between 18 and 45 years of age, and the rates were higher among men (93). On average, women experience symptoms 10 years later than men, and women are less likely to recognize symptoms and seek treatment (91). Women who are free of stress from work life show an increase in the diameter of their blood vessels, leading to decreased progression of atherosclerosis (94). Similarly, CHD was detected as 18.0% vs 13.2% in men and women in the present study , respectively ($p<0.05$).

Stroke is an important cause of death, and usually develops as an acute thromboembolic event on the chronic atherosclerotic background. Aging, male gender, smoking, alcohol, and excess weight may be the major underlying causes. Stroke is a common complication of the SCDs, too (95, 96). We detected prevalences of stroke as 12.1% vs 7.5% in males and females in the present study, respectively ($p<0.05$). Similar to the leg ulcers, stroke is particularly higher with the SCA and higher WBCs counts (97). Sickling-induced capillary endothelial damage, activations of WBCs, PLTs, and coagulation system, and hemolysis may cause inborn and severe capillary endothelial inflammation, edema, and fibrosis in the SCDs (98). Probably, stroke may not have a macrovascular origin in the SCDs, and diffuse capillary endothelial edema may be much more important (99). Infections, inflammations, medical or surgical emergencies, and emotional stress may precipitate stroke by increasing basal metabolic rate, sickling, and capillary endothelial edema. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed secondary to the increased WBCs and PLTs-induced exaggerated capillary endothelial inflammation and edema in the absence of prominent fibrosis, yet (46).

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

the treatment of choice in acute whereas hydroxyurea should be the treatment of choice in chronic phases (105). According to our experiences, hydroxyurea is highly effective for prevention of attacks and consequences of priapism if iniatiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillaries if initiated later in life.

Warfarin is an anticoagulant, and first came into large-scale commercial use in 1948 as a rat poison. It was formally approved as a medication to treat blood clots in human being by the U.S. Food and Drug Administration in 1954. In 1955, warfarin's reputation as a safe and acceptable treatment was bolstred when President Dwight David Eisenhower was treated with warfarin following a massive and highly publicized heart attack. Eisenhower's treatment kickstarted a transformation in medicine whereby CHD, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. Warfarin is found in the List of Essential Medicines of WHO. In 2020, it was the 58th most commonly prescribed medication in the United States. It does not reduce blood viscosity but inhibits blood coagulation. Warfarin is used to decrease the tendency for thrombosis, and it can prevent formation of future blood clots and reduce the risk of embolism. Warfarin is the best suited for anticoagulation in areas of slowly running blood such as in veins and the pooled blood behind artificial and natural valves, and in blood pooled in dysfunctional cardiac atria. It is commonly used to prevent blood clots in the circulatory system such as DVT and pulmonary embolism, and to protect against stroke in people who have atrial fibrillation (AF), valvular heart disease, or artificial heart valves. Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery. The warfarin initiation regimens are simple, safe, and suitable to be used in ambulatory and in patient settings (106). Warfarin should be initiated with a 5 mg dose, or 2 to 4 mg in the very elderly. In the protocol of low-dose warfarin, the target INR value is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR value is between 2.5 and 3.5 (107). When warfarin is used and international normalised ratio (INR) is in therapeutic range, simple discontinuation of the drug for five days is usually enough to reverse the effect, and causes INR to drop below 1.5 (108). Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Blood products should not be routinely used to reverse warfarin overdose, when vitamin K1 could work alone. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticlotting protein C and protein S are also inhibited, but to a lesser degree. A few days are required for full effect to occur, and these effects can last for up to five days. The consensus agrees that patient self-testing and patient self-management are effective methods of monitoring oral anticoagulation therapy, providing outcomes at least as good as, and possibly better than, those achieved with an anticoagulation clinic. Currently available self-testing/self-management devices give INR results that are comparable with those obtained in laboratory testing. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is low with a yearly rate of 1-3% (109). All types of bleeding may occur, but the most severe ones are those involving the brain and spinal cord (109). The risk is particularly increased once the INR exceeds 4.5 (109). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (110). But thirteen publications from 11 cohorts including more than 48.500 total patients with more than 11.600 warfarin users were included in the meta-analysis (111). In patients with AF and non-end-stage CRD, warfarin resulted in a lower risk of ischemic stroke ($p= 0.004$) and mortality ($p<0.00001$), but had no effect on major bleeding ($p>0.05$) (111). Similarly, warfarin resumption is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (112). Death occured in 18.7% of patients who resumed warfarin and 32.3% who did not resume warfarin ($p= 0.009$) (112). Ischemic stroke occured in 3.5% of patients who resumed warfarin and 7.0% of patients who did not resume warfarin ($p= 0.002$) (112). Whereas recurrent ICH occured in 6.7% of patients who resumed warfarin and 7.7% of patients who did not resume warfarin without any significant difference in between ($p>0.05$) (112). On the other hand, patients with cerebral venous thrombosis (CVT) those were anticoagulated either with warfarin or dabigatran had low risk of recurrent venous thrombotic events (VTEs), and the risk of bleeding was similar in both regimens, suggesting that both warfarin and dabigatran are safe and effective for preventing recurrent VTEs in patients with CVT (113). Additionally, an INR value of about 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted in no increase in the number of men ever reporting minor bleeding episodes, although rectal bleeding occurs more frequently in those men who report this symptom (114). Non-rheumatic AF increases the risk of stroke, presumably from atrial thromboemboli, and long-term low-dose warfarin therapy is highly effective and safe in preventing stroke in such patients (115). There were just two strokes in the warfarin group (0.41% per year) as compared with 13 strokes in the control group (2.98% per year) with a reduction of 86% in the risk of stroke ($p= 0.0022$) (115). The mortality was markedly lower in the warfarin group, too ($p= 0.005$) (115). The warfarin group had a higher rate of minor hemorrhage (38 vs 21 patients) but the frequency of bleedings that required hospitalization or transfusion was the same in both group ($p>0.05$) (115). Additionally, very-low-dose warfarin was a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer (116). The warfarin dose was 1 mg daily for 6 weeks, and was adjusted to maintain the INR value of 1.3 to 1.9 (116). The average daily dose was 2.6 mg, and the mean INR was 1.5 (116). On the other hand, new oral anticoagulants had a favourable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleeding as for warfarin, but increased

gastrointestinal bleeding (117). Interestingly, rivaroxaban and low dose apixaban were associated with increased risks of all cause mortality compared with warfarin (118). The mortality rate was 4.1% per year in the warfarin group, as compared with 3.7% per year with 110 mg of dabigatran and 3.6% per year with 150 mg of dabigatran ($p>0.05$ for both) in patients with AF in another study (119). On the other hand, infections, medical or surgical emergencies, or emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths in the SCDs. So lifelong aspirin with an anti-inflammatory dose plus low-dose warfarin may be a life-saving treatment regimen even at childhood both to decrease severity of capillary endothelial inflammation and to prevent thromboembolic complications in the SCDs (120).

The spleen is found in all vertebrates with a similar structure to the lymph nodes. It acts primarily as a blood filter, and removes old and abnormal RBCs and recycles the iron. Additionally, it synthesizes antibodies and removes antibody-coated bacteria and blood cells from the circulation. Like the thymus, the spleen has only efferent lymphatic vessels, and it is the major lymphatic organ of the body. It has a central role in the reticuloendothelial system, and retains the ability to produce lymphocytes after birth. The spleen acts as a pool of peripheral blood cells which are released in case of a need. For example, it stores half of the body's monocytes in mice (121). In case of an injury, the monocytes migrate to the injured tissues and transform into dendritic cells and macrophages, and assist tissue healing (122). It was detected in the present study that 56.2% of cases of the first and 45.6% of cases of the second groups ($p<0.05$) had autosplenectomy, and these ratios were the highest ones among all other affected tissues of the body. So the spleen is probably the primarily affected organ in the SCDs, and it may act as a chronic inflammatory focus, particularly due to the high WBCs content (123). Although, a 28-year follow-up study of 740 veterans of World War II with surgical removal of spleen on the battlefield found that they showed significant excesses of mortality from pneumonia and CHD (124), the prevalence of CHD was lower in females with the higher prevalence of autosplenectomy in the present study.

As a conclusion, the sickled or just hardened RBCs-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood. Although RBCs suspensions and corticosteroids in acute, and aspirin with an anti-inflammatory dose plus low-dose warfarin plus hydroxyurea both in acute and chronic phases decrease severity, survivals are still shortened in both genders, dramatically. Transfused units of RBCs in their lives, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, clubbing, CHD, CRD, and stroke were all higher, and autosplenectomy and mean age of mortality were lower in males which can not be explained by effects of smoking and alcohol alone at these younger mean ages, relatively.

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RED BLOOD CELL SUPPORTS PROLONG THE SURVIVAL IN SICKLE CELL DISEASES

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Abstract

Background: Hardened red blood cells (RBCs)-induced capillary endothelial damage initiates at birth in sickle cell diseases.

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

Results: There were 224 cases in the first and 92 cases in the second groups. Mean ages were similar in them (28.9 vs 30.0 years, respectively, p>0.05). Although the lower prevalence of autosplenectomy (56.2% vs 45.6%, p<0.05), male ratio (45.5% vs 64.1%, p<0.001), white blood cells (WBCs) (14.931 vs 15.346/μL, p<0.05) and platelets (PLTs) (435.670 vs 498.310/μL, p= 0.005) counts, painful crises per year (3.8 vs 8.4, p= 0.000), smoking (12.0% vs 17.3%, p<0.05), clubbing (7.1% vs 15.2%, p<0.01), chronic obstructive pulmonary disease (COPD) (6.6% vs 20.6%, p<0.001), leg ulcers (11.6% vs 21.7%, p<0.01), stroke (5.8% vs 11.9%, p<0.05), chronic renal disease (CRD) (4.9% vs 14.1%, p<0.001), coronary heart disease (CHD) (4.0% vs 8.6%, p<0.05), and mean age of mortality (29.5 vs 34.6 years, p<0.05) were all higher in the second group.

Conclusion: Although the lower prevalence of autosplenectomy, male ratio, WBCs and PLTs counts, painful crises per year, smoking, clubbing, COPD, leg ulcers, stroke, CRD, CHD, and mean age of mortality were higher in the second group. So autosplenectomy may be a good, and male gender alone may be a bad prognostic feature that can not be explained by smoking alone at the younger age, and RBCs supports prolong the survival.

Key words: Sickle cell diseases, hardened red blood cells, capillary endothelial damage, capillary endothelial edema, myocardial infarction, stroke, red blood cell supports

Introduction

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

Material and methods

The study was performed in the Hematology Service of the Mustafa Kemal University between March 2007 and February 2014. All patients with the SCDs were studied. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Their medical histories including numbers of painful crises per year, units of transfused RBCs in their lives, smoking habit, regular alcohol consumption, leg ulcers, stroke, and surgical operations were learnt. Cases with a history of one pack-year were accepted as smokers, and cases with a history of one drink a day for one year were accepted as drinkers. A check up procedure including serum iron, total iron binding capacity, serum ferritin, serum creatinine value on three occasions, hepatic function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves, and to measure the systolic BPs of pulmonary artery, an abdominal ultrasonography, a Doppler ultrasonography to evaluate the portal blood flow in required cases, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips was performed. Other bone areas for avascular necrosis were scanned according to the patients' complaints. Cases with acute painful crises or any other inflammatory event were treated at first, and then the spirometric pulmonary function tests to diagnose COPD, the Doppler echocardiography to measure the systolic BPs of pulmonary artery, peripheral blood counts, renal and hepatic function tests, and measurement of serum ferritin were performed on the silent phase. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70% (12). Systolic BPs of the pulmonary artery of 40 mmHg or higher during the silent phase are accepted as pulmonary hypertension (13). Avascular necrosis of bones was detected via MRI (14). Autosplenectomy is diagnosed, ultrasonographically. CRD is diagnosed with a permanently elevated serum creatinine level which is 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females on the silent phase. Cirrhosis is diagnosed with hepatic function tests, ultrasonographic findings, ascites, and histologic procedure in case of requirement. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (15, 16). Associated TMs were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC, becuase the SCDs with associated TMs show a milder clinic than the sickle cell anemia (SCA) (Hb SS) alone (17). A stress electrocardiography is performed in cases with an abnormal electrocardiogram and/or angina pectoris. A coronary angiography is obtained just for the stress electrocardiography positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders of the cardiac walls. Eventually, patients with RBCs transfusions of less than 50 units in their lives were put into the first and 50 units or higher were put into the second groups, and were compared in between. Mann-Whitney U test, Independent-Samples

t test, and comparison of proportions were used as the methods of statistical analyses.

Results

There were 224 cases in the first and 92 cases in the second groups (70.8% vs 29.1%, respectively, p<0.001). There was no patient with regular alcohol consumption among the study cases. The mean units of transfused RBCs in their lives were 12.9 vs 99.0, respectively (p<0.000). Mean ages of the groups were similar (28.9 vs 30.0 years, respectively, p>0.05). Interestingly, the male ratio was significantly higher in the second group (45.5% vs 64.1%, p<0.001). There was not a significant difference according to the prevalence of associated TMs between the groups (62.0% vs 58.6%, respectively, p>0.05) (Table 1). White blood cells (WBCs) (14.931 vs 15.346/µL, p<0.05) and platelets (PLTs) (435.670 vs 498.310/µL, p= 0.005) counts were higher in the second group (Table 2). Although the lower prevalence of autosplenectomy (56.2% vs 45.6%, p<0.05), painful crises per year (3.8 vs 8.4, p= 0.000), smoking (12.0% vs 17.3%, p<0.05), digital clubbing (7.1% vs 15.2%, p<0.01), COPD (6.6% vs 20.6%, p<0.001), leg ulcers (11.6% vs 21.7%, p<0.01), stroke (5.8% vs 11.9%, p<0.05), CRD (4.9% vs 14.1%, p<0.001), CHD (4.0% vs 8.6%, p<0.05), and mean age of the mortality (29.5 vs 34.6 years, p<0.05) were all higher in the second group, significantly (Table 3).

Table 1: Sickle cell patients with units of red blood cells transfusions in their lives

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

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

Table 2: Sickle cell patients with peripheric blood values

Variables	Cases with RBCs* transfusions of less than 50 units	*p*-value	Cases with RBCs transfusions of 50 units or higher
Mean WBCs† counts (µL)	***14.931 ± 6.791 (2.460-39.200)***	***<0.05***	***15.346 ± 5.640 (1.580-36.900)***
Mean PLTs‡ counts (µL)	***435.670 ± 236.693 (48.000-1.827.000)***	***0.005***	***498.310 ± 224.570 (53.000-1.370.000)***
Mean hematocrit value (%)	23.8 ± 4.8 (11-42)	ns§	23.7 ± 4.9 (13-39)

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

Table 3: Clinical features of the sickle cell patients

Variables	Cases with RBCs* transfusions of less than 50 units	*p*-value	Cases with RBCs transfusions of 50 units or higher
Painful crises per year	***3.8 ± 6.3 (0-52)***	***0.000***	***8.4 ± 10.9 (0-52)***
Smoking	***12.0% (27)***	***<0.05***	***17.3% (16)***
Digital clubbing	***7.1% (16)***	***<0.01***	***15.2% (14)***
Pulmonary hypertension	11.6% (26)	ns†	10.8% (10)
COPD‡	***6.6% (15)***	***<0.001***	***20.6% (19)***
Leg ulcers	***11.6% (26)***	***<0.01***	***21.7% (20)***
Stroke	***5.8% (13)***	***<0.05***	***11.9% (11)***
CRD§	***4.9% (11)***	***<0.001***	***14.1% (13)***
Avascular necrosis of bones	20.5% (46)	ns	17.3% (16)
Cirrhosis	4.4% (10)	ns	4.3% (4)
CHD¶	***4.0% (9)***	***<0.05***	***8.6% (8)***
Rheumatic heart disease	8.4% (19)	ns	3.2% (3)
Mean age of mortality (year)	***29.5 ± 9.8 (19-50)***	***<0.05***	***34.6 ± 6.7 (26-44)***

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

Discussion

Acute painful crises are the most disabling symptoms of the SCDs. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stress are the most common precipitating factors of the crises (18). Although the sickled or just hardened RBCs-induced capillary endothelial damage, inflammation, and edema are present even at birth, the increased basal metabolic rate during such stresses aggravates the sickling and capillary endothelial damage, inflammation, and edema, and may terminate with disseminated tissue hypoxia and multiorgan failures-induced sudden deaths in the SCDs (19). So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with the following crises by leaving some sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with sudden end-organ failures and death during a final acute painful crisis that may even be silent, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCDs. Unfortunately, most of the deaths develop just after the hospital admission, and majority of such cases are without hydroxyurea therapy (20). Rapid RBCs supports are usually life-saving for such patients, although preparation of RBCs units for transfusion usually takes time. Beside that RBCs supports in emergencies become much more difficult in such terminal patients due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBCs complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBCs transfusions should be kept just for acute events and emergencies in the SCDs (21). According to our experiences, simple and repeated transfusions are superior to RBCs exchange in the SCDs (22). First of all, preparation of one or two units of RBCs suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk cases. Secondly, transfusions of one or two units of RBCs suspensions in each time decrease the severity of pain and relax anxiety of the patients and their relatives because RBCs transfusions probably have the strongest analgesic effects during such crises. Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation in whole body. Thirdly, transfusions of lesser units of RBCs suspensions in each time by means of the simple transfusions decrease transfusions-related complications including infections, iron overload, and blood group mismatch. Fourthly, transfusions of RBCs suspensions in the secondary health centers prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices. On the other hand, pain is the result of complex and poorly understood interactions between RBCs, WBCs, PLTs, and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes is unknown. The adverse actions of WBCs on the capillary endothelium are of particular interest with regard to the cerebrovascular diseases in the SCDs. For instance, leukocytosis even in the absence of an infection was an independent predictor of the severity of the SCDs, and it was associated with the higher risk of stroke (23). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of

the intolerable pain. Because of the severity of pain, narcotic analgesics are usually required to control them (24), but according to our long term experience, simple and repeated RBCs transfusions are much more effective than the narcotics to control the intolerable pain in the SCDs.

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

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) used to reduce inflammation and acute thromboembolic events. Although aspirin has similar anti-inflammatory effects with the other NSAIDs, it also suppresses the normal functions of PLTs, irreversibly. This property causes aspirin being different from other NSAIDs, which are reversible inhibitors. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin's ability to suppress the production of prostaglandins (PGs) and thromboxanes (TXs) is due to its irreversible inactivation of the COX enzyme required for PGs and TXs synthesis. PGs are the locally produced hormones with some diverse effects, including the transmission of pain into the brain and modulation of the hypothalamic thermostat and inflammation. TXs are responsible for the aggregation of PLTs to form blood clots. In another definition, low-dose aspirin use irreversibly blocks the formation of TXA2 in the PLTs, producing an inhibitory effect on the PLTs aggregation during whole lifespan of the affected PLTs (8-9 days). Since PLTs do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin inhibited the enzyme. The antithrombotic property of aspirin is useful to reduce the incidences of myocardial infarction, transient ischemic attack, and stroke (35). Heart attacks are caused primarily by blood clots, and low dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction (36). According to the medical literature, aspirin may also be effective in prevention of colorectal cancers (37). On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Reye syndrome is a rapidly worsening brain disease (38). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (39). The syndrome mostly affects children, but it can only

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

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

PHT is a condition of increased BPs within the arteries of the lungs. Shortness of breath, fatigue, chest pain, palpitation, swelling of legs and ankles, and cyanosis are common symptoms of PHT. Actually, it is not a diagnosis itself, instead solely a hemodynamic state characterized by resting mean pulmonary artery pressure of 25 mmHg or higher. An increase in pulmonary artery systolic pressure, estimated noninvasively by the echocardiography, helps to identify patients with PHT (49). The cause is often unknown. The underlying mechanism typically involves inflammation, fibrosis, and subsequent remodelling of the arteries. According to World Health Organization (WHO), there are five groups of PHT including pulmonary arterial hypertension, PHT secondary to left heart diseases, PHT secondary to lung diseases, chronic thromboembolic PHT, and PHT with unknown mechanisms (50). PHT affects about 1% of the world population, and its prevalence may reach 10% above the age of 65 years (51). Onset is typically seen between 20 and 60 years of age (50). The most common causes are CHD and COPD (50, 52). The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy (53). But the pulmonary vascular remodeling in the COPD may have a much more complex mechanism than just being the medial hypertrophy secondary to the long-lasting hypoxic vasoconstriction alone (53). In fact, all layers of the vessel wall appear to be involved with prominent intimal changes (53). The specific pathological picture could be explained by the combined effects of hypoxia, prolonged stretching of hyperinflated lungs-induced mechanical stress and inflammatory reaction, and the toxic effects of cigarette smoke (53). On the other hand, PHT is also a common consequence, and its prevalence was detected between 20% and 40% in the SCDs (54, 55). Whereas we detected the ratio as 12.2% in the above study (44). The relatively younger mean ages of the study cases (30.8 years of males and 30.3 years of females) may be the cause of the lower prevalence of PHT in the above study (44). Although the higher prevalences of smoking and alcohol-like atherosclerotic risk factors in male gender, and although the higher prevalences of

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

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

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

Leg ulcers are seen in 10% to 20% of the SCDs (71), and the ratio was 13.5% in the above study (44). Its prevalence increases with aging, male gender, and SCA (72). Similarly, its ratio was higher in males (19.8% vs 7.0%, p<0.001), and mean age of the leg ulcer patients was higher than the remaining ones in the above study (35.3 vs 29.8 years, p<0.000) (44). The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (71). As an evidence of their atherosclerotic background, the leg ulcers occur in the distal segments of the body with a lesser collateral blood supply (71). The sickled or just hardened RBCs-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes, again (72). Prolonged exposure to the sickled or just hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCDs. The sickled or just hardened RBCs-induced venous insufficiencies may also accelerate the highly destructive process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood may be the main cause of delayed wound and fracture healings in the lower extremities. Smoking and alcohol may also have some additional atherosclerotic effects on the leg ulcers in males. Although presence of a continuous damage of hardened RBCs on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBCs counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBCs counts may decrease severity of pain and tissue damage (31). Because the main action of hydroxyurea may be the suppression of hyperproliferative WBCs and PLTs in the SCDs (30), prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBCs and PLTs counts-induced exaggerated capillary endothelial inflammation and edema.

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

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

CHD is the most common of the cardiovascular diseases (89). In adults who go to the emergency department with an unclear cause of pain, about 30% have pain due to CHD (90). Although half of cases are linked to genetics, physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, high BP, high blood glucose, dyslipidemia, smoking, alcohol, chronic inflammations, prolonged infections, and cancers may be the most common causes (91). It is the reduction of blood flow to the heart muscle due to build-up of atherosclerotic plaques secondary to the chronic inflammation of the arteries. It can present with stable angina, unstable angina, myocardial infarction, and sudden cardiac death (89). It is usually symptomatic with increased basal metabolic rate and emotional stress (92). It is the cause of deaths in 15.6% of all deaths, globally (92). So it is the most common cause of death in the world, nowadays (92). In the United States in 2010, about 20% of those over the age of 65 years had CHD, while it was present in 7% of those between the ages of 45 to 64 years, and 1.3% of those between 18 and 45 years of age, and the rates were higher among men (93). On average, women experience symptoms 10 years later than men, and women are less likely to recognize symptoms and seek treatment (91). Women who are free of stress from work life show an increase in the diameter of their blood vessels, leading to decreased progression of atherosclerosis (94). Similarly, CHD was detected as 18.0% vs 13.2% in men and women in the above study , respectively ($p<0.05$) (44).

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

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

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

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

The spleen is found in all vertebrates with a similar structure to the lymph nodes. It acts primarily as a blood filter, and removes old and abnormal RBCs and recycles the iron. Additionally, it synthesizes antibodies and removes antibody-coated bacteria and blood cells from the circulation. Like the thymus, the spleen has only efferent lymphatic vessels, and it is the major lymphatic organ of the body. It has a central role in the reticuloendothelial system, and retains the ability to produce lymphocytes after birth. The spleen acts as a pool of peripheral blood cells which are released in case of a need. For example, it stores half of the body's monocytes in mice (120). In case of an injury, the monocytes migrate to the injured tissues and transform into dendritic cells and macrophages, and assist tissue healing (121). It was detected in the present study that 56.2% of cases of the first and 45.6% of cases of the second groups (p<0.05) had autosplenectomy, and these ratios were the highest ones among all other affected tissues of the body. So the spleen is probably the primarily affected organ in the SCDs, and it may act as a chronic inflammatory focus, particularly due to the high WBCs content (122). Although, a 28-year follow-up study of 740 veterans of World War II with surgical removal of spleen on the battlefield found that they showed significant excesses of mortality from pneumonia and CHD (123), the prevalence of CHD were higher in the second group with the lower prevalence of autosplenectomy in the present study.

As a conclusion, although the lower prevalence of autosplenectomy, male ratio, WBCs and PLTs counts, painful crises per year, smoking, digital clubbing, COPD, leg ulcers, stroke, CRD, CHD, and mean age of mortality were all higher in patients with RBCs transfusions of 50 units or higher in their lives. So autosplenectomy may be a good, and male gender alone may be a bad prognostic feature that can not be explained by smoking alone at the younger mean age, and RBCs supports prolong the survival in the SCDs.

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