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Editorial

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Review

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This is the first issue this year which have a number of good papers from the region discussing issues of importance in the nursing field.

Dr. ALGHAMDI, did a descriptive correlation study conducted using an online survey comprised of the Connor-Davidson Resilience Scale-10 (CD-RSC), the Maslach Burnout Inventory (MBI) Student Survey, and the socio-demographic survey to collect data from a convenient sample of (n=243) undergraduate nursing students at Imam Abdullah bin Faisal University (IAU) in the Eastern region of Saudi Arabia. Descriptive and inferential tests were employed in the data analysis process. 61% of students experienced moderate to high levels of academic burnout, and only 17.3% experienced high psychological resilience. A significant negative relationship was found between Saudi undergraduate nursing students' academic burnout and psychological resilience ($r=-0.14$, $p<.022$). Differences were noted in academic burnout ($p=0.034$) and resilience ($p=0.024$) based on the student's academic year, as both increased with the student's level. Additionally, significant differences were found in students' psychological resilience concerning age ($p=0.011$). The author concluded that psychological resilience serves as a protective factor, as students with high resiliency reported less academic burnout and greater professional efficacy. These findings suggest that efforts are required to create supportive educational settings to enhance students' resilience to overcome academic burnout and address the nursing shortage issue.

Dr Ebtisam, looked at the misconception around black natural henna. Although the risk of P-phenylenediamine (PPD) contained in henna is well-known and well-documented in the medical literature. Other ways of using other temporary tattoos in henna like Jagua are scarce to know. Dr Ebtisam, looked at the myth of squatting toilets. Have we wondered why nowadays there are many bowel cancers compared relatively to the old era? The question is now lifestyle diseases are quite commonly seen globally and the main culprits are sedentary life habits, lack of physical activities, and lack of fiber intake. All of which contributed to the development of non-communicable diseases like obesity, type II diabetes, and heart diseases. Modernized sitting toilets are favoured worldwide because they provide a fairly restful posture in endeavouring defecation. However, comparatively, on the other hand, squat toilets were well known in the old era time and are still used in some places across the world, namely Asian and African countries including China and India, Indonesia, Bangladesh, Pakistan, Yaman, sir Lanka, Malaysia, Myanmar, Iran, Iraq, Egypt, and Libya and they have the advantages, of personal hygiene, easy cleaning, and health benefits to the bowel. They are also found in Japan, South Korea, Taiwan, Thailand, and Singapore. Studies showed that squat toilets exert less pressure, and less angle and make the stool smoothly expelled with less strain. This consequently will help prevent stool stagnation, ease constipation, less bowel irritation, prevent hemorrhoids, and thus less bowel cancer. Squatting pose for defecation is the most appropriate way, as the abdominal muscles work actively and complete evacuation takes place.

Dr Helvaci looked at 2 topics of great interest. Prolonged tonsillar hypertrophy may be an indicator of disease-induced immunosuppression in sickle cell patients. The study included 334 cases (164 females). There were 27 patients (8.0%) with tonsilectomy and 307 patients without (91.9%). The mean age, female ratio, and smoking were similar in both groups ($p>0.05$ for all). Although the white blood cells and platelets counts of peripheric blood were higher in patients without tonsilectomy, the mean hematocrit value was lower in them, but the differences were nonsignificant probably due to the small sample size of the tonsilectomy group ($p>0.05$ for all). Similarly, although the painful crises per year, digital clubbing, leg ulcers, pulmonary hypertension, chronic obstructive pulmonary disease, rheumatic heart disease, avascular necrosis of bone, cirrhosis, stroke, and mortality were all higher in patients without tonsilectomy, the differences were nonsignificant probably due to the same reason again ($p>0.05$ for all).

The other topic is Severity of sickle cell diseases restricts smoking. SCDs are severe inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with an accelerated atherosclerosis and end-organ failures in early years of life. There may be an inverse relationship between prevalence of tonsilectomy and severity of SCDs, and the tonsils may act as chronic inflammatory foci accelerating the chronic endothelial damage all over the body.

ACADEMIC BURNOUT AND PSYCHOLOGICAL RESILIENCE RELATIONSHIP IN UNDERGRADUATE NURSING STUDENTS IN THE EASTERN PROVINCE OF THE KINGDOM OF SAUDI ARABIA: A QUANTITATIVE CROSS-SECTIONAL STUDY

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Abstract

Background: Academic burnout has a role in nursing student attrition, which contributes to the Saudi nursing shortage. Resilience increases students' capacity to overcome academic stressors that can lead to academic burnout. However, no studies have been conducted in Saudi Arabia to investigate their relationship. Therefore, this study aims to investigate the relationship between academic burnout and psychological resilience among Saudi undergraduate nursing students.

Method: A descriptive correlation study was conducted using an online survey comprised of the Connor-Davidson Resilience Scale-10 (CD-RSC), the Maslach Burnout Inventory (MBI) Student Survey, and the socio-demographic survey to collect data from a convenient sample of (n=243) undergraduate nursing students at Imam Abdullah bin Faisal University (IAU) in the Eastern region of Saudi Arabia. Descriptive and inferential tests were employed in the data analysis process.

Results: 61% of students experienced moderate to high levels of academic burnout, and only 17.3% experienced high psychological resilience. A significant negative relationship was found between Saudi undergraduate nursing students' academic burnout and psychological resilience ($r=-0.14$, $p<.022$). Differences were noted in academic burnout ($p=0.034$) and resilience ($p=0.024$) based on the student's academic year, as both increased with the student's level. Additionally, significant differences were found in students' psychological resilience concerning age ($p=0.011$).

Conclusions and recommendations: Psychological resilience serves as a protective factor, as students with high resiliency reported less academic burnout and greater professional efficacy. These findings suggest that efforts are required to create supportive educational settings to enhance students' resilience to overcome academic burnout and address the nursing shortage.

Key Words: Academic Burnout, Psychological Resilience, Nursing Students, Saudi Arabia.

Introduction

It is widely acknowledged that the demands and pressures associated with healthcare school pose a significant threat to the well-being of healthcare students, resulting in high rates of anxiety and exhaustion (1). Nursing students experience significantly higher levels of stress than students in other health-related fields (2). In a study that focused on nursing students in the Kingdom of Saudi Arabia, nursing students reported moderate levels of stress (3). Additionally, nursing students reported the highest prevalence of stress-induced self-medication (59.09%) in a study on health and non-health colleges in Saudi Arabia (4). The presence of numerous stressors can adversely affect the health and academic performance of nursing students (5). Some examples of course-related stresses that Saudi nursing students encounter include challenging coursework, a lack of knowledge and skills, clinical practice pressure, and critical thinking requirements (6). A mix of these stressors can contribute to burnout among nursing students (7).

The World Health Organization has recognised burnout as a phenomenon caused by unmanaged long-term stress (8). Academic burnout syndrome occurs when a student's mental exhaustion, cynicism, and low perception of their efficacy all increase (9). Academic burnout among nursing students can have significant consequences. For example, students who experience academic burnout are more likely not to complete their degrees, resulting in a shortage of nursing graduates that will result in a shortage of nurses in the workforce (10).

In 2020 there was a global nursing shortage of 5.9 million nurses (11), including the Kingdom of Saudi Arabia, with only 56 nurses available for every 10,000 residents (12). Nursing contributes significantly to the achievement of the Sustainable Development Goals (SDGs), particularly SDG 3, which is concerned with the well-being and health of the population (13). Given the shortage and importance of nursing staff, the Kingdom of Saudi Arabia has released 100,000 nursing jobs to be filled by Saudi nurses by 2030 (14). Thus, in order to fill the shortage of nurses in Saudi Arabia, nursing students' psychological well-being must be protected in order for them to overcome the academic stressors that lead to the development of burnout issues.

Resilience helps nursing students handle the academic stressors that lead to academic burnout (15). In the context of nursing education, resilience is defined as the process of development that occurs when nursing students learn to cope effectively with perceived academic stress and adversity by drawing on their own strengths (16). Resilience assists students in enhancing their capacity to complete their studies and achieving academic and clinical success (17, 18, 19). Therefore, enhancing psychological resilience among nursing students has shown promise as a means of preventing or reducing academic burnout. To date, Saudi nursing students' psychological resilience and academic burnout have rarely been studied, and no study has investigated the relationship between the impact of resilience and academic burnout. Thus, understanding the prevalence of academic burnout, psychological resilience, and their relationship among Saudi undergraduate nursing students assists in how interventions can be tailored to best serve the population and to ensure that there are enough nursing graduates available to meet Saudi Arabian healthcare system needs and help in achieving SDG3.

Methods

1. Study Design and Settings: The author conducted a quantitative correlation study at a nursing college at Imam Abdulrahman bin Faisal University (IAU) in the eastern province of Saudi Arabia during the academic year 2023.

2. Sampling Method and Study Population: A convenience sample technique was used with a sample size of 169 participants. This number was determined by utilising an automated calculator created by Raosoft (2009), based on a population of 300, with a margin of error of 5% and a 95% confidence level (20). The study sample included all 3rd and 4th year nursing students aged 18 and above. This sample was selected due to the fact that their curriculum is mainly centred on extensive practical training as well as theoretical parts. Students in their 1st and 2nd years were not included since they had not yet begun clinical training. Additionally, graduate students and students under the age of 18 were excluded from this study sample.

3. Data Collection: A web-based tool, Qualtrics, was used to distribute an online survey. In compliance with the researcher's agreement with the gatekeeper, the IAU nursing college sent an email invitation to all participants' academic email containing the QR code and electronic link for this study survey. The questionnaires were distributed between 1 April and 30 April 2023. On the first page of the survey, students' consent and the confidentiality and anonymity of information were assured. Also, participants were informed in the participation information sheet that participation is entirely voluntary and can be withdrawn anytime, and in the case of any further questions, the information of the principal investigator was provided. Following the participant's completion of the questionnaire, the web tool transferred the data into a password-protected Excel sheet for further use.

4. Instruments: Three sections of the questionnaire were added to be completed once per student as intended and not adapted in any way.

Section A: Socio-demographic characteristics of the **students including: age, gender, academic year, and overall GPA.**

Section A: Socio-demographic characteristics of the students including: age, gender, academic year, and overall GPA.

Section B: Maslach Burnout Inventory-Student Survey (MBI-SS): The MBI-SS comprises 16 elements which correspond to the following scales: Emotional Exhaustion (EE) (five questions), Cynicism (CY) (five questions) and Professional Effectiveness (PE) (six questions). On the MBI-SS, questions are given a score between 0 and 6 based on how often they are indicated to be used, with 0 suggesting (never), 1 indicating (a few times a year), 2 indicating (monthly), 3 indicating (a few times a month), 4 indicating (weekly), 5 indicating (a few times a week), and 6 indicating (daily). According to the MBI-SS manual, the score is calculated in two ways. First, the sum of responses of items for each subscale to determine academic burnout levels (9). A score of 16 or greater indicated high EE. Similarly, a CY score of 11 or more indicated high EE. Conversely, a score of 23 or less on the PE scale indicated high EE; these cutoff scores were used to define a high level of academic burnout. Further, moderate burnout has scores spanning from 11 to 15 for EE, 6 to 10 for CY, and 24 to 29 for PE. Also, low burnout is defined as scores below these ranges for each. By using these cutoff scores, participants were classified according to their burnout levels, and the data was analysed accordingly. Additionally, using the second method of calculating the mean score, the frequency with which participants experienced academic burnout symptoms within each domain was quantified. This allows for comparisons between various domains and a more nuanced data analysis. In addition, the mean scores varied between 0 (never) and 6 (daily) (9).

Furthermore, for MBI-SS internal reliability, Cronbach's coefficient alpha was used, yielding values of 0.90 for EE, 0.79 for CY, and 0.60 for PE (9). In this study, the reliability of the MBI-SS was measured, and Cronbach's alpha was reported to be 0.90 for EE, 0.75 for CY, and 0.77 for PE. Also, MBI-SS has been proven to be valid in studies conducted in Saudi Arabia on healthcare specialities (21; 22), which indicates its trustworthiness in measuring academic burnout.

Section C: Connor-Davidson Resilience Scale 10 (CD-RISC-10): CD-RISC contains 10 items and is based on a five-point Likert scale where 0 represents (not true at all), 1 represents (rarely true), 2 represents (sometimes true), 3 represents (often true), and 4 represents (true nearly all the time). In addition, CD-RISC-10 had five domains. Flexibility (questions 1 and 5), self-efficacy (questions 2, 4, and 9), optimism (questions 3, 6, and 8), question (10) for the ability to regulate emotion, and question (7) for cognitive focus/maintaining attention under stress. According to Connor Davidson's Resilience 10-item scale scoring system, each item has a minimum of 0 and a maximum of 4 points (23). The CD-RISC 10 has a maximum score of 40 and a minimum score of 0 (23). By adding up all ten items, one can determine the final score. To illustrate, a score of (0-29) suggests that psychological resilience is low, (30-32) indicates that psychological resilience is moderate, and (33-40) indicates it is high (23).

Moreover, the CD-RISC 10 Cronbach's alpha for reliability analysis was (0.89), which is in line with the original instrument psychometric assessment, which showed an internal consistency reliability coefficient of 0.89 (23). In addition, a previous study conducted on Saudi healthcare students demonstrated the scale's validity in assessing resilience (24).

5. Data Analysis: The survey Excel sheet was examined for any missing MBI-SS, CD-RISC-10, and socio-demographic survey data. Incomplete data disqualified its participants from the study. As a result, a total of 243 questionnaires were completed (81% response rate) and entered for analysis. The analysis was performed using the SPSS for Windows, version 20.0 (SPSS, Chicago, IL). The normality of the data was checked by the Shapiro-Wilk test. The results showed a normal distribution for all variables. Descriptive and frequency statistics were used to analyse the student's academic burnout, psychological resilience, and socio-demographic characteristics. Pearson's Coefficient Correlation Test was used to determine the correlation between students' academic burnout and psychological resilience. The independent T-test was used to examine significant differences between students' (gender and academic year) and academic burnout and psychological resilience levels. The ANOVA test was used to compare resilience and academic burnout among students with various age ranges and GPAs. The significance level was set at $p < 0.05$.

6. Ethical Considerations: Ethical approval was attained from the School of Health and Social Care Research Ethics Committee at Swansea University (20 March 2023). Certification of training for protecting human research participants (number 2986761) was obtained. Authorisation of use for MBI-SS (number TVZKOEKIF) and CD-RISC-10 was granted. Contact information of the IAU Counselling Services Centre was included in the debriefing sheet to avoid any risk foreseen by participants while filling out the survey.

Results

1. The Description of Students' Socio-Demographic Characteristics: Approximately one-third of the students (36.2%) were males, while two-thirds (63.8%) were females. The average age of participants was 21 years old, with 70% of participants between the ages of 21 and 22 years. The mean GPA was reported at (4.13 ± 0.48), which represents an academic record of "very good", and 67.1 % of students had a GPA between (3.5 and 4.5), 23.5% had a GPA of (4.5 and above), and 9.5% had a GPA of (3.5 and less). Most participants were in their third year (58%), while 42% were in their fourth year. (Table 1)

Table 1. Number and distribution of the socio-demographic characteristics of the undergraduate nursing students (N=243).

	n	%
Age (Years)		
< 21	31	12.8
21 – 22	172	70.8
23 or More	40	16.5
Mean ±SD	21.41 ±1.03	
Gender		
Male	88	36.2
Female	155	63.8
GPA*		
< 3.5	23	9.5
3.5 – 4.5	163	67.1
More than 4.5	57	23.5
Mean ±SD	4.13 ±0.48	
Academic Year		
3rd Year	141	58.0
4th Year	102	42.0

*Note GPA = General Point Average is out of 5.

The full sample (N). A proportion of the sample (n). Percentage distribution (%). Standard deviation (SD).

2. The Prevalence of Academic Burnout and Psychological Resilience: The MBI-SS total score indicates that 18.1% of nursing students experience high academic burnout, 42.8% experience moderate academic burnout, and 39.1% experience low academic burnout (Table 2). Regarding psychological resilience, approximately half of the nursing students (52.7%) had a moderate level of psychological resilience. (Table 3)

Table 2. Maslach Burnout Inventory-Student Survey assessment and total averaged score.	n	%
Exhaustion		
Low	63	25.9
Moderate	107	44.0
High	73	30.0
Mean ±SD	3.69 ±1.44	
Cynicism		
Low	126	51.9
Moderate	78	32.1
High	39	16.0
Mean ±SD	2.93 ±1.42	
Professional Efficacy		
Low	96	39.5
Moderate	127	52.3
High	20	8.2
Mean ±SD	2.81 ±1.02	
Maslach Burnout Inventory-Student Survey (Total) Score		
Low	95	39.1
Moderate	104	42.8
High	44	18.1
Mean ±SD	3.14 ±0.91	

A proportion of the sample (n). Percentage distribution (%). Standard deviation (SD).

Table 3: Assessment of the Connor – Davidson Resilience-10 items scale score.	Low		Moderate		High		
	n	%	n	%	n	%	Mean ±SD
CD-RISC score	73	30.0	128	52.7	42	17.3	22.90 ±7.14

A proportion of the sample (n). Percentage distribution (%). Standard deviation (SD).

4. Correlations Analysis between Academic Burnout and Psychological Resilience: A significant negative relationship was found between academic burnout and psychological resilience (r=-147, p=.022) among IAU nursing students. Additionally, a negative correlation was observed in the academic burnout subdomain of EE and CY with psychological resilience (r=-0.348, p<0.001 and r=-0.528, p<0.001), respectively. In contrast, students' PE and psychological resilience had a positive relationship (r=0.596, p<0.001). (Figure 1) (Table 4)

Figure 1. The correlation between Maslach Burnout Inventory-Student Survey and Connor–Davidson Resilience-10 items scale Scores

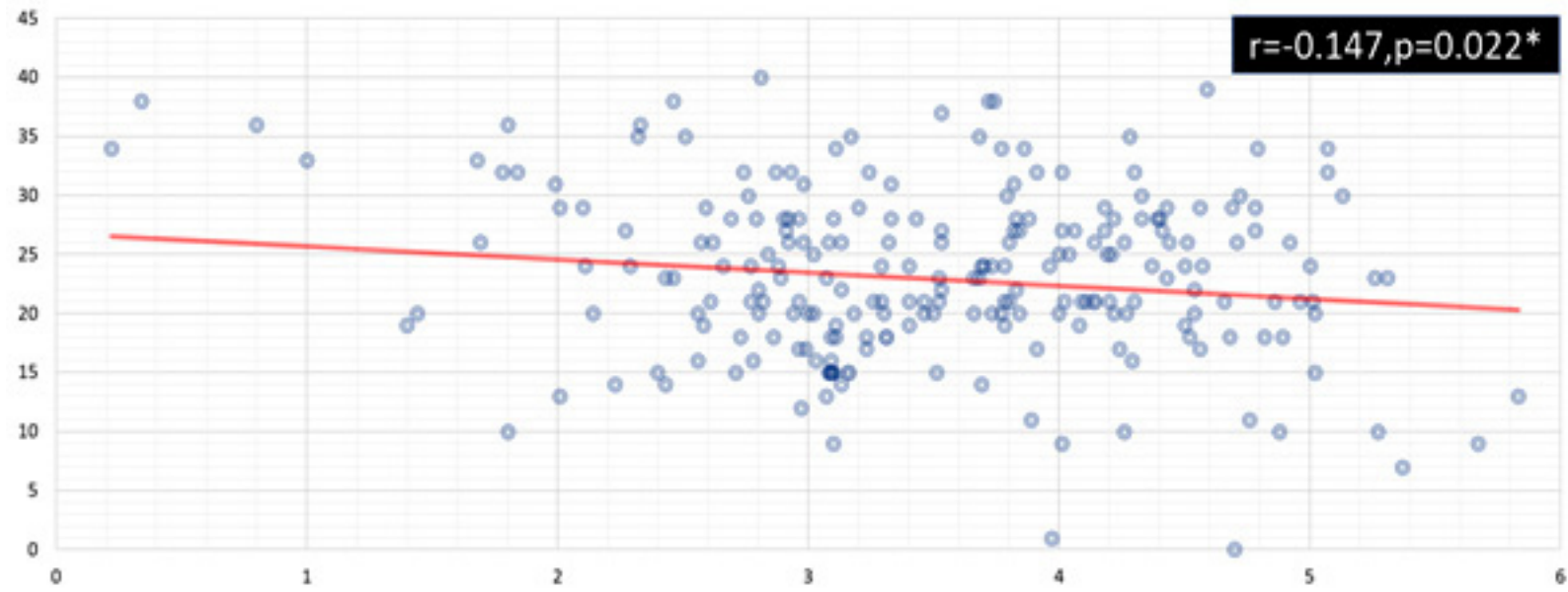

Table 4. The correlation between MBI-SS domains with total CD-RISC-10 scores.

	Correlation	
	r	p
Exhaustion	-0.348	<0.001**
Cynicism	-0.528	<0.001**
Professional Efficacy	0.596	<0.001**

*The Pearson correlation coefficient (r). *Statistically significant p-value at ≤0.05.

5. Differences in Academic Burnout and Psychological Resilience Based on Participants' Socio-Demographic Characteristics: There was a statistically significant difference between psychological resilience and students' age (p=0.011); the differences were in favour of students aged 21-22 years old with mean ± SD of (24.17 ±6.45). Furthermore, there was a statistically significant difference in psychological resilience measures and students' academic year (p=0.024). The differences were in favour of fourth-year nursing students, with a mean ± SD of (23.78 ± 6.78) when compared with third-year nursing students, with a mean ± SD of (21.69 ± 7.47). Also, the result indicates no significant difference in students' levels of psychological resilience and academic burnout according to gender or GPA.

Table 5. The statistical significance of the students' socio-demographic characteristics with MBI-SS and CD-RISC-10 scores.

	Academic Burnout (MBI-SS)		Psychological Resilience (CD-RISC-10)	
	Mean ±SD	Significance Test	Mean ±SD	Significance Test
Age (Years)				
< 21	3.21 ±0.90		19.45 ±7.31	
21 – 22	3.52 ±0.97		24.17 ±6.45	
23 or More	3.51 ±0.84	F=1.485, P=0.228	23.23 ±7.11	F=4.575, P=0.011*
Gender				
Male	3.41 ±0.96		22.64 ±7.43	
Female	3.52 ±0.93	T=0.970, P=0.333	23.05 ±6.99	T=0.430, P=0.668
GPA*				
< 3.5	3.55 ±0.67		21.95 ±6.61	
3.5 – 4.5	3.41 ±0.98		22.79 ±7.17	
More than 4.5	3.67 ±0.91	F=1.797, P=0.168	23.61 ±7.31	F=0.500, P=0.607
Academic Year				
3rd Year	3.34 ±0.82		21.69 ±7.47	
4th Year	3.59 ±1.01	T=2.132, P=0.034*	23.78 ±6.78	T=2.272, P=0.024*

* Note GPA = General Point Average is out of 5. *Statistically significant p-value at ≤0.05. SD: Standard deviation.

Discussion

The purpose of this study was to examine undergraduate nursing students' psychological resilience and academic burnout prevalence and relationship. The findings of the current study revealed that most of the participants experienced an average level of academic burnout, and this aligns with the finding of the Alshammari et al. (14) study that was carried out on Saudi nursing students. During college education, students handle heavy workloads, numerous assignments, worries about their future careers, and financial issues. These stressors can contribute to nursing students' academic burnout levels (15; 24; 25). In terms of the psychological resilience of nursing students, participants reported a moderate level of resilience with a mean score of (22.90). This finding was incongruent with Grande et al. (26), who used the same tool (CD-RISC-10) as this study and was conducted on Saudi undergraduate nursing students. Grande et al. (26) found a higher psychological resilience than this study, with a mean score of (32.23). This may be due to the fact that the current study collected the data at a time when there were no exams or pressures, as opposed to the Grande et al. (26) study that measured the resilience among nursing students during the stressful period of the COVID-19 crisis. However, the current study sample's level of psychological resilience was comparable to other international studies that used the CD-RISC-10 and studied undergraduate nursing students from China and Nigeria (27, 28).

Furthermore, a high level of resilience can help students cope with the stress and difficulties associated with their studies (25; 29), which can lower their risk of academic burnout. According to the present study's findings, academic burnout and psychological resilience are significantly linked and negatively correlated. This illustrated that students with a higher level of psychological resilience have lower academic burnout (EE, CY) and vice versa. Also, the present study found a positive relationship between resilience level and PE of students. These findings provide additional evidence as they support those of other studies conducted on nursing students from countries across the globe, including Korea, Iran, and Spain (25, 30, 31, 32, 33, 34).

The present study also revealed that students' psychological resilience differed based on age. Chow et al. (28), Ros-Risquez et al. (33), and Hasson et al. (35) support the current study findings as they identified age-related differences in the resilience levels of nursing students from China and Spain. Based on these findings, age can be considered a factor influencing psychological resilience levels. Additionally, the present study found that students' academic level can influence their academic burnout and psychological resilience, as fourth-year nursing students had higher academic burnout and psychological resilience than third-year nursing students. This can be justified by the fact that students at higher academic levels are required to take advanced courses and have a heavier practical load (36). Also, this can be related to nursing students' concerns regarding their entry into the labour market, acceptance into selective processes, and expectations of their professional success (37; 38). In addition, the statistically significant difference among fourth-year students is in line with the fact that the greater the pressure, the greater the need to establish protective factors such as resilience (16). The result of this study provides additional evidence as it supports previous studies done on undergraduate nursing students (28; 36).

Limitation:

Although this research is the first in Saudi Arabia to investigate the relationship between academic burnout and undergraduate nursing students' psychological resilience, it had some limitations. First, the convenient sampling technique limits this study's ability to generalise its findings to all Saudi nursing students nationwide. Secondly, the data was obtained through self-report questionnaires which may affect the accuracy of the data provided by the participants.

Conclusion and Recommendations

The psychological resilience of nursing students serves as a protective factor, as students with high resiliency reported less academic burnout and greater professional efficacy. These findings suggest that efforts are required to create supportive educational settings to enhance students' resilience to overcome academic burnout and increase students' professional efficacy to succeed in their studies and graduate enough nurses to fill the nursing shortage in Saudi Arabia. Ultimately, it aids Saudi Arabia in achieving the sustainable development goal of promoting population health and well-being. Also, it would be beneficial to conduct qualitative research and look into the impact of additional social factors such as students' marital status, family size, economic status, and behavioural factors like smoking, exercise, and sleeping patterns, to more comprehensively identify the factors that may influence Saudi nursing students' resilience and academic burnout.

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PROLONGED TONSILLAR HYPERTROPHY MAY BE AN INDICATOR OF DISEASE-INDUCED IMMUNOSUPPRESSION IN SICKLE CELL PATIENTS

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Abstract

Background: The hardened red blood cells-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood in sickle cell diseases (SCDs).

Methods: All patients with the SCDs were taken into the study.

Results: The study included 334 cases (164 females). There were 27 patients (8.0%) with tonsilectomy and 307 patients without (91.9%). The mean age, female ratio, and smoking were similar in both groups (p>0.05 for all). Although the white blood cells and platelets counts of peripheric blood were higher in patients without tonsilectomy, the mean hematocrit value was lower in them, but the differences were nonsignificant probably due to the small sample size of the tonsilectomy group (p>0.05 for all). Similarly, although the painful crises per year, digital clubbing, leg ulcers, pulmonary hypertension, chronic obstructive pulmonary disease, rheumatic heart disease, avascular necrosis of bone, cirrhosis, stroke, and mortality were all higher in patients without tonsilectomy, the differences were nonsignificant probably due to the same reason again (p>0.05 for all).

Conclusion: There may be an inverse relationship between prevalence of tonsilectomy and severity of SCDs, and the tonsils may act as chronic inflammatory foci accelerating the chronic endothelial damage all over the body in such patients. On the other hand, such a high prevalence of tonsilectomy may show the fact that the prolonged tonsillar hypertrophy may be an indicator of disease-induced immunosuppression in sickle cell patients.

Key words: Sickle cell diseases, immunosuppression, tonsillar hypertrophy, tonsilectomy, hardened red blood cells, arterial endothelial damage, sudden deaths

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 Medical Faculty of the Mustafa Kemal University between March 2007 and August 2014. All patients with SCDs were included. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Associated TMs are detected by serum iron, total iron binding capacity, ferritin, and the hemoglobin electrophoresis performed via HPLC because the SCDs with associated TMs show a milder clinic than the sickle cell anemia (SCA) (Hb SS) alone (12). Their medical histories including painful crises per year, 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 one drink a day for three years were accepted as drinkers. A check up procedure including 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 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 laboratory tests and clinical measurements 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% (13). Systolic BPs of the pulmonary artery of 40 mmHg or higher during the silent phase are accepted as pulmonary hypertension (PHT) (14). Avascular necrosis of bone was detected via MRI (15). 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 (16). Cirrhosis is diagnosed with hepatic function tests, ultrasonographic findings, and liver biopsy in case of indication. Digital clubbing is diagnosed with the ratio of distal phalangeal to interphalangeal diameters which is greater than 1.0, and with the presence of Schamroth's sign (17,18). A stress electrocardiography is performed in case of 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 in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Eventually, the SCDs patients with tonsilectomy and without were collected into the two groups, and compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 334 patients with the SCDs (164 females and 170 males). There were 27 cases (8.0%) with tonsilectomy and 307 cases without. The mean ages were similar in both groups (29.2 versus 29.6 years, respectively, p>0.05). Female ratios were also similar in them (51.8% versus 48.8%, respectively, p>0.05). Prevalences of smoking were similar in both groups, too (11.1% versus 14.3%, respectively, p>0.05) (Table 1). Although the white blood cells (WBCs) and platelets (PLTs) counts of peripheric blood were higher in patients without tonsilectomy, the mean hematocrit value was lower in them (24.9% versus 23.6%), but the differences were nonsignificant probably due to the small sample size of the tonsilectomy group (p>0.05 for all) (Table 2). Similarly, although the painful crises per year, digital clubbing, leg ulcers, PHT, COPD, rheumatic heart disease, avascular necrosis of bone, cirrhosis, stroke, and mortality were higher in cases without tonsilectomy, the differences were nonsignificant probably due to the same reason again (p>0.05 for all) (Table 3). There were four patients with regular alcohol consumption who are not cirrhotic at the moment. Although antiHCV was positive in seven of the cirrhotics, HCV RNA was detected as positive by polymerase chain reaction just in two.

Table 1: Characteristic features of the study cases

Variables	Cases with tonsilectomy	*p*-value	Cases without tonsilectomy
Prevalence	8.0% (27)		91.9% (307)
Female ratio	51.8% (14)	Ns*	48.8% (150)
Mean age (year)	29.2 ± 10.0 (14-54)	Ns	29.6 ± 9.8 (5-59)
Thalassemias	51.8% (14)	Ns	66.7% (205)
Smoking	11.1% (3)	Ns	14.3% (44)

*Nonsignificant (p>0.05)

Table 2: Peripheric blood values of the study cases

Variables	Cases with tonsilectomy	*p*-value	Cases without tonsilectomy
Mean WBCs* counts (µL)	14.502 ± 4.655 (5.000-27.000)	Ns†	15.170 ± 6.654 (1.580-39.200)
Mean hematocrit value (%)	24.9 ± 5.4 (13-39)	Ns	23.6 ± 4.9 (11-42)
Mean PLTs‡ counts (µL)	468.680 ± 139.002 (149.000-795.000)	Ns	481.140 ± 236.932 (48.800-1.827.000)

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

Table 3: Associated pathologies of the study cases

Variables	Cases with tonsilectomy	*p*-value	Cases without tonsilectomy
Painful crises per year	4.1 ± 7.1 (0-36)	Ns*	5.2 ± 8.2 (0-52)
Digital clubbing	0.0% (0)	Ns	10.4% (32)
Leg ulcers	3.7% (1)	Ns	15.6% (48)
PHT†	11.1% (3)	Ns	11.7% (36)
COPD‡	11.1% (3)	Ns	13.3% (41)
CHD§	11.1% (3)	Ns	6.1% (19)
CRD**	11.1% (3)	Ns	8.1% (25)
Rheumatic heart disease	3.7% (1)	Ns	7.1% (22)
Avascular necrosis of bone	14.8% (4)	Ns	21.8% (67)
Cirrhosis	0.0% (0)	Ns	4.8% (15)
Stroke	7.4% (2)	Ns	9.1% (28)
Mortality	0.0% (0)	Ns	5.2% (16)

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 (21). 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 (22). 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 (23). 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 (24). According to our experiences, simple and repeated transfusions are superior to RBCs exchange in the SCDs (25). 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 (26). 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 (27), but according to our long term experience, simple and repeated RBCs transfusions are much more effective than the narcotics to control the intolerable pain.

Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCDs (11). 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 (28, 29). 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 Hb F, its main action may be the prevention of leukocytosis and thrombocytosis by blocking the DNA synthesis (30, 31). 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 (32). Similarly, final Hb F levels in the hydroxyurea users did not differ from their pretreatment levels (33). 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 (34). 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 (34). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (34). 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 (34). 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, $p<0.000$) (29). The higher WBCs ($p=000$) and PLTs counts ($p=007$), PHT ($p<0.05$), digital clubbing ($p<0.05$), and autosplenectomy ($p<0.001$) and the lower mean hematocrit value ($p<0.000$) may also indicate the severity of chronic inflammatory process on vascular endothelium in the SCA alone (35). The total bilirubin value of the plasma may have prognostic significance due to the higher prevalences of ileus, digital clubbing, leg ulcers, PHT, cirrhosis, CRD, and exitus in patients with the plasma bilirubin values of 5.0 mg/dL or greater (36). The significantly lower prevalence of the SCA alone in adults and the higher total bilirubin value of the plasma in them may indicate the relative severity of hemolytic process, vascular endothelial inflammation, and hepatic involvement in the SCA alone (36). 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 (37). The complications start to be seen even in infancy in the SCDs. For instance, infants with lower Hb 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 (38). 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 (39). 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 (40). According to the medical literature, aspirin may also be effective in prevention of colorectal cancers (41). 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 (42). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (43). The syndrome mostly affects children, but it can only affect fewer than one in a million children a year (43). It usually starts just after recovery from a viral infection, such as influenza or chicken pox (43). Symptoms

of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (42). Although the liver toxicity typically occurs in the syndrome and the liver is enlarged in most cases, jaundice is usually not seen with it (42). Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling (43). Although the death occurs in 20-40% of patients, about one third of survivors get a significant degree of brain damage (42). Interestingly, about 90% of cases in children are associated with an aspirin use (44). 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 (45). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (42). 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 (43). 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 (46).

Acute chest syndrome (ACS) is a significant cause of mortality in the SCDs (47). It occurs most often as a single episode, and a past history is associated with a higher mortality rate (47). 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 (48). The remaining 12 patients were still alive without a recurrence at the end of the 10-year follow up period (48). ACS is the most common between two to four years of age, and its incidence decreases with aging (49). As a difference from atherosclerotic consequences, the incidence of ACS did not show an increase with aging in the above study (48), 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 (47, 49). 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 (50). 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) in the above study (48). Additionally, ACS did not show an infectious etiology in 66% (47, 49), and 12 of 27 cases with ACS had evidence of fat embolism in the other study (51). Beside that some authors indicated that antibiotics did not shorten the clinical course (52). 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 (53). 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 (54). PHT affects about 1% of the world population, and its prevalence may reach 10% above the age of 65 years (55). Onset is typically seen between 20 and 60 years of age (54). The most common causes are CHD and COPD (54, 56). The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy (57). 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 (57). In fact, all layers of the vessel wall appear to be involved with prominent intimal changes (57). 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 (57). On the other hand, PHT is also a common consequence, and its prevalence was detected between 20% and 40% in the SCDs (58, 59). Whereas we detected the ratio as 12.2% in the above study (48). 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 (48). 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 (48). 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 (60). Although COPD and CHD are the most common causes of PHT in the society (56, 61), 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 (48), 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 (62, 63), because the mean age of ACS was lower than PHT (30.3 and 34.0 years, p<0.05) in the above study (48), but its mortality was much higher than PHT in the literature (47, 49, 54).

COPD is the third leading cause of death with various underlying etiologies all over the world (64, 65). 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 (66). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (67). 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 (68, 69). For example, there may be close relationships between COPD, CHD, PAD, and stroke (70), and CHD was the most common cause of deaths in the COPD in a multi-center study of 5.887 smokers (71). When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again (71). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (72). Similarly, COPD may just be the pulmonary consequence of the systemic atherosclerotic process caused by the sickled or just hardened RBCs in the SCDs (64).

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 (73). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (74). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (20). 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 (48). 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 (48).

Leg ulcers are seen in 10% to 20% of the SCDs (75), and the ratio was 13.5% in the above study (48). Its prevalence increases with aging, male gender, and SCA (76). 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 (35.3 vs 29.8 years, p<0.000) in the above study (48). The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (75). As an evidence of their atherosclerotic background, the leg ulcers occur in the distal segments of the body with a lesser collateral blood supply (75). The sickled or just hardened RBCs-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes, again (76). 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 (33). Because the main action of hydroxyurea may be the suppression of hyperproliferative WBCs and PLTs in the SCDs (32), 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 (77). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (77). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases (78). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (79). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCDs (80). 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 (81). 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 (82). 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 (83, 84). 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 (84, 85). 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 (86). 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 (85). 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 (87). 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 (87). However, along with the increased BPs, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (88). 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 (87). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (89). Although some authors reported that alcohol was not related with the CRD (89), 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 (82). 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 (90), and the most common cause of death was the cardiovascular diseases in the CRD again (91). The sickled or just hardened RBCs-induced capillary endothelial damage may be the main cause of CRD in the SCDs, again (92).

CHD is the most common of the cardiovascular diseases (93). In adults who go to the emergency department with an unclear cause of pain, about 30% have pain due to CHD (94). Although half of cases are linked to genetics, physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, high BPs, high blood glucose, dyslipidemia, smoking, alcohol, chronic inflammations, prolonged infections, and cancers may be the most common causes (95). 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 (93). It is usually symptomatic with increased basal metabolic rate and emotional stress (96). It is the cause of deaths in 15.6% of all deaths, globally (96). So it is the most common cause of death in the world, nowadays (96). 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 (97). On average, women experience symptoms 10 years later than men, and women are less likely to recognize symptoms and seek treatment (95). 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 (98). Similarly, CHD was detected as 18.0% vs 13.2% in men and women in the above study respectively ($p<0.05$) (48).

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 (99, 100). We detected prevalences of stroke as 12.1% vs 7.5% in males and females in the above study, respectively ($p<0.05$) (48). Similar to the leg ulcers, stroke is particularly higher with the SCA and higher WBCs counts (101). 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 (102). Probably, stroke may not have a macrovascular origin in the SCDs, and diffuse capillary endothelial edema may be much more important (103). 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 (50).

The venous capillary endothelium may also be involved in the SCDs (104). 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. Deep venous thrombosis (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 (BMI) 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) (48), 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 (105). 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 (105). It is mainly seen with SCDs, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (106, 107). Ischemic (veno-occlusive), stuttering (recurrent ischemic), and nonischemic priapisms (arterial) are the three types (108). 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 (105, 108). RBCs support is the treatment of choice in acute whereas hydroxyurea should be the treatment of choice in chronic phases (109). 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 (110). 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 international normalised ratio (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 (111). When warfarin is used and 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 (112). 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. 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% (113). All types of bleeding may occur, but the most severe ones are those involving the brain and spinal cord (113). The risk is particularly increased once the INR exceeds 4.5 (113). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (114). 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 (115). 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) (115). Similarly, warfarin resumption is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (116). Death occured in 18.7% of patients who resumed warfarin and 32.3% who did not resume warfarin (p= 0.009) (116). Ischemic stroke occured in 3.5% of patients who resumed warfarin and 7.0% of patients who did not resume warfarin (p= 0.002) (116). 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) (116). 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 (117). 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 (118). 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 (119). 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) (119). The mortality was markedly lower in the warfarin group, too (p= 0.005) (119). 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) (119). Additionally, very-low-dose warfarin was a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer (120). The warfarin dose was 1 mg daily for 6 weeks, and was adjusted to maintain the INR value of 1.3 to 1.9 (120). The average daily dose was 2.6 mg, and the mean INR was 1.5 (120). 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 (121). Interestingly, rivaroxaban and low dose apixaban were associated with increased risks of all cause mortality compared with warfarin (122). 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 (123). 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 (124).

Just after excess weight, smoking may be the second common cause of disseminated vasculitis in human body. It may cause a systemic inflammation on vascular endothelium terminating with an accelerated atherosclerosis-induced end-organ insufficiencies all over the body (125). Its atherosclerotic effect is the most obvious in Buerger's disease. Buerger's disease is an obliterative vasculitis characterized by inflammatory changes in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking. Fasting plasma glucose and high density lipoproteins may be negative whereas triglycerides, low density lipoproteins (LDL), erythrocyte sedimentation rate, and C-reactive protein may be positive acute phase reactants indicating such inflammatory effects of smoking on vascular endothelium (126). Parallel to the systemic inflammatory and atherosclerotic effects, smoking in human being and nicotine administration in animals were associated with the lower values of BMI (127). Some evidences revealed an increased energy expenditure during smoking both on the rest and light physical activity (128). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (129). According to an animal study, nicotine may lengthen intermeal time, and decrease amount of meal eaten (130). Smoking may be associated with a postcessation weight gain, but the risk is the highest during the first year, and decreases with the following years (131). On the other hand, although the CHD was detected with similar prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher white coat hypertension, BMI, LDL, triglycerides, HT, and DM in females (132). Beside that the prevalence of myocardial infarctions is increased three-fold in men and six-fold in women who smoked at least 20 cigarettes per day (133). In another word, smoking may be more dangerous for women about the atherosclerotic end-points probably due to the higher BMI in them. Several toxic substances found in the cigarette smoke get into the circulation, and cause the vascular endothelial inflammation in various organ systems of the body. For example, smoking is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis in the literature (134). There may be several underlying mechanisms to explain these associations (135). First of all, smoking may have some antidepressant properties with several

potentially lethal side effects. Secondly, smoking-induced vascular endothelial inflammation may disturb epithelial functions for absorption and excretion in the gastrointestinal and genitourinary tracts which may terminate with urolithiasis and components of the IBS including loose stool, diarrhea, and constipation. Thirdly, diarrheal losses-induced urinary changes may even cause urolithiasis (136). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the gastrointestinal and genitourinary tracts terminating with the IBS and urolithiasis. Eventually, immunosuppression secondary to smoking-induced vascular endothelial inflammation may even terminate with the gastrointestinal and genitourinary tract infections causing loose stool, diarrhea, and urolithiasis, because some types of bacteria can provoke urinary supersaturation, and modify the environment to form crystal deposits in the urine. Actually, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infections with the bacteria producing urease. Parallel to the results above, urolithiasis was detected in 17.9% of cases with the IBS and 11.6% of cases without in the other study ($p<0.01$) (136).

Tonsillar hypertrophy is a common physical examination finding in the SCDs patients even during the silent periods, and it may be a result of relative immunosuppression in them, since sinusitis, pneumonia, osteomyelitis, rheumatic heart disease, and meningitis like infections are common in such patients. Tonsils are collections of lymphoid tissue facing into the aerodigestive tract. The set of lymphatic tissue known as Waldeyer's tonsillar ring includes the adenoid tonsil, two tubal tonsils, two palatine tonsils, and the lingual tonsil. When used unqualified, the term most commonly refers specifically to the palatine tonsils, which have non-keratinized stratified squamous epithelium, and are incompletely encapsulated. They are located at the sides of oropharynx between palatoglossal and palatopharyngeal arches. Tonsils are the largest in diameter in childhood, and they gradually undergo atrophy after puberty. These immunocompetent tissues are the immune system's first line of defense against ingested or inhaled foreign pathogens. Tonsils can become enlarged and inflamed and may need surgical removal. Tonsilectomy may be indicated if they obstruct the airway, interfere with swallowing, affect speech, or in case of recurrent tonsillitis. Similar to the spleen (137), the tonsils are probably found among the primarily affected organs in the SCDs, and they may act as chronic inflammatory foci, and surgical removal may decrease secondary systemic inflammatory mediators and endothelial damage in such patients.

As a conclusion, SCDs are severe inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with an accelerated atherosclerosis and end-organ failures in early years of life. There may be an inverse relationship between prevalence of tonsilectomy and severity of SCDs, and the tonsils may act as chronic inflammatory foci accelerating the chronic endothelial damage all over the body. The relatively suppressed hemoglobin S synthesis in the SCDs secondary to the associated thalassemias may decrease severity of sickle cell-induced chronic endothelial damage, inflammation, edema, fibrosis, and end-organ failures. On the other hand, severity of SCDs may restrict smoking habit due to some immediately felt harmfull effects on health.

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SEVERITY OF SICKLE CELL DISEASES RESTRICTS SMOKING

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Abstract

Background: The hardened red blood cells-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood in sickle cell diseases (SCDs).

Methods: All patients were studied.

Results: The study included 334 cases (164 females). There were 27 patients (8.0%) with tonsilectomy and 307 patients without (91.9%). The mean age and female ratio were similar in both groups (p>0.05 for all). Although smoking (11.1% versus 14.3%), white blood cells and platelets counts of peripheric blood, thalassemias (51.8% versus 66.7%), painful crises per year, digital clubbing, leg ulcers, pulmonary hypertension, chronic obstructive pulmonary disease, rheumatic heart disease, avascular necrosis of bone, cirrhosis, stroke, and mortality were all higher in patients without tonsilectomy, the mean hematocrit value was lower in them, but the differences were nonsignificant probably due to the small sample size of the tonsilectomy group (p>0.05 for all).

Conclusion: SCDs are severe inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with an accelerated atherosclerosis and end-organ failures in early years of life. There may be an inverse relationship between prevalence of tonsilectomy and severity of SCDs, and the tonsils may act as chronic inflammatory foci accelerating the chronic endothelial damage all over the body. The relatively suppressed hemoglobin S synthesis in the SCDs secondary to the associated thalassemias may decrease severity of sickle cell-induced chronic endothelial damage, inflammation, edema, fibrosis, and end-organ failures. On the other hand, severity of SCDs may restrict smoking habit due to some immediately felt harmfull effects on health.

Key words: Sickle cell diseases, smoking, thalassemias, immunosuppression, tonsilectomy, chronic endothelial damage, atherosclerosis

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 chronic inflammatory processes on vascular endothelium terminating with an accelerated atherosclerosis induced end-organ failures in early years of life (7, 8). SCDs are characterized by sickle-shaped RBC which are caused by homozygous inheritance of hemoglobin S (Hb S). They are chronic hemolytic anemias including sickle cell anemia (SCA) (Hb SS) and SCDs associated with thalassemias. The SCDs are subdivided as sickle cell-Hb C, sickle cell-beta-thalassemias, and sickle cell-alpha-thalassemias. SCA alone or SCDs are particularly common in malaria-stricken areas of the world. The responsible allele is autosomal recessive that located on the short arm of the chromosome 11. Glutamic acid is replaced with valine in the sixth position of the beta chain of the Hb S. Under stressful conditions including cold, surgical operations, pregnancy, inflammations, infections, emotional distress, and hypoxia, presence of a less polar amino acid promotes polymerisation of Hb S, which distorts red blood cells (RBCs) into sickle shaped structures with a decreased elasticity. The decreased elasticity may be the major pathology of the diseases, since the normal RBCs can deform to pass through capillaries easily and sickling is very rare in peripheric blood samples of the SCDs with associated thalassemias. Additionally, overall survival is not affected in hereditary spherocytosis or elliptocytosis. In another word, Hb S causes RBCs to change their normal elastic and biconcave disc shaped structures to hard and sickle shaped bodies. RBCs can take their normal shape and elasticity after normalization of the stressful conditions, but after repeated cycles of sickling and unsickling, they become hard bodies, permanently, and the chronic endothelial damage and hemolysis develop. So the lifespan of the RBCs decreases up to 15-25 days. The abnormally hardened RBCs induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia and infarcts all over the body (9, 10). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level, since the capillary system is the main distributor of the abnormally hardened RBCs into the tissues (11). The hardened cells induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages, and the life expectancy of the SCA alone cases is decreased by 25 to 30 years (12). On the other hand, thalassemias are chronic hemolytic anemias, too and 1.6% of the population are alpha- or beta-thalassemias minors in the world (13). They are autosomal recessively inherited disorders, too. They result from unbalanced Hb synthesis caused by decreased production of at least one globin polypeptide chain (alpha, beta or delta) that builds up the normal Hb. HbA1 is composed of two pairs of alpha and beta chains that represents about 97% of total Hb in adults. Alpha-thalassemias result from decreased alpha chain synthesis, and beta-thalassemias result from decreased beta chain synthesis. The relatively suppressed Hb S synthesis in the SCDs with associated thalassemias may decrease sickle cell-induced chronic endothelial damage, inflammation, edema, fibrosis, and end-organ failures.

Material and methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and August 2014. All patients with SCDs were included. SCDs are diagnosed by the Hb electrophoresis performed via high performance liquid chromatography (HPLC). Associated thalassemias are detected by serum iron, total iron binding capacity, ferritin, and the Hb electrophoresis performed via HPLC because the SCDs with associated thalassemias show a milder clinic than the SCA alone (14). Their medical histories including painful crises per year, 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 one drink a day for three years were accepted as drinkers. A check up procedure including 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 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 laboratory tests and clinical measurements 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% (15). Systolic BPs of the pulmonary artery of 40 mmHg or higher during the silent phase are accepted as pulmonary hypertension (PHT) (16). Avascular necrosis of bone was detected via MRI (17). 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 (18). Cirrhosis is diagnosed with hepatic function tests, ultrasonographic findings, and liver biopsy in case of indication. Digital clubbing is diagnosed with the ratio of distal phalangeal to interphalangeal diameters which is greater than 1.0, and with the presence of Schamroth's sign (19, 20). A stress electrocardiography is performed in case of 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 in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Eventually, the SCDs patients with tonsilectomy and without were collected into the two groups, and compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 334 patients with the SCDs (164 females and 170 males). There were 27 cases (8.0%) with tonsilectomy and 307 cases without. The mean ages (29.2 versus 29.6 years, respectively, p>0.05) and female ratios were similar in them (51.8% versus 48.8%, respectively, p>0.05). Although the prevalences of thalassemias (66.7% versus 51.8%, p>0.05) and smoking (11.1% versus 14.3%, p>0.05) were higher in cases without tonsilectomy, the differences were nonsignificant probably due to the small sample size of the tonsilectomy group (Table 1). Although the white blood cells (WBCs) and platelets (PLTs) counts of peripheric blood were also higher in patients without tonsilectomy, the mean hematocrit value was lower in them (24.9% versus 23.6%), but the differences were nonsignificant probably due to the same reason above (p>0.05 for all) (Table 2). Similarly, although the painful crises per year, digital clubbing, leg ulcers, PHT, COPD, rheumatic heart disease, avascular necrosis of bone, cirrhosis, stroke, and mortality were higher in cases without tonsilectomy, the differences were nonsignificant probably due to the same reason again (p>0.05 for all) (Table 3). There were four patients with regular alcohol consumption who are not cirrhotic at the moment. Although antiHCV was positive in seven of the cirrhotics, HCV RNA was detected as positive by polymerase chain reaction just in two.

Table 1: Characteristic features of the study cases

Variables	Cases with tonsilectomy	*p*-value	Cases without tonsilectomy
Prevalence	8.0% (27)		91.9% (307)
Female ratio	51.8% (14)	Ns*	48.8% (150)
Mean age (year)	29.2 ± 10.0 (14-54)	Ns	29.6 ± 9.8 (5-59)
Thalassemias	51.8% (14)	Ns	66.7% (205)
Smoking	11.1% (3)	Ns	14.3% (44)

*Nonsignificant (p>0.05)

Table 2: Peripheric blood values of the study cases

Variables	Cases with tonsilectomy	*p*-value	Cases without tonsilectomy
Mean WBCs* counts (µL)	14.502 ± 4.655 (5.000-27.000)	Ns†	15.170 ± 6.654 (1.580-39.200)
Mean hematocrit value (%)	24.9 ± 5.4 (13-39)	Ns	23.6 ± 4.9 (11-42)
Mean PLTs‡ counts (µL)	468.680 ± 139.002 (149.000-795.000)	Ns	481.140 ± 236.932 (48.800-1.827.000)

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

Table 3: Associated pathologies of the study cases

Variables	Cases with tonsilectomy	*p*-value	Cases without tonsilectomy
Painful crises per year	4.1 ± 7.1 (0-36)	Ns*	5.2 ± 8.2 (0-52)
Digital clubbing	0.0% (0)	Ns	10.4% (32)
Leg ulcers	3.7% (1)	Ns	15.6% (48)
PHT†	11.1% (3)	Ns	11.7% (36)
COPD‡	11.1% (3)	Ns	13.3% (41)
CHD§	11.1% (3)	Ns	6.1% (19)
CRD**	11.1% (3)	Ns	8.1% (25)
Rheumatic heart disease	3.7% (1)	Ns	7.1% (22)
Avascular necrosis of bone	14.8% (4)	Ns	21.8% (67)
Cirrhosis	0.0% (0)	Ns	4.8% (15)
Stroke	7.4% (2)	Ns	9.1% (28)
Mortality	0.0% (0)	Ns	5.2% (16)

*Nonsignificant (p>0.05) †Pulmonary hypertension ‡Chronic obstructive pulmonary disease §Coronary heart disease
**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 (21). 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 (22). 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 (23). 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 (24). According to our experiences, simple and repeated transfusions are superior to RBCs exchange in the SCDs (25). 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 (26). 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 (27), but according to our long term experience, simple and repeated RBCs transfusions are much more effective than the narcotics to control the intolerable pain.

Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCDs (11). 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 (28, 29). 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 Hb F, its main action may be the prevention of leukocytosis and thrombocytosis by blocking the DNA synthesis (30, 31). 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 (32). Similarly, final Hb F levels in the hydroxyurea users did not differ from their pretreatment levels (33). 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 (34). 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 (34). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (34). 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 (34). 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, $p<0.000$) (29). The higher WBCs ($p=000$) and PLTs counts ($p=007$), PHT ($p<0.05$), digital clubbing ($p<0.05$), and autosplenectomy ($p<0.001$) and the lower mean hematocrit value ($p<0.000$) may also indicate the severity of chronic inflammatory process on vascular

endothelium in the SCA alone (35). The total bilirubin value of the plasma may have prognostic significance due to the higher prevalences of ileus, digital clubbing, leg ulcers, PHT, cirrhosis, CRD, and exitus in patients with the plasma bilirubin values of 5.0 mg/dL or greater (36). The significantly lower prevalence of the SCA alone in adults and the higher total bilirubin value of the plasma in them may indicate the relative severity of hemolytic process, vascular endothelial inflammation, and hepatic involvement in the SCA alone (36). 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 (37). The complications start to be seen even in infancy in the SCDs. For instance, infants with lower Hb 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 (38). 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 (39). 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 (40). According to the medical literature, aspirin may also be effective in prevention of colorectal cancers (41). 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 (42). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (43). The syndrome mostly affects children, but it can only affect fewer than one in a million children a year (43). It usually starts just after recovery from a viral infection, such as influenza or chicken pox (43). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (42). Although the liver toxicity typically occurs in the syndrome and the liver is enlarged in most cases, jaundice is usually not seen with it (42). Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling (43). Although the death occurs in 20-40% of patients, about one third of survivors get a significant degree of brain damage (42). Interestingly, about 90% of cases in children are associated with an aspirin use (44). 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 (45). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (42). 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 (43). 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 (46).

Acute chest syndrome (ACS) is a significant cause of mortality in the SCDs (47). It occurs most often as a single episode, and a past history is associated with a higher mortality rate (47). 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 (48). The remaining 12 patients were still alive without a recurrence at the end of the 10-year follow up period (48). ACS is the most common between two to four years of age, and its incidence decreases with aging (49). As a difference from atherosclerotic consequences, the incidence of ACS did not show an increase with aging in the above study (48), 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 (47, 49). 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 (50). 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) in the above study (48). Additionally, ACS did not show an infectious etiology in 66% (47, 49), and 12 of 27 cases with ACS had evidence of fat embolism in the other study (51). Beside that some authors indicated that antibiotics did not shorten the clinical course (52). 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 (53). 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 (54). PHT affects about 1% of the world population, and its prevalence may reach 10% above the age of 65 years (55). Onset is typically seen between 20 and 60 years of age (54). The most common causes are CHD and COPD (54, 56). The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy (57). 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 (57). In fact, all layers of the vessel wall appear to be involved with prominent intimal changes (57). 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 (57). On the other hand, PHT is also a common consequence, and its prevalence was detected between 20% and 40% in the SCDs (58, 59). Whereas we detected the ratio as 12.2% in the above study (48). 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 (48). 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 (48). 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 (60). Although COPD and CHD are the most common causes of PHT in the society (56, 61), 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 (48), 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 (62, 63), because the mean age of ACS was lower than PHT (30.3 and 34.0 years, $p<0.05$) in the above study (48), but its mortality was much higher than PHT in the literature (47, 49, 54). COPD is the third leading cause of death with various underlying etiologies all over the world (64, 65). 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 (66). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (67). 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 (68, 69). For example, there may be close relationships between COPD, CHD, PAD, and stroke (70), and CHD

was the most common cause of deaths in the COPD in a multi-center study of 5.887 smokers (71). When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again (71). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (72). Similarly, COPD may just be the pulmonary consequence of the systemic atherosclerotic process caused by the sickled or just hardened RBCs in the SCDs (64).

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 (73). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (74). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (20). 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 (48). 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 (48).

Leg ulcers are seen in 10% to 20% of the SCDs (75), and the ratio was 13.5% in the above study (48). Its prevalence increases with aging, male gender, and SCA (76). 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 (35.3 vs 29.8 years, $p<0.000$) in the above study (48). The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (75). As an evidence of their atherosclerotic background, the leg ulcers occur in the distal segments of the body with a lesser collateral blood supply (75). The sickled or just hardened RBCs-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes, again (76). 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 (33). Because the main action of hydroxyurea may be the suppression of hyperproliferative WBCs and PLTs in the SCDs (32), 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 (77). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (77). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases (78). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (79). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCDs (80). 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 (81). 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 (82). 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 (83, 84). 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 (84, 85). 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 (86). 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 (85). 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 (87). 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 (87). However, along with the increased BPs, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (88). 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 (87). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (89). Although some authors reported that alcohol was not related with the CRD (89), 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 (82). 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 (90), and the most common cause of death was the cardiovascular diseases in the CRD again (91). The sickled or just hardened RBCs-induced capillary endothelial damage may be the main cause of CRD in the SCDs, again (92).

CHD is the most common of the cardiovascular diseases (93). In adults who go to the emergency department with an unclear cause of pain, about 30% have pain due to CHD (94). Although half of cases are linked to genetics, physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, high BPs, high blood glucose, dyslipidemia, smoking, alcohol, chronic inflammations, prolonged infections, and cancers may be the most common causes (95). 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 (93). It is usually symptomatic with increased basal metabolic rate and emotional stress (96). It is the cause of deaths in 15.6% of all deaths, globally (96). So it is the most common cause of death in the world, nowadays (96). 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 (97). On average, women experience symptoms 10 years later than men, and women are less likely to recognize symptoms and seek treatment (95). 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 (98). Similarly, CHD was detected as 18.0% vs 13.2% in men and women in the above study , respectively (p<0.05) (48).

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 (99, 100). We detected prevalences of stroke as 12.1% vs 7.5% in males and females in the above study, respectively (p<0.05) (48). Similar to the leg ulcers, stroke is particularly higher with the SCA and higher WBCs counts (101). 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 (102). Probably, stroke may not have a macrovascular origin in the SCDs, and diffuse capillary endothelial edema may be much more important (103). 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 (50).

The venous capillary endothelium may also be involved in the SCDs (104). 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. Deep venous thrombosis (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 (BMI) 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) (48), indicating an additional venous involvement of the SCDs. Similarly, priapism is the painful erection of penis that cannot return

to its flaccid state within four hours in the absence of any stimulation (105). 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 (105). It is mainly seen with SCDs, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (106, 107). Ischemic (veno-occlusive), stuttering (recurrent ischemic), and nonischemic priapisms (arterial) are the three types (108). 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 (105, 108). RBCs support is the treatment of choice in acute whereas hydroxyurea should be the treatment of choice in chronic phases (109). 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 (110). 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 international normalised ratio (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 (111). When warfarin is used and 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 (112). 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% (113). All types of bleeding may occur, but the most severe ones are those involving the brain and spinal cord (113). The risk is particularly increased once the INR exceeds 4.5 (113). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (114). 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 (115). 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 ($p>0.05$) (115). Similarly, warfarin resumption is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (116). Death occured in 18.7% of patients who resumed warfarin and 32.3% who did not resume warfarin ($p= 0.009$) (116). Ischemic stroke occured in 3.5% of patients who resumed warfarin and 7.0% of patients who did not resume warfarin ($p= 0.002$) (116). 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 ($p>0.05$) (116). 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 (117). 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 (118). 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 (119). 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 ($p= 0.0022$) (119). The mortality was markedly

lower in the warfarin group, too (p= 0.005) (119). 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) (119). Additionally, very-low-dose warfarin was a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer (120). The warfarin dose was 1 mg daily for 6 weeks, and was adjusted to maintain the INR value of 1.3 to 1.9 (120). The average daily dose was 2.6 mg, and the mean INR was 1.5 (120). 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 (121). Interestingly, rivaroxaban and low dose apixaban were associated with increased risks of all cause mortality compared with warfarin (122). 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 (123). 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 (124).

Just after excess weight, smoking may be the second common cause of disseminated vasculitis in human body. It may cause a systemic inflammation on vascular endothelium terminating with an accelerated atherosclerosis-induced end-organ insufficiencies all over the body (125). Its atherosclerotic effect is the most obvious in Buerger's disease. Buerger's disease is an obliterative vasculitis characterized by inflammatory changes in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking. Fasting plasma glucose and high density lipoproteins may be negative whereas triglycerides, low density lipoproteins (LDL), erythrocyte sedimentation rate, and C-reactive protein may be positive acute phase reactants indicating such inflammatory effects of smoking on vascular endothelium (126). Parallel to the systemic inflammatory and atherosclerotic effects, smoking in human being and nicotine administration in animals were associated with the lower values of BMI (127). Some evidences revealed an increased energy expenditure during smoking both on the rest and light physical activity (128). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (129). According to an animal study, nicotine may lengthen intermeal time, and decrease amount of meal eaten (130). Smoking may be associated with a postcessation weight gain, but the risk is the highest during the first year, and decreases with the following years (131). On the other hand, although the CHD was detected with similar prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher white coat hypertension, BMI, LDL, triglycerides, HT, and DM in females (132). Beside that the prevalence of myocardial infarctions is increased three-fold in men and six-fold in women who smoked at least 20 cigarettes per day (133). In another word, smoking may be more dangerous for women about the atherosclerotic end-points probably due to the higher BMI in them. Several toxic substances found in the cigarette smoke get into the circulation, and cause the vascular endothelial inflammation in various organ systems of the body. For example, smoking is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis in the literature (134). There may be several underlying mechanisms to explain these associations (135). First of all, smoking may have some antidepressant properties with several potentially lethal side effects. Secondly, smoking-induced vascular endothelial inflammation may disturb epithelial functions for absorption and excretion in the gastrointestinal and genitourinary tracts which may terminate with urolithiasis and components of the IBS including loose stool, diarrhea, and constipation. Thirdly, diarrheal losses-induced urinary changes may even cause urolithiasis (136). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the gastrointestinal and genitourinary tracts terminating with the IBS and urolithiasis. Eventually, immunosuppression secondary to smoking-induced vascular endothelial inflammation may even terminate with the gastrointestinal and genitourinary tract infections causing loose stool, diarrhea, and urolithiasis, because some types of bacteria can provoke urinary supersaturation, and modify the environment to form crystal deposits in the urine. Actually, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infections with the bacteria producing urease. Parallel to the results above, urolithiasis was detected in 17.9% of cases with the IBS and 11.6% of cases without in the other study (p<0.01) (136).

Tonsillar hypertrophy is a common physical examination finding in the SCDs patients even during the silent periods, and it may be a result of relative immunosuppression in them, since sinusitis, pneumonia, osteomyelitis, rheumatic heart disease, and meningitis like infections are common in such patients. Tonsils are collections of lymphoid tissue facing into the aerodigestive tract. The set of lymphatic tissue known as Waldeyer's tonsillar ring includes the adenoid tonsil, two tubal tonsils, two palatine tonsils, and the lingual tonsil. When used unqualified, the term most commonly refers specifically to the palatine tonsils, which have non-keratinized stratified squamous epithelium, and are incompletely encapsulated. They are located at the sides of oropharynx between palatoglossal and palatopharyngeal arches. Tonsils are the largest in diameter in childhood, and they gradually undergo atrophy after puberty. These immunocompetent tissues are the immune system's first line of defense against ingested or inhaled foreign pathogens. Tonsils can become enlarged and inflamed and may need surgical removal. Tonsilectomy may be indicated if they obstruct the airway, interfere with swallowing, affect speech, or in case of

recurrent tonsillitis. Similar to the spleen (137), the tonsils are probably found among the primarily affected organs in the SCDs, and they may act as chronic inflammatory foci, and surgical removal may decrease secondary systemic inflammatory mediators and endothelial damage in such patients.

As a conclusion, SCDs are severe inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with an accelerated atherosclerosis and end-organ failures in early years of life. There may be an inverse relationship between prevalence of tonsilectomy and severity of SCDs, and the tonsils may act as chronic inflammatory foci accelerating the chronic endothelial damage all over the body. The relatively suppressed hemoglobin S synthesis in the SCDs secondary to the associated thalassemias may decrease severity of sickle cell-induced chronic endothelial damage, inflammation, edema, fibrosis, and end-organ failures. On the other hand, severity of SCDs may restrict smoking habit due to some immediately felt harmfull effects on health.

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THE MISCONCEPTION AROUND BLACK NATURAL HENNA

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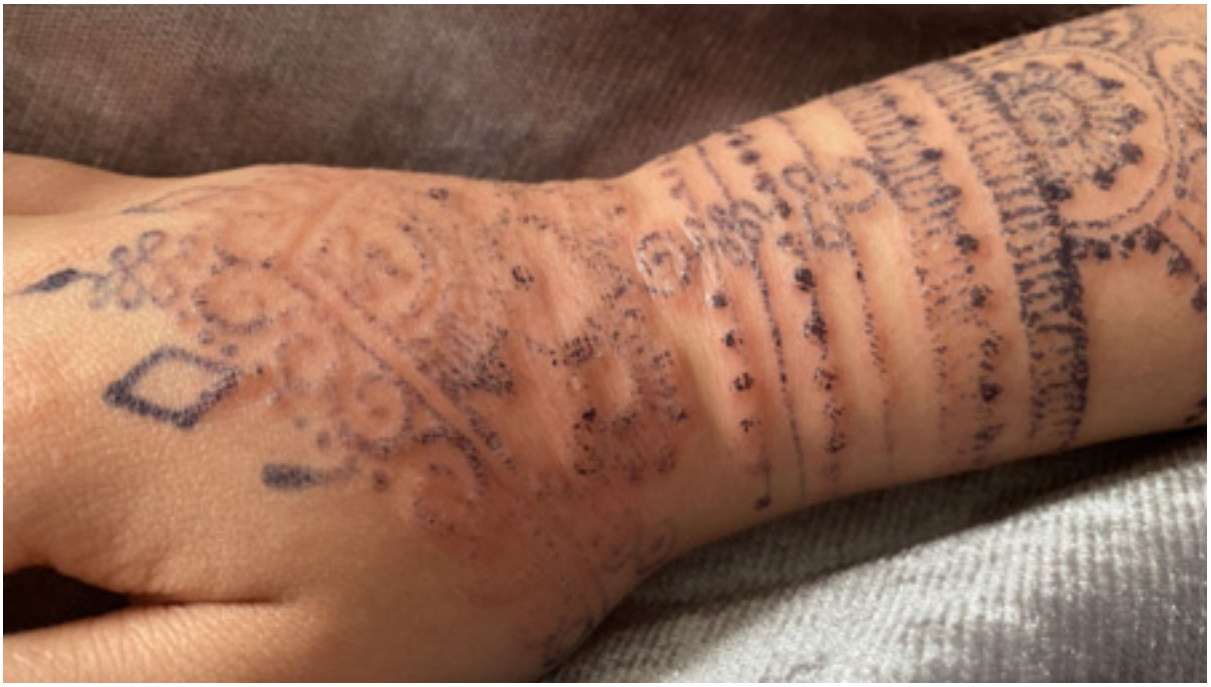
Abstract

Although the risk of P-phenylenediamine (PPD) contained in henna is well-known and well-documented in the medical literature, other ways of using temporary tattoos in henna such as Jagua are little known.

Keywords: black henna, blisters, itch

Figure 1: Allergic reaction on the hands after 5 days. Dr Elghblawi ®

Figure 2 Allergic reaction post black henna and sunbed Dr Elghblawi ®



Case report:

18-year-old Yemini British, skin type IV, presented with an itchy red skin reaction on the inscription of the henna for the Eid feast. She described her hands as on fire. She said that she didn't have any reactions at all post henna by day 5 and then went for sunbed for 9 minutes, whereby 2 days later she developed intense itchy red skin reactions following the pattern of the henna, and some minute blisters followed later (Figures 1-3). She had, however, multiple henna art on her hands in the past without any known reactions whatsoever. The henna brand used is called Jagua henna, which is a fruit that grows in Amazon, and its juice gel is claimed to give the natural black dye colour. The main ingredients in Jagua henna are genipin and geniposide, which have emerged as an interesting option for stained henna. She is otherwise fit and well.

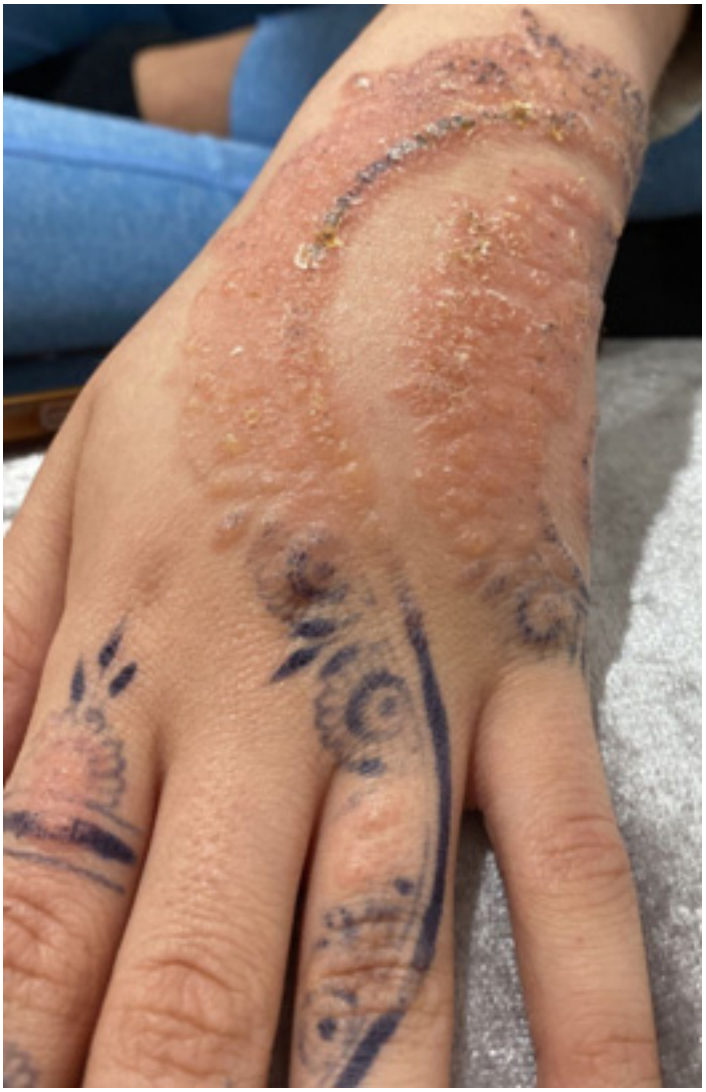
I made some searches online and found that Jagua claimed to have a quite high allergy and reaction rate and especially in those allergic to strawberries, kiwi fruit, and berries. However, in this case, she has no allergies to those claimed fruits.

Henna is an art that many Muslim women love to have for certain occasions, namely Eid and weddings. Certain women have this done at their home rather than at a licensed salon which is used and applied by specialists or professionals, who follow rules and won't apply these products unless they are FDA certified and meet the regulatory requirements for composition and purity, because any temporary tattoo products that don't comply with restrictions on colour and additives are considered adulterated and unlawful.

Her GP gave her an oral antibiotic (Floxacillin capsules 500mg, numbing cream (Lidocaine 2%), painkillers (Cocodamol tablet), and an antihistamine tablet (Citrizine 10mg).

In this case scenario, the lady allegedly using black natural henna which caused her no issues in the past; however, she also used sunbeds post-henna after 5 days. Natural henna does not have a natural black colour, but either a brownish, orange-brown or reddish-brown tint. The attained black colour is due to adding a coal tar hair PPD to stain black and last longer, which is well known in causing dangerous skin allergies and is unsafe for the skin. Having his said, it will increase the risk of later having a severe allergic reaction to hair dyes in the future. Therefore, it is advisable to have a patch test on a small area of the skin before having them just in case.

Figure 3 some minutes after blisters Dr Elghblawi ®



Discussion and conclusion:

Contextual skin painting (pseudo-tattooing) with henna is traditionally performed mainly in Muslim or Hindu cultures(1).

Temporary tattoos made with an extract of the jagua fruit are becoming steadily popular, and is claimed to be 'dermatologically tested' and does not contain p-phenylenediamine.

While it is illegal to use PPD-containing hair dye in henna tattoos. The lady used a different henna, which claimed to be natural (Jagua henna). It's an extract of Amazonian jagua fruit which is used extensively by indigenous people of southeast Asia for dying bodies, hair, and clothing dye(2,3), and has been in traditional Chinese medicine, for epochs(4).

However, the reaction, in this case, might be attributed to perhaps multiple causations, including using the artificial heating lamps exposing the body to UV rays leading to those whitish/reddish puffy bumps, and itchy rashes in the patterns of the henna design, after using a tanning bed. Moreover, tanning can cause heat rash (miliaria) due to hindering the flow of sweat between the skin layers. Also, the cleaning wipes can be associated as well. The lady denied using any tanning lotions, oils, or other products prior to the sunbed session, which could clog pores and cause reactions.

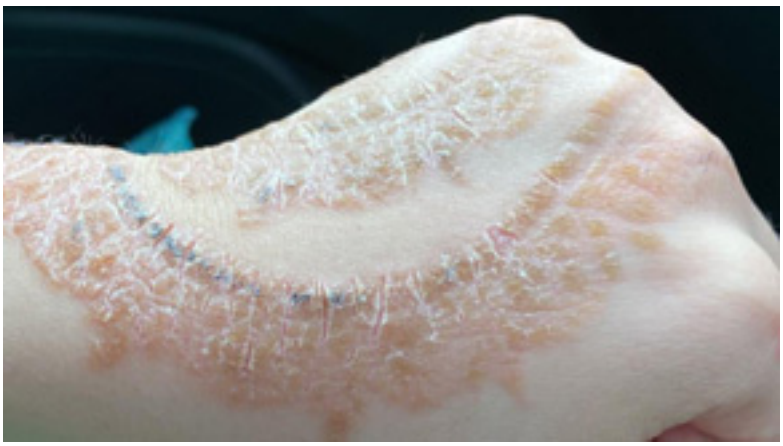
There is however, an increase in the reported number of allergic reactions to 'black henna' temporary tattoos in the UK, according to the British Skin Foundation, in 2015.

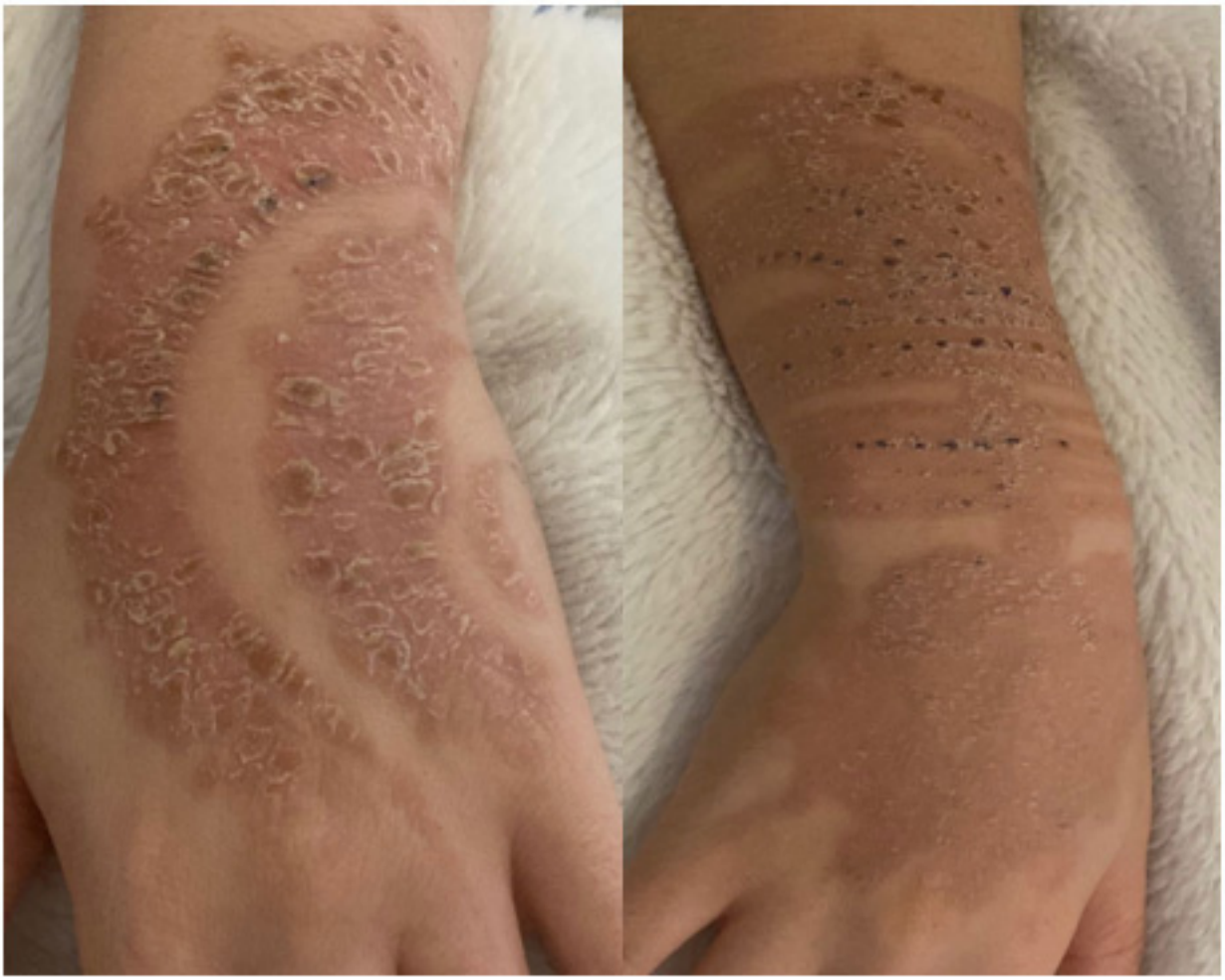
It has been said that more than 80% of the reactions they had seen were in children under the age of 16.

The studies showed that the allergen identified is genipin, which could result in an increase in the number of allergic reactions in the future.

It's advisable to avoid direct sun rays while the rash recovers and to wear loose-fitting clothes. Also, it's advisable to give antihistamines to alleviate itching and topical steroids to counteract the inflammations. Also, sunbeds are known to cause skin cancer, so it's wise to avoid them. The lady's hands recovered well with some remanent darkish brown stains which will take time to fade out slowly (Figure 4). I advised keep using emollients to ease the exfoliations and flaking process.

Figure 4 notes the exfoliation with darkening. Dr Elghblawi ®





Consent was taken from the patient for educational purposes.

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THE MYTH OF SQUATTING TOILETS

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Have we wondered why nowadays there are many bowel cancers compared relatively to the old era? The question is now lifestyle diseases are quite commonly seen globally and the main culprits are sedentary life habits, lack of physical activities, and lack of fiber intake, all of which contribute to the development of non-communicable diseases like obesity, type II diabetes, and heart diseases.

Defecation in its humblest form entails 3 mechanisms: spontaneous rectal contraction (autonomic), straightening anorectal angle due to relaxation of puborectalis and external anal sphincter (largely somatic), and straining (somatic), and that of which is under our control is the somatic(1).

Modernized sitting toilets are favoured worldwide because they provide a fairly restful posture in endeavouring defecation. However, comparatively, squat toilets were well known in the old eras and are still used in some places across the world, namely Asian and African countries including China and India, Indonesia, Bangladesh, Pakistan, Yemen, Sri Lanka, Malaysia, Myanmar, Iran, Iraq, Egypt, and Libya and they have the advantages of personal hygiene, easy cleaning, and health benefits to the bowel. They are also found in Japan, South Korea, Taiwan, Thailand, and Singapore.

Studies showed that squat toilets exert less pressure, and less angle and allows the stool to be expelled smoothly with less strain. This consequently will help prevent stool stagnation, ease constipation, less bowel irritation, prevent hemorrhoids, and thus less bowel cancer. Squatting pose for defecation is the most appropriate way, as the abdominal muscles work actively and complete evacuation takes place (2).

Western cultures have stimulated intense debate in both the East and the West. The question is why are we witnessing so many different uncommon bowel diseases all of a sudden, and they became common in the late nineteenth century.

Researchers have endorsed the squatting posture owing to its health benefits from a physiological perspective. Unambiguously, in the squatting bearing, the anorectal angle is broadened and straightened (100–110°) and the rectum is straightened, resulting in higher rectal pressure and lower anal pressures with possible levator ani relaxation resulting in smoother defecation and rectal emptying (Figure-1). Additionally, squat toilets can protect users from colon and prostate diseases and help in reducing the occurrence of diseases related to the digestive system, such as constipation and haemorrhoids (2).

Previous studies have acknowledged that squatting enhances the angle of the anorectal canal, reduces strain, increases sensation of adequate bowel emptying, and lessens time linked with defecation when compared with sitting toilets.

The average time for defecation was 6.1±4.7 minutes (3) for patients between age 18 to 35 years old. Remarkably, a recent Iranian study found that more than half of survey patients were toilet readers with significantly longer time on the toilets.

For pregnant women, the squatting posture prevents pressure from being applied to the uterus; and daily squatting helps prepare them for a more natural delivery.

Moreover, squat toilets are eco-friendly because they consume less water than other toilets.

As stated those toilet styles are not found in the west, and thus can be modified by applying the defecation postural modification devices (DPMDs) on normal bowel patterns to increase awareness to bowel habits in western populations. The introduction of defecation postural modification devices (DPMDs) was developed to replicate the alignment achieved with squatting while using a toilet (3). DPMDs may offer a nonpharmacologic option for a common diagnosis such as constipation (Figure-2).

Figure 1: The mechanism of defecation in squatting pose.

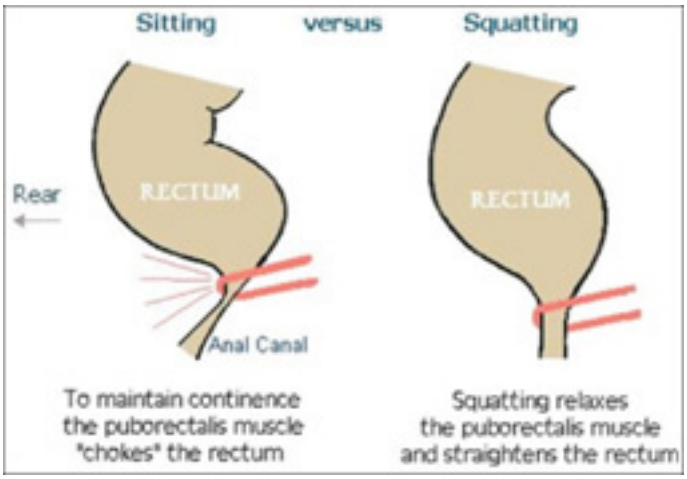
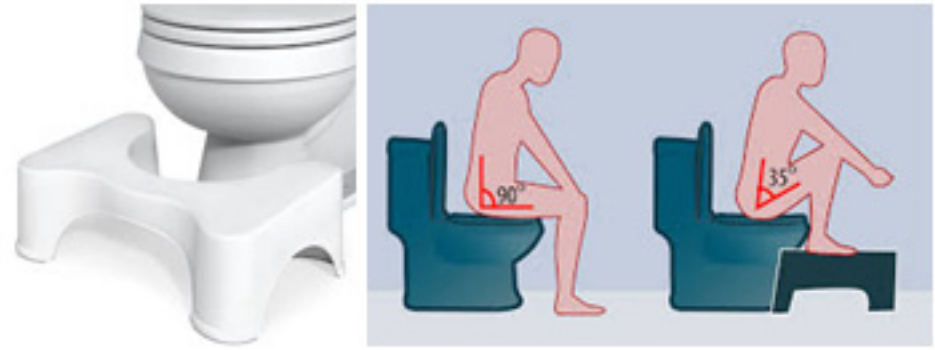


Figure 2: Modified squatting technique by elevating knees and creating the ergonomic angle.



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ANTIBIOTIC-RESISTANT BACTERIA IN INTENSIVE CARE UNITS IN THE KINGDOM OF SAUDI ARABIA: A SYSTEMATIC REVIEW

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Abstract

Background: The emergence of bacterial pathogens and their associated resistance to antibiotic therapy is one of the most serious public health concerns threatening today's society, including Saudi Arabia's intensive care units (ICUs).

Aim: This study used a systematic review to explore the antibiotic-resistant bacteria in the intensive care units (ICUs) in Saudi Arabia.

Methods: The review adhered to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 guidelines. The search was limited to studies published within 13 years between 2010 and 2023 through CINAHL, Web of Knowledge, PubMed, Science Direct, and Google Scholar.

Results: Fifteen studies were reviewed: 12 were retrospective, 1 was comparative historical, 1 was descriptive epidemiologic and 1 was a surveillance study. Most frequently isolated antibiotic-resistant bacteria were Klebsiella pneumonia, Pseudomonas aeruginosa, Acinetobacter baumannii, Escherichia coli, and Enterobacter. These pathogens were found resistant to various antibiotics including methicillin, tazobactam, cilastatin, meropenem, tigecycline, imipenem, meropenem, piperacillin, colistin, penicillin, ampicillin, oxacillin, vancomycin, carbapenems, amoxicillin, ceftriaxone, amikacin, gentamicin, clindamycin, azithromycin, levofloxacin, nitrofurantoin, trimethoprim, cefuroxime, ciprofloxacin, aztreonam, and cefotaxime.

Conclusion: To eradicate future infection outbreaks of K. pneumonia, P. aeruginosa, A. baumannii, and other antibiotic-resistant pathogens in Saudi Arabia's ICUs, comprehensive surveillance programs, strict infection control and prevention guidelines, and stringent implementation of proactive antimicrobial stewardship program are warranted.

Keywords: antibiotic; antibiotic-resistant bacteria; intensive care unit; Saudi Arabia

Introduction

Antibiotics are one of the most frequently used medications worldwide [1], and these drugs reduce mortality rates among critically ill patients [2]. However, the use of any antibiotic drug produces unwanted adverse events, and it is the main driver for the increasing problems with antibiotic resistance [3]. Specifically, intensive care units (ICUs) provide care for vulnerable and critically ill patients by using varied invasive devices; ICUs have encountered increased antibiotic resistance, leading to high nosocomial infection burden [4,5]. In addition, the most essential issue facing ICUs is the spread of nosocomial infections caused by antibiotic resistance [6,7]. Infections with antibiotic-resistant bacteria in ICUs lead to increased negative effects on morbidity and mortality and patients' survival, prolonged hospitalization, and elevated healthcare costs [5,7,8,9]. Thus, the emergence and spread of antibiotic resistance have become a public health priority in healthcare settings, primarily in ICUs, where it may become the leading cause of death by the year 2050 [8,10].

Globally, numerous investigations in ICUs have explored bacterial pathogens and their resistance to antibiotic therapy as one of the most serious health concerns threatening today's society [11]. In Saudi Arabia, a substantial number of studies have investigated the antibiotic-resistant incidences of bacteria in ICUs [4-9,12-18]. With this synopsis about the antibiotic resistance of bacteria, this review presents trends in ICU settings in the Kingdom of Saudi Arabia (KSA). This work may add to the existing knowledge on how to implement control and interventions geared toward reducing morbidity and mortality, decreasing healthcare costs and hospital stay, and improving survival rates of critically ill patients infected with antibiotic-resistant bacteria. The results of this review may reveal the need for continued and vigilant national monitoring for antibiotic-resistant bacteria to reduce the risk of new resistant isolates and avoid complications in ICU settings. Thus, the current study aimed to review the antibiotic-resistant bacteria in the ICUs in KSA between January 2010 and December 2023.

Methods

Design

A systematic review of literature was conducted in this study. The review adhered to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 checklist.

Search strategy

The literature search of studies that investigated the antibiotic resistance of bacteria in the ICUs in KSA was performed online and manually using the following electronic databases: CINAHL, Web of Knowledge, PubMed, Science Direct, and Google Scholar. The search terms used were "antibiotic-resistant bacteria," "antibiotic-resistant pathogens," "intensive care units," "critically ill patients," and "Saudi Arabia." The electronic search was accomplished by limiting studies only to the last 13 years (January 2010–December 2023) to include contemporary studies on antibiotic resistance of bacteria in the ICUs in KSA. The studies included in the review were those that 1) focused on the antibiotic resistance of bacteria; 2) were conducted in the ICUs either in general or sub-units, or in other hospital units that included the ICU; 3) were published in English and in peer-reviewed journals; and 4) were full-text articles with an abstract. Studies without an abstract, not full text, not carried out in the ICU, and not conducted in KSA were excluded from the review.

Outcomes and data extraction

Initially, the search retrieved 2,670 hits in all electronic databases, as shown in Figure 1. Most of the articles were conducted not in the ICU and outside KSA. Filtered screening through reading of titles and abstracts from these articles resulted in the selection of 21 articles based on the inclusion and exclusion criteria. After the final review and analysis of the author, 15 articles were selected. Details of the author of the study, year of publication, aim of the study, location of the study in KSA, sample (antibiotic-resistant bacteria), design used, and major findings as remarks were extracted from each study (Refer to Table 1).

Results

This systematic review involved 15 studies conducted in different regions in KSA including two in the western region, three in the eastern region, two in the southwest region, and most (8) in the central region. Surprisingly, no study was conducted in the northern regions of the kingdom. Among those studies, 12 were retrospective, 1 was comparative historical, 1 was descriptive epidemiologic, and 1 was a surveillance study. The most frequently isolated antibiotic-resistant bacteria in this review were Klebsiella pneumonia described in 11 studies, Pseudomonas aeruginosa investigated in 9 studies, Acinetobacter baumannii reported in 8 studies, Escherichia coli studied in 5 studies, Enterobacter stated in 5 studies, and others included Providencia spp., Citrobacter spp., Serratia spp., Proteus mirabilis, Staphylococcus aureus, Candida albicans, and Clostridium difficile. Finally, most of the pathogens presented above were resistant to various antibiotics including methicillin, tazobactam, cilastatin, meropenem, tigecycline, imipenem, meropenem, piperacillin, colistin, penicillins, ampicillin, oxacillin, vancomycin, carbapenems, amoxicillin, ceftriaxone, amikacin, gentamicin, clindamycin, azithromycin, levofloxacin, nitrofurantoin, trimethoprim, cefuroxime, ciprofloxacin, aztreonam, and cefotaxime.

Discussion

This study reviewed related literature about antibiotic-resistant bacteria in ICUs in Saudi Arabia. After an extensive search, most of the studies were conducted in tertiary hospitals in the central region of the kingdom [4-5,7,11,13,15-17], and few were carried out in the eastern [8,9,14], southwest regions [6,18], and western region [19,20]. However, no work was conducted in the western and northern regions of the kingdom. This does not mean that there were no investigations about antibiotic-resistant pathogens in these regions; studies may have been conducted in different hospital units, and researchers possibly did not focus on ICUs, such as in the work of Alam et al. [21] and Yagoub et al. [22]. Another reason could be that reports were submitted to the Ministry of Health but not published in journals. Nonetheless, most of the studies were retrospective in design [4-7,9,12-13,16-20], and others were comparative historically controlled studies [15], descriptive epidemiologic hospital-based case–control studies [14], and surveillance studies [8]. These studies were mostly conducted in general ICUs, and few were performed in specific sub-units such as coronary, neonatal, and adult ICUs.

The most frequently isolated antibiotic-resistant bacteria in this review were (1) K. pneumonia [4-9,11,13,17-19], (2) P. aeruginosa [4-7,9,11,13,16,18], (3) A. baumannii [4-7,9,11,16,18], (4) E. coli [4,6,7,11,18], (5) other Enterobacter species [4-5,13,14,18], and (6) others, including Stenotrophomonas maltophilia, Providencia spp., Citrobacter spp., Serratia spp., P. mirabilis, S. aureus, C. albicans, and C. difficile. Therefore, this study revealed that the top three antibiotic-resistant bacteria isolated in the ICUs in Saudi Arabia were K. pneumonia, P. aeruginosa, and A. baumannii, which are all categorized as Gram-negative bacteria.

Among those above-identified pathogens in ICUs, the susceptibility patterns of antibiotics significantly decreased with E. coli, A. baumannii, Enterobacter, and Serratia marcescens [4]. Specifically, A. baumannii showed high resistance with ventilator-associated pneumonia patients in the ICU [16]. In terms of samples collected for antibiotic susceptibility, respiratory samples, blood samples, and urinary samples [4-5,11] were the three specimens most frequently indicative of multidrug-resistant bacteria typically found in general ICUs [11,18]. Factors that were identified to be associated with vancomycin-resistant enterococci included multi-organ failure admission, gastrointestinal oral contrast procedure, chronic renal failure, hemodialysis, and prior use of antimicrobial drugs in the past 3 months and before admission in the ICU [14]. Moreover, being admitted in the ICU, including mechanical ventilation and parenteral feeding, was revealed to be a marginally significant risk factor for susceptibility to antibiotic-resistant pathogens [8,17].

Most of these pathogens, particularly K. pneumonia, P. aeruginosa, and A. baumannii, show resistance to methicillin [11], tazobactam, cilastatin, meropenem, tigecycline [15], imipenem, meropenem, piperacillin [6,15], colistin [9,13], penicillin [16,18], ampicillin, oxacillin [16], vancomycin [14-17], carbapenems [5], amoxicillin, ceftriaxone, amikacin, gentamicin, clindamycin, azithromycin, levofloxacin, nitrofurantoin, [18], trimethoprim, cefuroxime, ciprofloxacin [6,18,19], aztreonam and cefotaxime [6,20]. In particular, with low dose of colistin, the incremental costs per nephrotoxicity case can be avoided [9]. With the call for stringent implementation of proactive antimicrobial stewardship programs as a vital approach to prevent the emergence of antibiotic resistance [13,15], antibiotic use was lessened and unfitting, leading to reduced direct cost [9,15].

Conclusions

K. pneumonia, P. aeruginosa, and A. baumannii were the three most frequently isolated Gram-negative bacteria in the ICUs in Saudi Arabia. Comprehensive surveillance programs, strict infection control and prevention guidelines, and stringent implementation of a proactive ASP are warranted to eliminate future infection outbreaks with these antibiotic-resistant pathogens.

Conflict of Interest

No conflict of interest has been declared by the author.

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Figure 1: PRISMA flow chart of the review

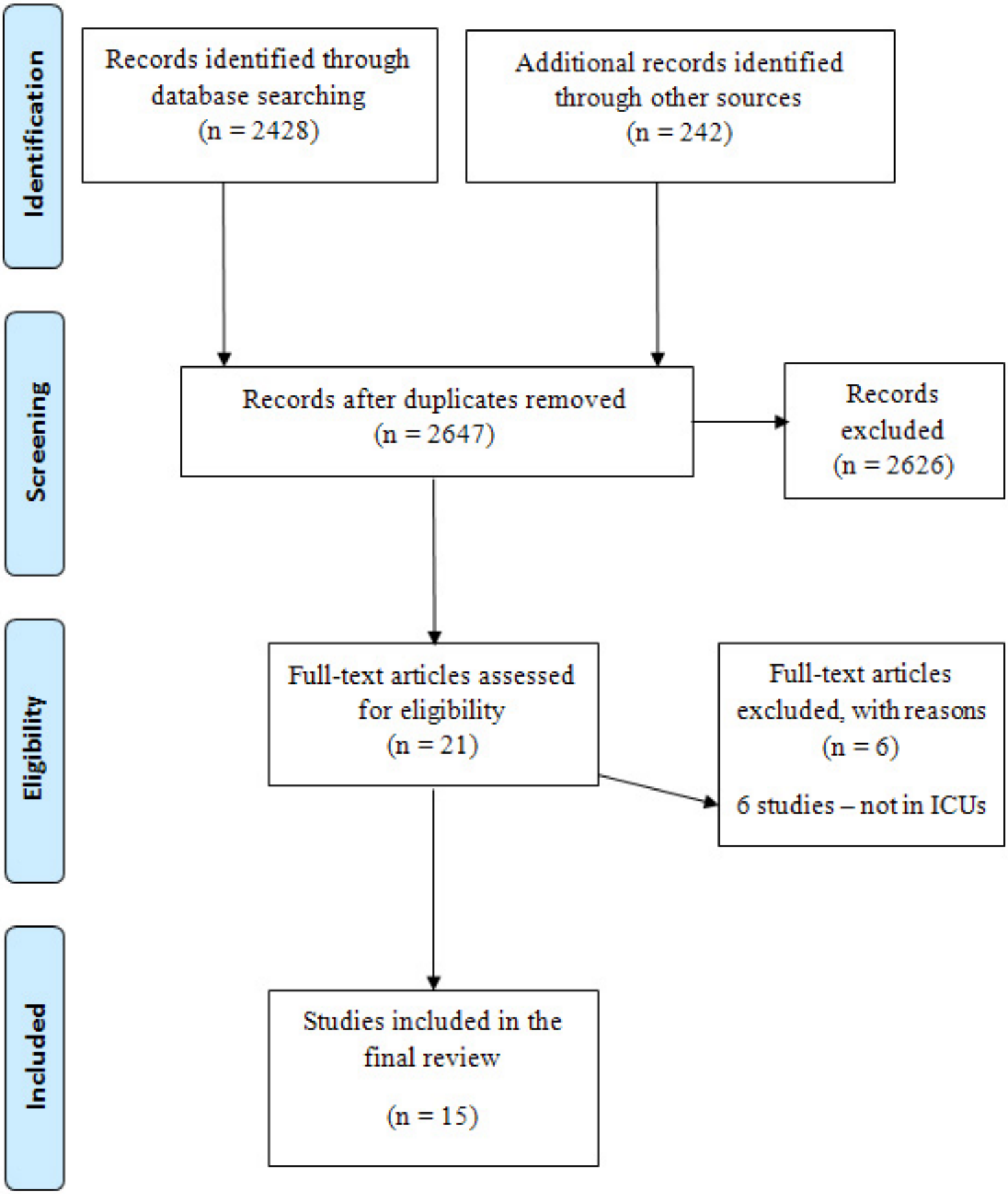

Table 1. Study Characteristics

Author/s & Year	Purpose	Design and Location	Findings
Al Johani et al. (2010)	To examine patterns of antimicrobial susceptibility in gram-negative isolates to commonly used drugs in an adult intensive care unit (ICU)	A retrospective study in adult ICU at King Fahad National Guard Hospital (KFNGH) in Riyadh, Central Kingdom of Saudi Arabia (KSA)	- Acinetobacter baumannii was the most frequently isolated organism. - Others were Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Stenotrophomonas maltophilia, and Enterobacter. - Antibiotic susceptibility patterns significantly declined in many organisms, especially A baumannii, E coli, S marcescens, and Enterobacter. - Respiratory samples were the most frequently indicative of multidrug-resistant pathogens followed by urinary samples.
Saeed et al. (2010)	To assess the prevalence of multi-drug resistant (MDR) bacteria causing infections in patients as well as their antimicrobial resistance patterns for one year	A retrospective, cohort investigation at the intensive care units (ICUs) of Riyadh Military Hospital (RMH), Central KSA	- Acinetobacter baumannii (A. baumannii) comprised 40.9%, Klebsiella pneumonia (K. pneumonia) - 19.4%, while Pseudomonas aeruginosa (P. aeruginosa) formed 16.3% of these isolates. - A total of 1210 isolates were collected from various specimens such as: respiratory (469), blood (400), wound/ tissue (235), urinary (56), nasal swabs (35), and cerebro-spinal fluid (15). - Regardless of the specimen, there was a high rate of nosocomial MDR organisms isolated from patients enrolled in the General ICU (GICU) in Riyadh.
Amer et al. (2013)	To compare the prescribing appropriateness rate of the empirical antibiotic therapy before and after the antimicrobial stewardship programs (ASP) implementation in a tertiary care hospital	A comparative, historically controlled study involving Clostridium difficile bacteria in the medical ICU at KKUH, Riyadh, Central KSA	A total of 73 subjects were recruited, 49 in historical control and 24 in the active arm where for the ASP group, initial uses of antibiotic were inappropriate and diminished by ASPs to 0% on the recommendations implementation with a reduction in antibiotics utilization and direct cost were also noticed in the ASP arm. - A proactive ASP is a vital approach in optimizing the appropriate empirical antibiotics utilization in an ICU setting in tertiary care hospitals.
Garbati et al. (2013)	To highlight the growing prevalence of infections with colistin-resistant Enterobacteriaceae in response to the rising incidence of drug resistance	A retrospective observational study was conducted in the ICU of King Fahad Medical City, Riyadh, Central KSA	- Nine episodes of infection with colistin-resistant Enterobacteriaceae were recorded in seven patients. - In five of the episodes, Klebsiella pneumoniae was responsible, Serratia marcescens was reported in two, while Enterobacter aerogenes and Providencia stuartii were responsible for one episode of infection each.

Shorman & Al-Tawfiq (2013)	To determine the risk factors associated with vancomycin-resistant enterococci (VRE) infection or colonization in intensive care unit (ICU) settings	A descriptive, epidemiologic hospital-based case-control study at King Fahad Specialist Hospital in Dammam, Eastern KSA	- Factors associated with VRE included ICU admission for multi-organ failure, chronic renal failure, prior use of antimicrobial agents in the past three months and before ICU admission, gastrointestinal oral contrast procedure, and hemodialysis which are often complex and may be confounded by local variables.
Balkhy et al. (2014)	To examine the extent of multiple-drug resistance among common microbial causes of ventilator-associated pneumonia (VAP).	A retrospective susceptibility study in the adult ICU at King Abdulaziz Medical City, Riyadh, Central KSA	- A total of 248 isolates including 9 different pathogens were included. - Acinetobacter species were highly resistant to all tested antimicrobials. - Acinetobacter in the current study was an increasingly resistant VAP-associated pathogen.
Somily et al. (2014)	To determine possible risk factors for infection or colonization with extended spectrum-β-lactamase-producing Klebsiella pneumoniae (ESBLKp) during an outbreak in the NICU	A retrospective cohort study in NICU in KFSHRC, Riyadh, Central KSA	- Out of 118 neonates, 4 became infected, and 8 were colonized with ESBLKp. - Among 14 neonates who were treated with vancomycin, 9 developed infection or colonization with ESBLKp, whereas, among 104 neonates who were not treated with vancomycin, 3 were affected. - Parenteral feeding and mechanical ventilation were found to be marginally significant risk factors.
Al Yousef (2016)	To study epidemiology and resistant pattern of bacteria causing infection in different hospital units including ICUs.	A surveillance method was carried out at King Khalid Hospital in Hafr Al-Batin, Eastern KSA	- Escherichia coli, Klebsiella pneumonia, and Pseudomonas aeruginosa were the commonly identified Gram-negative bacteria where Staphylococcus aureus was the only identified Gram-positive bacterium. - The most common antibiotic-resistant bacteria were found on female surgical ward followed by ICU and male surgical ward.

Abujheisha et al. (2017)	To explore the multidrug-resistant bacteria, Extended Spectrum β- lactamase bacteria [ESBLs] and the possibility of carbapenems resistant bacteria isolated from clinical samples of patients	A retrospective study of 317 samples for cultivation and antibiogram according to Clinical and laboratory standard institute (CLSI) guidelines in ICUs at King Khalid Hospital, Al-Kharj, Central KSA	- Out of 317 total samples processed, significant growth was shown in 62 samples where respiratory samples showed the highest rate of positive growth followed by urine samples. - Fifty-seven isolates were gram-negative and five isolates were gram-positive. - K. pneumoniae was the most frequently isolated among Gram-negative with16 isolates followed by P. aeruginosa. - All isolates of P. aeruginosa, Acinetobacter spp., Providencia spp., Enterobacter spp., Citrobacter spp., Serratia spp. were MDR while five isolates of Proteus mirabilis, and 11 of K. pneumoniae were MDR. - ESBLs were confirmed in 39 isolates out of 47 MDR gram-negatives; among them, 11 were K. pneumoniae and10 isolates of P. aeruginosa. - Resistance to carbapenems was detected in 23 isolates of MDR gram-negative bacteria; among them, 10 isolates of P. aeruginosa, and 6 isolates each of Acinetobacter spp. and K. pneumoniae.
Alavudeen et al. (2017	. To determine the prevalence of bacterial pathogens and to assess the multi-drug resistant (MDR) strains to different antibiotics in Aseer Region, Southwest KSA	A retrospective analysis of 163 subjects diagnosed with variable infections	- A total of 15 different strains of gram positive and negative were isolated where, a urine specimen was found to have the highest number of bacterial isolates and inten¬sive care unit (ICU) had higher number of isolates. - Among 46 antibiotics tested, only 12 antibiotics were included in the analysis. - Almost, the majority of the gram positive and gram negative bacterial isolates had resistance to more than three antimicrobials, which satisfies the criteria to call them multidrug resistant bacterial isolates.
Cara et al. (2018)	To evaluate the cost effectiveness of low versus high dose colistin in the treatment of Pneumonia caused by colistin-only sensitive gram negative bacteria	A retrospective review was conducted in ICU and non-ICU at King Abdulaziz Hospital in AlHasa, Eastern KSA	- The main outcomes were cure, nephrotoxicity, total direct costs per episode, cost per additional cure and cost per nephrotoxicity avoided. - No significant difference between high and low dose colistin with regards to clinical cure. - Significantly more patients experienced nephrotoxicity with high versus low dose colistin. - With low dose colistin, the incremental costs per nephrotoxicity were avoided.
Ibrahim (2018)	To determine the distribution and resistance profiles of Gram-negative bacteria (GNB) in intensive care units (ICUs)	A record based retrospective study at King Abdullah Hospital in Bisha, Southwest KSA	- Of 3,736 specimens, 358 were positive for pathogens and GNB constituted the majority. - Increased antimicrobial resistance with high proportions of multidrug resistant patterns was found among GNB from ICUs.

Azim et al. (2019)	To investigate the widespread multidrug resistance (MDR) gram-negative bacterial pathogens isolated from ICUs	A retrospective study at King Khalid University Hospital (KKUH), Riyadh, Central KSA	- A total of 70 MDR isolates from different body sites comprised P. aeruginosa, K. pneumoniae, E. coli, and A. baumannii. - The essential resistance mechanisms in the evaluated strains were extended spectrum-β-lactamase (ESBL) and Metallo-β-lactamase (MBL). - Molecular testing is recommended to confirm the phenotypic results and to detect the resistant genes.
Kabrah et al. (2021)	To identify the antibiotic resistance patterns of prevalent bacterial strains obtained from lower respiratory tract infections (LRTIs), bloodstream infections (BSIs), and urinary tract infections (UTIs) within ICUs	A retrospective study at King Faisal Hospital (KFH), Makkah, KSA	- Klebsiella pneumoniae (K. pneumoniae, 59.4%), Coagulase-negative staphylococci (CoNS, 11.5%), Escherichia coli (E. coli, 8.4%), Acinetobacter baumannii (A. baumannii, 7.3%), and Staphylococcus aureus (S. aureus, 6.2%). BSI were frequently caused by CoNS (35.7%) and K. pneumoniae (35.7%), while Methicillin-resistant Staphylococcus aureus (MRSA, 10.7%) - Vancomycin, Synercid, and Teicoplanin are frequently utilized antibiotics that demonstrated complete (100%) sensitivity in Staphylococcus aureus, including methicillin-resistant Staphylococcus aureus (MRSA). While 100% resistance was noted for penicillin and oxacillin in relation to these bacterial strains. - The highest levels of resistance were recorded for aztreonam at 96.4%, followed by ampicillin at 87.3%. Co-amoxiclav exhibited a resistance rate of 83.9%, while cotrimoxazole showed 79.5% resistance, along with the antibiotics belonging to the cephalosporin group.
Obaid et al. (2023)	To examine the antimicrobial-resistant pathogens responsible for catheter-associated urinary tract infections (CAUTIs) within ICUs.	A multi-center retrospective study in the Western region, KSA	- A total of twenty distinct pathogenic microorganisms have been identified as causative agents of CAUTIs. Among these, Candida albicans accounts for 18.4% of cases, followed by Escherichia coli at 13.5%, other yeasts excluding Candida at 10.4%, and Klebsiella pneumoniae at 8.5%. - A total of 19.67% of the pathogens identified as causative agents in CAUTIs were found to be resistant to antibiotics. - The isolates exhibiting the highest resistance from CAUTIs in ICUs included carbapenem-resistant Enterobacteriaceae, specifically Klebsiella pneumoniae (n = 17), as well as extended-spectrum β-lactamase-producing strains of Klebsiella pneumoniae and Escherichia coli, with counts of 11 and 19, respectively. - The most observed resistance was to ciprofloxacin at 16.5% and to trimethoprim or sulfamethoxazole at 16.1%.

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