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FROM THE EDITOR

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This is the first issue this year that is rich with papers from Qatar, the UK, and Australia and Turkey. Blanco, et al., stressed that the COVID-19 pandemic brought the world to a standstill, forcing businesses to close or adjust operations to online platforms. Nursing Educational Institutions (NEIs) were similarly affected by the implementation of public health measures to reduce the transmission of COVID-19, leading to abrupt lockdowns and campus closures, reduced or no face-to-face time in labs, and a sudden loss of clinical placement sites for students. To combat this problem, NEIs had to adjust their conventional practices and find alternative, novel approaches to fulfill the required hands-on lab teaching and clinical practice hours for their students. Many NEIs turned to simulation to close this gap for nursing students. Therefore, this integrative review seeks to explore what innovative simulation strategies were used during the pandemic era and the lessons that can be learned from these innovations.

Itaiwah, et al., stressed that Diabetic management programs play an important role in supporting people who live with diabetes and preventing diabetes related complications. These programs need to be culturally relevant to be successful. The authors explored culturally specific diabetic management programs within primary health care settings that can be adapted to the context of Qatar. This literature review was guided by Cronin et al.'s (2008) framework and included 17 scholarly articles published between 2011 and 2021. The Mixed Method Appraisal Tool was used to critically appraise the quality of these articles. The main components of culturally specific diabetic management programs are information and understanding, cultural norms, cultural interventions, and personal motivation. The authors concluded that in order to ameliorate diabetes management for clients, culture needs to be considered when providing education.

Helvacı, et al; looked at depression causing various inflammatory processes in human body. They followed consecutive patients with IBS and age and sex-matched control cases were included. The study included 936 patients with IBS (592 females) and 346 control cases. Although gastric sample biopsies were taken just in suspected cases, CG was diagnosed nearly in all of the patients with the IBS (80.4% vs 15.0%, $p < 0.001$). Interestingly, prevalence of antidepressants use was also higher in the IBS cases, significantly (46.4% vs 16.1%, $p < 0.001$). Similarly, smoking (35.2% vs 20.8%, $p < 0.001$), hemorrhoids (37.1% vs 7.2%, $p < 0.001$), and urolithiasis (22.0% vs 9.5%, $p < 0.001$) were all higher in the IBS patients, again. The authors concluded because FPG and triglycerides are well-known acute phase reactants in the body, IBS and CG may be some low-grade inflammatory processes initiated with anxiety, depression, infection, inflammation, trauma, and cancer fear-like stresses of the body, and eventually terminate with hemorrhoids and urolithiasis. Due to the highly significant associations between IBS, CG, and depression, IBS and CG may actually be the two sides of the same paper, and just be two examples of depression-induced various inflammatory processes in human body.

Helvacı, et al; looked at the use of corticosteroids during acute painful crises of sickle cell diseases. The authors stated that sickle cell diseases (SCD) are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of hardened red blood cells (RBC) into the tissues.

The study included 222 males and 212 females with similar ages. The authors concluded that although the hardened RBC-induced capillary endothelial damage is present in whole body even at birth, severe exacerbations during additional stresses are called as acute painful crises. An increased basal metabolic rate, exaggerated sickling, diffuse capillary endothelial damage, exaggerated capillary endothelial inflammation and edema, generalized tissue hypoxia, and multiorgan insufficiencies may be the main causes of mortality during the crises. Although rapid RBC supports are the main treatment option, corticosteroids should also be added to decrease severity of endothelial inflammation and edema, and to prevent tissue hypoxia and multiorgan insufficiencies during such crises.

Dr Elghblawi. Reviewed the Purple urine bag syndrome (PUBS) is an exceptional clinical finding in the clinical setting and is featured by its distinctive purplish urine discoloration. It has been claimed due to many culprits namely, long term indwelling catheterisation, dementia, urinary tract infection with alkaline urine that is fully loaded with bacteria, bed or chair bound patients, female gender, constipation and chronic kidney disease. It is seen more in the geriatric words. It is said that it's related to tryptophan aberrant metabolism by-products into red and blue pigments, due to the bacterial colonization in urinary catheter. Its distinctive colour is due to indigo-producing (bluish) and indirubin-producing (reddish) which react with the plastic tube to yield the striking purplish colour.

ASSESSING THE EFFECTIVENESS OF CULTURALLY SPECIFIC DIABETIC MANAGEMENT PROGRAMS WITHIN PRIMARY HEALTH CARE SETTINGS: A REVIEW OF THE LITERATURE

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Abstract

Introduction: Diabetic management programs play an important role in supporting people who live with diabetes and preventing diabetes related complications. These programs need to be culturally relevant to be successful.

Aim: To explore culturally specific diabetic management programs within primary health care settings that can be adapted to the context of Qatar.

Method: This literature review was guided by Cronin et al.'s (2008) framework and included 17 scholarly articles published between 2011 and 2021. The Mixed Method Appraisal Tool was used to critically appraise the quality of these articles.

Results: The main components of culturally specific diabetic management programs are information and understanding, cultural norms, cultural interventions, and personal motivation.

Discussion: In order to ameliorate diabetes management for clients, culture needs to be considered when providing education.

Key terms: Diabetes, cultural, self-management

Introduction

Diabetes Mellitus (DM) is a metabolic disease caused by a high glucose level in the blood. DM occurs when the body becomes resistant to insulin or when it produces little or no insulin. Serious health problems such as retinopathy, nephropathy, neuropathy, and cerebrovascular diseases may occur due to increased glucose levels in the blood over a long period of time (Mehring et al., 2017). Within the health care field, it has been noted that DM remains a primary health challenge (Al Busaidi et al., 2019). Globally, the prevalence of DM is increasing. The number of people who live with diabetes has quadrupled worldwide in the previous three decades, and DM is considered the ninth leading cause of death (Zheng et al., 2018). Farinha et al. (2020) mentioned that the number of people who live with diabetes had risen to 463 million people worldwide in 2019. These researchers mentioned that this number is expected to continue to reach 578 million by 2030 and a further 700 million by 2045. In 2019, it was estimated that 19.3% of people between the ages of 65 and 99 years will have diabetes, and it is projected that the number of people older than 65 years with diabetes will be 195.2 million by 2030 and 276.2 million by 2045 (Sinclair et al., 2020).

When caring for a person who lives with diabetes, it is important to note that diabetes can happen to anyone and people with diabetes may come from many diverse backgrounds. Therefore, culturally specific diabetic management programs (DMP) are an essential determinant of care. It is key for healthcare providers to understand the influence culture has on personal health care practices and how to encourage self-efficacy. A person's health and cultural beliefs should be considered to improve the quality of life for those who live with diabetes. Positive health behaviour changes that are aimed at reducing diabetes related complications cannot be forced upon people. It is imperative that the health care provider understands how culture guides individual behaviours, and gets insight not just from the person with diabetes but also from the family involved in the care. Therefore, this literature review aims to assess the effectiveness of culturally specific diabetic management programs that are being employed in other countries within primary health care settings to determine an approach that may be used in Qatar.

Methodology

The process used in guiding this project was a literature review. The purpose of selecting Cronin et al.'s (2008) model for a literature review was to provide a comprehensive search for background and recent literature related to the use of culturally specific Diabetes Management Plans (DMP) within primary health care.

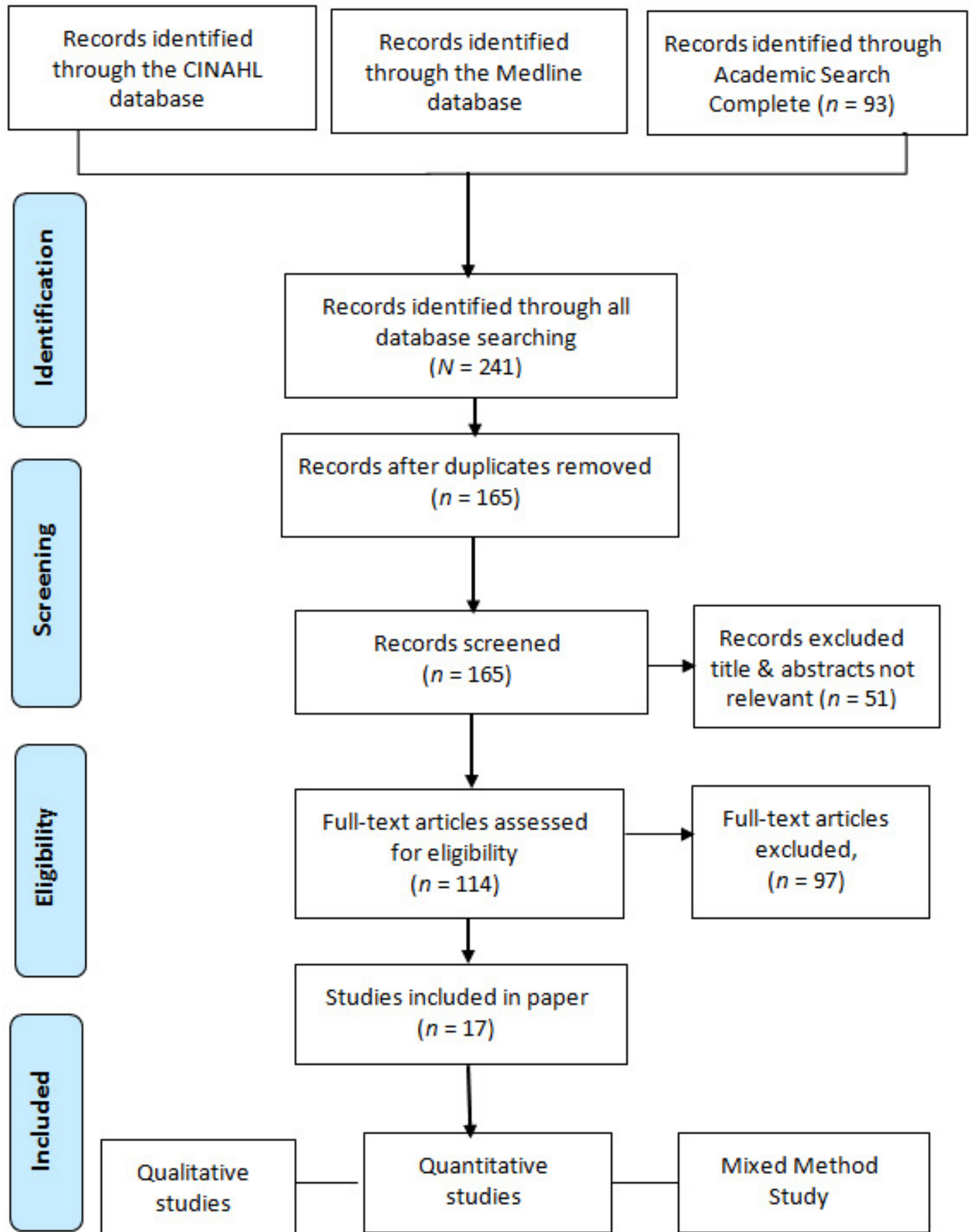
Literature Search

The databases used in this review were Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, and Academic Search Complete. These databases were used to assess the cultural interventions in DMPs within primary health care settings worldwide. The following search terms were used in the literature search: diabetes*, Glycemic, manag*, self-manag*, prevent*, control*, education*, care*, self-car*, Awarene*, support*, N4 program*, Diabetes-Program*, Diabet*-management-Program, community health", "community care", "primary healthcare", "primary health care", "primary care", "Health Center*", "public healthcare", and cultur*. The Boolean operators AND and OR were used to identify and search for literature. The search outcome was restricted by using search limiters. These limiters were peer-reviewed, English language, and published between January 2011 and December 2021. The search resulted in 53 articles from CINAHL, 95 articles from Medline, and 93 articles from Academic Search Complete.

Data Evaluation

241 articles were evaluated to find the most suitable literature to be used in this project. Seventy-six of these articles were removed because of duplication. The title and abstracts of the remaining 165 articles were reviewed according to inclusion and exclusion criteria. The inclusion criteria were (a) adult patients above 18 years old, (b) studies from 2011 to 2021, (c) studies about culturally specific DMPs within primary health care, (d) articles written in English, and (e) peer-reviewed articles. The exclusion criteria were (a) studies older than 10 years, (b) studies involving those under 18 years of age, (c) studies within hospitals or long-term care, (d) articles not written in English, and (e) articles that were not peer-reviewed. Fifty-one articles were excluded after reviewing the titles and abstracts. The full text was reviewed of the remaining 114 articles to find articles that assessed culturally specific DMPs in primary health care settings worldwide. The final review provided 17 articles acceptable for inclusion in this project (see Figure 1).

Figure 1: Literature Search Flow Diagram



Data Appraisal

This project used the Mixed Methods Appraisal Tool (MMAT) version 2018 to evaluate the 17 studies. Three of these studies were qualitative in their design, seven of these studies were mixed methods in their design, and seven of these studies were quantitative design. All of these studies met all five of the required criteria.

Data Analysis

Data from the 17 articles was organized and summarized in an extraction table to facilitate the analysis of the data. The 17 articles were presented in alphabetical order according to the authors' names. The table includes the title, authors' names, year of publication, country, study purpose, method, design, sample size, type of cultural interventions, results, and recommendations. This extraction table helped in providing data, exploring similarities and differences, comparing and highlighting results, and synthesizing the related information to find the common themes among these articles. Four common themes that emerged from these articles are information and understanding, cultural norms, cultural interventions, and personal motivation. The four themes that emerged through this process will be presented in the results section.

Results

The 17 retrieved studies were primary studies that included three approaches: qualitative, quantitative, and mixed methods. These studies were conducted in different countries: Australia (n = 1), China (n = 2), Guatemala (n = 1), The Netherlands (n = 2), Qatar (n = 1), United Kingdom (n = 1), and United States (n = 9). These studies used different types of designs. There were three qualitative studies including phenomenological, case study, and grounded theory approaches. Brunk et al. (2017) used the phenomenological approach to evaluate the viability of a patient-centred educational intervention for T2DM self-management for Hispanic people. Dragomanovich and Shubrook (2021) used the case study approach to focus on health disparities that occur among people who live with diabetes. Kohinor et al. (2011) used the grounded theory approach to discover the sociocultural aspects affecting the dietary behaviours of Hindustani

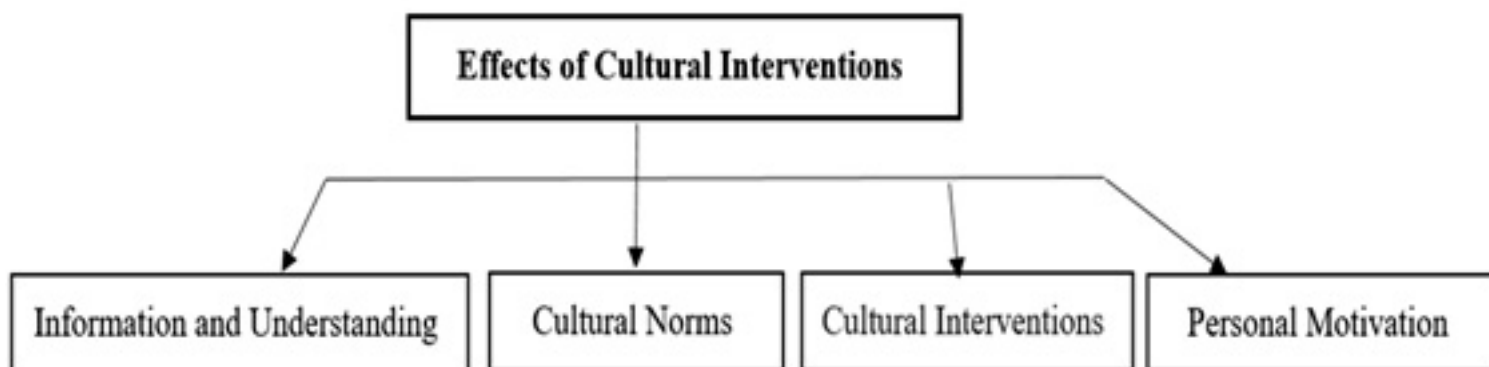
and African Surinamese immigrants with T2DM living in the Netherlands.

There were seven quantitative studies, including three randomized controlled trials, two quasi-experimental studies, one cohort study, and one descriptive study. These studies assessed the efficacy of culturally specific diabetic management programs. Four of these studies assessed the effectiveness of culturally specific diabetic educational programs on knowledge, attitude, and practice methods among people who live with diabetes (Choi & Rush, 2012; Mohamed et al., 2013; Ockene et al., 2012; Yin et al., 2018). The other three quantitative studies found improvement in glycemic control levels among people who live with diabetes by using a culturally specific diabetic educational program (Brown et al., 2021; Flores-Luevano et al., 2020; Le et al., 2013).

There were seven mixed methods studies. Flood et al. (2017) assessed a home-based diabetes self-management intervention program in rural Guatemala. Goff et al. (2021) assessed the suitability of healthy eating and an active lifestyle program for T2DM self-management education and support for Black-British adults. Ho et al. (2021) defined the development and feasibility of integrative nutritional counselling for Chinese Americans with T2DM. Seear et al. (2019) evaluated a locally adapted community-led diabetes prevention program with local young Aboriginal facilitators. Valen et al. (2012) provided a culturally related diabetes education program to Hispanic people. Weber et al. (2020) assessed the possibility of a cultural diabetes prevention program in the southern USA. Nicolaou et al. (2014) defined the development of a lifestyle intervention program that aimed to prevent diabetes in Surinamese adults living in the Netherlands.

Several types of cultural intervention programs were identified in the 17 articles included in this review. These programs impact people who live with diabetes, their families, health care providers, and entire organizations. The impacts of these programs were classified into four themes: (a) information and understanding (b) cultural norms (c) cultural interventions, and (d) personal motivation (see Figure 2).

Figure 2: Identified themes



Information and Understanding

Compliance with the management of diabetes is better in patients with correct knowledge about diabetes. Participants in studies included in this review demonstrated improvements in knowledge-related diabetes and selected self-care activities during interventions (Flood et al., 2017; Flores-Luevano et al., 2020; Goff et al., 2021; Mohamed et al., 2013). Valen et al. (2012) delivered 28 hours of education focused on basic diabetes awareness and self-management strategies to participants in their study. These researchers found that this education improved their participants' diabetes awareness. Brunk et al. (2017) provided a diabetes-related educational program for a T2DM Hispanic population about dietary choices, self-glucose monitoring, and physical activity. These researchers found that their participants became satisfied with and interested in making lifestyle changes related to their cultural norms. Seear et al. (2019) assessed an 8-week cultural intervention program focusing on the causes and consequences of diabetes, practical activities, and stress management. Participants in this study reported that they increased their knowledge which led to changes in behaviours including shopping choices, eating more vegetables and low-fat foods, drinking more water, and avoiding soft drinks.

The main elements of a program may deliver important information in a way participants understand and may ensure programs are culturally appropriate and enjoyable. Brown et al. (2021) used a culturally appropriate diabetic education program to improve glycemic control in lower socioeconomic level Hispanic and Latino people who live with diabetes. These researchers found that empowerment and knowledge scores enhanced from baseline, which suggests that participants were involved in the content. Dragomanovich and Shubrook (2021) helped people who live with diabetes to register for a diabetic education session with a Spanish-speaking diabetes educator to improve diabetes treatment through cultural competency. These researchers found that this program allowed people who live with diabetes to continue eating a culturally important diet while still doing healthy modifications to reach the glycemic control level. Ho et al. (2021) showed the development and feasibility of an integrative nutritional counselling program based on the nutritional curriculum for Chinese Americans living with diabetes using the Chinese language, different colours of vegetable pictures, and Chinese food. These researchers found that their participants were satisfied with gaining new information that improved their dietary health habits and decreased their weight.

Cultural Norms

This review identified several cultural norms that were seen as barriers to success in diabetic maintenance (Choi & Rush, 2012; Flood et al., 2017; Kohinor et al., 2011; Nicolaou et al., 2014; Weber et al., 2020). These cultural norms had a major role in influencing how people who live with diabetes managed their diabetes. Cultural norms which were seen as barriers were considered the

biggest challenge for people when managing diabetes. Some of these barriers relate to gender roles (Weber et al., 2020), hospitality and identity (Kohinor et al., 2011), diet management (Choi & Rush, 2012; Flood et al., 2017; Nicolaou et al., 2014; Weber et al., 2020), beliefs about behaviours (Kohinor et al., 2011), and physical activity (Nicolaou et al., 2014). Weber et al. (2020) found that culturally prescribed gender roles impact the lifestyle behaviours of people who live with diabetes. As a result, they prioritize their family's life requirements rather than their health. Men in Weber et al.'s study worked on the land, saved money for the family, and left little time to exercise. Women in their study took care of their families and made their traditional food with little consideration for managing their diabetes. Kohinor et al. (2011) found hospitality and identity were important cultural norms that presented as barriers to following dietary guidelines in different societies. These researchers found that Surinamese people provided high-fat foods to their guests because these foods were considered as being an important component that added a specific flavour to Surinamese dishes. Surinamese people found it hard to change this behaviour because it was closely linked to their feelings of and identity in being Surinamese.

Some people who live with diabetes cannot manage their dietary requirements because of their cultural dietary preferences. Nicolaou et al. (2014) mentioned that using different ingredients, such as brown rice, or using different ways of providing food were noticed as negatively affecting the flavour of food. Weber et al. (2020) found that women were unable to use less oil in food preparation, mainly on social occasions, and efforts to lower fat or sodium were often met with resistance. Choi and Rush (2012) and Flood et al. (2017) found that Korean immigrants and largely rural and Maya indigenous populations often had fewer chances offered to people who live with diabetes to gain the required abilities and information to effectively self-manage diabetes. Kohinor et al. (2011) found that their participants expressed a behavioural belief that Surinamese people used bitter herbal therapies as treatment for diabetes. Participants in Nicolaou et al.'s (2014) study reported that physical activity is not encouraged within their communities. They explained that physical activity was culturally acceptable for men, while women were culturally not involved in activities outside the home. Spending time to exercise was considered by these participants as interfering with other, more important social responsibilities.

Cultural Interventions

This literature review showed that the use of culturally specific education and activities must be included for the success of DMPs. Culturally specific DMPs in this review used different facilitators which included using a native language (Ockene et al., 2012; Valen et al., 2012), providing dietary health education (Brunk et al., 2017; Choi & Rush 2012; Ho et al., 2021), family engagement (Dragomanovich & Shubrook, 2021; Nicolaou et al., 2014), group discussions (Brown et al., 2021; Choi &

and Rush's (2012) study found that food can be modified to a lower glycemic diet. Brunk et al. (2017) found that several strategies were presented to their participants to use fiber, fats, vinegar, and cinnamon in traditional Mexican food. Choi and Rush (2012) found other cultural interventions included diet management for traditional Korean food, counting the number of calories and carbohydrates, and gaining information on familiar food by nutrition label reading and carbohydrate counts. Choi and Rush's program provided advice for the adjustment of traditional food, demonstrated healthy food choices, and provided cooking instructions.

Family engagement plays an important role in culturally specific DMPs and activities to promote diabetes health conditions. Dragomanovich and Shubrook (2021) and Nicolaou et al. (2014) found that dieticians provided a family meeting at the participants' homes to encourage the families to support the individual participants in reaching dietary goals. These participants were provided group cooking classes to increase their self-efficacy and to learn skills for modifying traditional dishes to follow dietary advice. Brown et al. (2021) and Choi and Rush (2012) found that participants were encouraged to participate in group practical activities and engage in discussions that promoted a better understanding of diabetes, complications, risks, and treatment. Participants in Seear et al.'s (2019) study reported that they gained new information regarding exercise, outside cooking, and stress management. Stress management included 30 minutes focused on physical activity and practical skills for healthy eating. Goff et al. (2021) found that culturally sensitive self-management education and support programs provided physical activity classes. These classes had instructors who provided exercises in five sessions, including resistance band training, circuit training, and cardiorespiratory exercises, such as Zumba, dance aerobics, and walking groups.

Personal Motivation

Many studies reported the importance of personal motivation for the participants in educational programs (Brown et al., 2021; Brunk et al., 2017; Dragomanovich & Shubrook, 2021; Ho et al., 2021; Kohinor et al., 2011; Mohamed et al., 2013; Nicolaou et al., 2014; Seear et al., 2019; Valen et al., 2012; Weber et al., 2020; Yin et al., 2018). Brunk et al. (2017) found that new awareness by the participants regarding blood glucose levels and variations in blood glucose was effective in motivating their behavioural changes during their cultural self-management educational course. Ho et al. (2021) found that integrative nutritional counselling programs provided a feeling of respect for the traditional culture. Kohinor et al. (2011) mentioned that culturally sensitive diabetes education should address cultural values that motivate dietary change to be effective. Yin et al. (2018) found that health care screenings motivated their participants to change their lifestyles, resulting in an improvement in the outcome measures. Seear et al.'s (2019) participants reported increased healthy

lifestyle changes after attending a community-led diabetes prevention program. Weber et al. (2020) found that lifestyle interventions can be an effective tool to motivate the South Asian population to change their diet and physical activity behaviours. Brown et al. (2021) found that participants were motivated by a certificate of achievement at the end of a cultural diabetes education program to maintain their follow-up appointments and to evaluate their understanding of the program contents.

Healthcare providers need to conduct cultural intervention programs during diabetic health education to motivate people who take these programs. Dragomanovich and Shubrook (2021) and Valen et al. (2012) found that primary health care providers who used health beliefs during diabetes education classes provided a strong connection for the participants that motivated them to apply the program information to treatment decisions. Mohamed et al. (2013) mentioned that health educators counseled their participants in a culturally sensitive, structured education program about coping strategies, which offered the participants the motivation to control their diseases. Brown et al. (2021) found that their culturally tailored diabetes education program motivated Hispanic and Latino patients living with diabetes in group education about diet and lifestyle changes. These participants were motivated to explain their disease self-management and common barriers to treatment plans. Weber et al. (2020) and Nicolaou et al. (2014) found that family engagement in culturally tailored diabetes prevention programs can be a motivator for other family members to exercise and follow a healthy diet plan.

Discussion

The purpose of this review was to find an approach to a culturally specific DMP that can be adopted and utilized in Qatar. Several components of culturally specific DMPs in PHCC facilities can fill the present gap among people who live with diabetes. According to this literature review, four important components should be involved in the culturally specific DMP in Qatar: information and understanding, cultural norms, cultural interventions, and personal motivation.

Information and Understanding

Information and understanding were found in this review to be two of the most important components of culturally specific DMPs. It was found that participants in these programs need information and understanding about diabetes management because they are essential in the self-management of blood glucose levels. This finding is consistent with the findings of Pamungkas et al. (2020) who noted that information and understanding of diabetes management are linked with a better possibility of diabetes self-management practice and blood glucose monitoring. It was also found in this review that involving people who live with diabetes in the cultural diabetic educational program content is considered

Cultural Norms

Cultural norms have been considered an important component of culturally specific diabetic management programs. Some cultural norms were noted in this review to present barriers to behavioural change and hinder the successful implementation of culturally specific DMPs. These barriers were hospitality and identity as well as gender roles. Hospitality was considered a challenge because high-calorie food with fat is expected to be a part of the identity of some people who live with diabetes. This is similar to the findings of Smith-Miller et al.'s (2017) study. Participants in their study reported that they faced pressure from family members and friends to eat or drink food with high calories during family and social events to maintain their identity. In addition, it was found in this literature review that traditional gender roles affected people who live with diabetes, especially after becoming parents. Mailey et al. (2014) also found that people who live with diabetes focused on their family needs and responsibilities more than their health needs when they had children. Many people connect to their culture through the food they eat. The cultural importance of food is passed from one generation to the next generation, connecting people to their families. Changing the way a person eats can be a challenge at first, especially if the person is diagnosed with diabetes.

Cultural Interventions

Culturally specific DMPs were found in this review to be an important component in increasing the success level of the DMPs. The most important cultural interventions include using the native language of the person living with diabetes and providing family support for changing lifestyle and physical activity. It was found in this review that native language can be used in cultural diabetic educational programs to explain the program content. This finding is consistent with the findings of Balagopal et al. (2012) who found their participants preferred educational material in the Gujarati language to explain the advantages of dietary food because it increased their level of discussion and communication. In addition, it was found in this review that family support is another important facilitator because it can help people who live with diabetes to change their lifestyles. Similarly, Shepherd-Banigan et al. (2014) found that positive lifestyle changes occurred in people who live with diabetes when family support levels increased. It was also found in this review that health care providers can teach the family as a group to improve the health behaviours of people who live with diabetes by increasing family-based physical activity and social support. This finding is supported by Wheeler et al. (2012) who found that Hispanic people increased their amount of self-reported exercise after receiving support from their families.

Personal Motivation

Personal motivation was found in this review to be needed while implementing culturally specific DMPs. This review highlighted different factors that motivate people who live with diabetes to avoid diabetic complications. It was found that increasing awareness about glucose levels and differences in blood test readings can motivate people who live with diabetes to change their dietary behaviours. This finding is consistent with the finding of Gopalan et al. (2015) who noted that their participants' awareness of pre-diabetes motivated them to change their dietary behaviours. It was also noted in this literature review that a feeling of respect for culture in nutritional counselling programs is considered important because it can motivate diabetic patients to continue lifestyle changes. Similarly, Ndjaboue et al. (2020) found that feeling one's culture was respected is an important motivator because it increases communication and understanding. In addition, family engagement was found in this review to motivate people who live with diabetes to control their diabetes and improve their health conditions. Rotberg et al. (2016) also found that patients who attended diabetic health educational meetings with their families were motivated to be engaged in social support, improve their quality of life, and increase diabetes control levels during follow-up diabetic clinic appointments. People who live with diabetes can be motivated in different ways by support from their families and friends, such as exercising with them, helping them to make healthy food choices, and encouraging them to take their medication and check their blood sugar regularly. This motivation was key in being able to communicate, share goals, and understand what it means to live with diabetes.

Conclusion

Culturally specific DMPs have an important effect on diabetes care. This literature review aimed to assess the effectiveness of culturally specific DMPs employed in other countries within primary health care settings to determine an approach that can be used in Qatar. The most important components of culturally specific DMPs for people who live with diabetes are information and understanding, cultural norms, cultural interventions, and personal motivation. These components help to increase the amount of information provided to people who live with diabetes and their understanding of diabetes; clarify the cultural norms that affect them; provide cultural interventions to facilitate solving these barriers; and motivate these people to keep changing their lifestyles. Qatar is a country that has culturally diverse populations, thus tailoring diabetic management programs to the individual's culture is crucial. For DMPs to be successful, the PHCC needs to consider the significance of culturally specific DMPs in supporting people who live with diabetes.

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Appendix A
Mixed Methods Appraisal Tool (MMAT), version 2018

Category of study designs	Methodological quality criteria	Responses		
		Yes	No	Can't tell
Screening questions (for all types)	S1. Are there clear research questions?			
	S2. Do the collected data allow to address the research questions? <i>Further appraisal may not be feasible or appropriate when the answer is 'No' or 'Can't tell' to one or both screening questions.</i>			
1. Qualitative	1.1. Is the qualitative approach appropriate to answer the research question?			
	1.2. Are the qualitative data collection methods adequate to address the research question?			
	1.3. Are the findings adequately derived from the data?			
	1.4. Is the interpretation of results sufficiently substantiated by data?			
	1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?			
2. Quantitative randomized controlled trials	2.1. Is randomization appropriately performed?			
	2.2. Are the groups comparable at baseline?			
	2.3. Are there complete outcome data?			
	2.4. Are outcome assessors blinded to the intervention provided?			
	2.5. Did the participants adhere to the assigned intervention?			
3. Quantitative non-randomized	3.1. Are the participants representative of the target population?			
	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?			
	3.3. Are there complete outcome data?			
	3.4. Are the confounders accounted for in the design and analysis?			
	3.5. During the study period, is the intervention administered (or exposure occurred) as intended?			
4. Quantitative descriptive	4.1. Is the sampling strategy relevant to address the research question?			
	4.2. Is the sample representative of the target population?			
	4.3. Are the measurements appropriate?			
	4.4. Is the risk of nonresponse bias low?			
	4.5. Is the statistical analysis appropriate to answer the research question?			
5. Mixed methods	5.1. Is there an adequate rationale for using a mixed methods design to address the research question?			
	5.2. Are the different components of the study effectively integrated to answer the research question?			
	5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted?			
	5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?			
	5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?			

Note. From "Mixed Methods Appraisal Tool (MMAT) Version 2018: User Guide," by Q. N. Hong, P. Pluye, P. S. Fábregues, G. Bartlett, F. Boardman, M. Cargo, P. Dagenais, M. P. Gagnon, F. Griffiths, B. Nicolau, A. O'cathain, M.C. Rousseau, & I. Vedel, 2018. (https://mixedmethodsappraisaltoolpublic.pbworks.com/attachment/127916259/MMAT_2018_criteria-manual_2018-08-01_ENG.pdf)

Appendix B

Data Extraction Matrix for Articles

Author, Date, Title & Country	Design, Sample & Data Collection	Purpose	Cultural Interventions	Outcomes	Recommendations
<p>Author & Date: Brown et al. (2021)</p> <p>Title: A culturally tailored diabetes education program in an underserved community clinic</p> <p>Country: USA</p>	<p>Design: A quantitative non-randomized study, quasi-experimental design was used to compare pre/post data of a single group of participants.</p> <p>Sample: $N = 16$</p>	<p>To improve glycemic control in lower socioeconomic status Hispanic & Latino patients diagnosed with DM in a medically underserved community clinic using a culturally tailored DM education program.</p>	<p>Diabetes Empowerment Education Program (DEEP) was selected as the intervention for this project.</p>	<p>-Reduction in A1C levels</p> <p>-Increased diabetes knowledge</p> <p>-Improvement in diabetes Empowerment</p> <p>-Reduction in weight</p>	<p>The patient centered principles of culturally competent care should guide both practitioners in caring for Hispanic patients with T2DM and those involved in program planning regarding diabetes in the Hispanic community.</p>
<p>Author & Date: Brunk et al. (2017)</p> <p>Title: A culturally appropriate self-management program for Hispanic adults with type 2 diabetes and low health literacy skills.</p> <p>Country: USA</p>	<p>Design: A descriptive qualitative study design and phenomenological analysis used.</p> <p>Sample: $N = 9$ from rural community health care centers</p> <p>Data collection through focus group</p>	<p>To assess the feasibility of adapting a patient-centered educational intervention for T2DM self-management for a Hispanic population with low health literacy skills.</p>	<p>An educational program that instructed on low glycemic food choices, meaningful glucose self-monitoring, and physical activity to decrease blood glucose spikes.</p>	<p>Data supported the feasibility of adapting an established health-enhancing approach for promoting self-management of T2DM to a low health literacy Spanish-speaking population.</p>	<p>This report includes a recommendation that professional schools incorporate health literacy in the curricula to ensure that future practitioners can engage in effective information exchange with patients, their</p>

<p>sessions</p> <p>Participants' feedback was recorded during four weekly, 2 hour evening focus group sessions.</p>	<p>family members, and other health care professionals.</p>
<p>Author & Date: Choi and Rush (2012)</p> <p>Title: Effect of a short-duration, culturally tailored, community-based diabetes self-management intervention for Korean immigrants</p> <p>Country: USA</p>	<p>To assess the effectiveness, feasibility, and acceptability of a short-duration, culturally tailored, community-based diabetes self-management program for Korean immigrants with T2DM delivered at a non-clinic-affiliated community center.</p>
<p>Design: A quantitative descriptive study</p> <p>Sample: <i>N</i> = 53</p>	<p>Short-duration, culturally tailored, community-based diabetes self-management program</p>
<p>Author & Date: Dragomanovich and Shubrook (2021)</p> <p>Title: Improving cultural humility and competency in diabetes care for primary care providers</p> <p>Country: USA</p>	<p>Individualized treatment plan, helping the patient of this study to enroll in a diabetes education class with a Spanish-speaking diabetes educator.</p>
<p>Design: Qualitative design/ case study</p> <p>Sample: <i>N</i> = 1</p> <p>Data collection through face to face interview</p>	<p>-The community-based, culturally tailored education was effective.</p> <p>-Improved physiological outcomes and self-care behaviors.</p>
<p>Health care providers should face the challenges by keep training and confronting the uncomfortable reality of health disparities in the US.</p>	<p>Future studies with a larger sample size are needed to further examine changes in diabetes management behaviors across the intervention</p>

cultural competency and humility.

Author & Date: Flood et al. (2017) Title: A home-based type 2 diabetes self-management intervention in rural Guatemala Country: Guatemala	Design: Mixed methods: A prospective study of a diabetes self-management education intervention using a quasi-experimental, single-group pretest-posttest design. Sample: $N = 90$ Descriptive statistics used to summarize data on participants' visits and demographic characteristics.	To evaluate a home-based diabetes self-management intervention in rural Guatemala.	This program consisted of 6 home visits (May 2014–July 2016) conducted by a diabetes educator using a curriculum culturally and linguistically tailored program to rural Mayan populations	-Participants' glycemic control and systolic level improved (but not diastolic) blood pressure at 12 months. -Improved significantly during the intervention.	This study pored to the need for diabetes self-management education research in resource-limited settings globally.
Author & Date: Flores-Luevano et al. (2020) Title: Impact of a culturally tailored diabetes education and empowerment program in a Mexican American population along the US/Mexico border: A pragmatic study Country: USA	Design: A quantitative study, Quasi-experimental design. Non-randomized Sample: $N = 209$ Data collection through group discussion sessions Descriptive analysis was used	To deliver a diabetes education program under real world conditions and evaluate its effect on diabetes-related clinical, self-management and psychosocial outcomes among Mexican Americans residing along the	A bilingual culturally tailored diabetes education program incorporating hands-on participatory techniques was delivered in 4 - 8 weekly group sessions. Clinical, self-	Improvements in clinical (glycaemia, cholesterol), self-management (glucose self-monitoring, exercise and diet), knowledge and psychosocial outcomes.	This article did have recommendatic

US/Mexico border.	management and psychosocial outcomes were evaluated pre-intervention with surveys and medical record review.			
Author & Date: Goff et al. (2021)	Title: Healthy eating and active lifestyles for diabetes (HEAL-D), a culturally tailored self-management education and support program for type 2 diabetes in black-British adults: a randomized controlled feasibility trial.	Design: mixed-methods randomized controlled trial in black-British adults with T2DM. Sample: N = 102 T2DM patients	To evaluate acceptability, fidelity and trial feasibility of the healthy eating and active lifestyles for diabetes ('HEAL-D') culturally tailored T2DM self-management education and support program.	Healthy eating and active lifestyles for diabetes The intervention is highly acceptable for both patients and healthcare providers. A future trial should assess clinical and cost-effectiveness of healthy eating and active lifestyles for diabetes.
Author & Date: Ho et al. (2021)	Title: Integrative nutritional counseling combining Chinese medicine and biomedicine for Chinese Americans with type 2	Design: mixed methods Sample: N = 15 Data collection through semi structured interview Descriptive analysis was used	To describe the development and feasibility of integrative nutritional counseling (INC), a Chinese medicine	Integrative nutritional counseling program -Improved attitudes and dietary habits aligning directly with INC, -Improvement in biomedical valued measure so for Future research should examine INC with a larger population and explore optimal delivery of INC

diabetes: A mixed-methods feasibility study
Country: USA

(biomedicine-based nutrition curriculum for Chinese Americans with T2DM.

T2DM, such as weight loss, and CM-valued measures of digestion
 -Elimination and hot/cold feeling.
 Satisfaction with INC was high.

Author & Date: Kohinor et al. (2011)
Title: Considerations affecting dietary behavior of immigrants with type 2 diabetes: a qualitative study among Surinamese in the Netherlands
Country: Netherlands/Holland

To explore the sociocultural factors affecting the dietary behavior of Hindustani and African Surinamese immigrants with T2DM living in the Netherlands.

Culturally sensitive diabetes education program

Highlights how the cultural values and customs influence the way in which immigrants with T2DM perceive and manage their diet.

Culturally appropriate approaches to education show attentive to aspects of culture that inhibit as well as enhance health behavior.

Author & Date: Le et al. (2013)
Title: Characterization of factors affecting attainment of glycemic control in Asian Americans with diabetes in a culturally specific program.
Country: China

To compare glycemic control between Asian American (AA) and white patients (WA) and to characterize the factors associated with AA group reaching or not reaching glycemic target.

Analyzing data in electronic health medical records (EMR)

-Show the effectiveness of a culturally tailored diabetes program for AA group while raising concerns toward a trend of poorer glycemic control in certain AA subgroups.
 -Help as a beginning step in

Future research should study various cultural factors related to diabetes care in high-risk patients.

diabetes: A mixed-methods feasibility study
Country: USA

(biomedicine-based nutrition curriculum for Chinese Americans with T2DM.

T2DM, such as weight loss, and CM-valued measures of digestion
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Highlights how the cultural values and customs influence the way in which immigrants with T2DM perceive and manage their diet.

Culturally appropriate approaches to education should be attentive to aspects of culture that may inhibit as well as enhance healthy behavior.

Author & Date: Le et al. (2013)
Title: Characterization of factors affecting attainment of glycemic control in Asian Americans with diabetes in a culturally specific program.
Country: China

Design: Quantitative – cohort study
Sample: $N = 327$
Data collection: through using retrospective study
Analyzing data on electronic.

-Show the effectiveness of a culturally tailored diabetes program for AA group while raising concerns toward a trend of poorer glycemic control in certain AA subgroups.
-Help as a beginning step in

Future research should study the various cultural factors related to diabetes care in high-risk patient

exploring the various factors that may contribute to the lack of success in reaching glyceemic goal.

Author & Date: Mohamed et al. (2013)					The significant improvement in biomedical and psychosocial parameters provide a great opportunity for the study to be replicated in the Arabian countries.
Title: Culturally sensitive patient-centered educational program for self-management of type 2 diabetes: A randomized controlled trial	Design: Quantitative-Randomized controlled trial Sample: N = 430 T2DM Arab countries patients Data collection through questionnaire, and focus groups/3 to 4 hours per session. 10 to 20 patients per session	To assess the effectiveness of a culturally sensitive, structure education program (CSSEP) on biomedical, knowledge, attitude and practice measures among Arabs with T2DM	The intervention was based on theory of empowerment, health belief models and was culturally sensitive in relation to language (Arabic), food habits and health beliefs. 4 sessions discussed diabetes pathophysiology and complications, healthy lifestyle, exercise benefits and goal setting, and enhancing attitude and practice using counselling techniques.	Primary outcomes: -reduction in HbA1C, lipid profile, albumin/creatinine ratio, BMI and blood pressure. Secondary outcomes Improvement in diabetes knowledge, attitude and practice.	
Country: Qatar					

<p>Author & Date: Nicolaou et al. (2014)</p> <p>Title: Development of a diabetes prevention program for Surinamese South Asians in the Netherlands</p> <p>Country: Netherlands/Holland</p>	<p>Design: pilot study</p> <p>Sample: $N = 35$</p> <p>Data collection through focus group discussions and in-depth interviews</p>	<p>To describe the development of the lifestyle intervention used in DH! AAN, a program that aimed to prevent diabetes in Surinamese adults of South Asian (SA) origin living in the Netherlands.</p>	<p>The intervention was based on personal lifestyle counseling with use of motivational interviewing in line with a successful diabetes prevention intervention that targeted the general ethnic Dutch population.</p>	<p>Provided valuable information about the place of food in the culture and the general values regarding physical activities that are relevant for the individual.</p>	<p>Motivation intervention should ensure that cultural components are employed according to the needs of each participant.</p>
<p>Author & Date: Ockene et al. (2012)</p> <p>Title: Outcomes of a Latino community-based intervention for the prevention of diabetes: the Lawrence Latino diabetes prevention project</p> <p>Country: USA</p>	<p>Design: Quantitative randomized controlled trial study</p> <p>Sample: $N = 312$</p> <p>Data collection through focus group session</p>	<p>To test the effectiveness of a community-based, literacy sensitive, and culturally tailored lifestyle intervention on weight loss and diabetes risk reduction among low-income, Spanish-speaking Latinos at increased diabetes risk.</p>	<p>Cultural tailoring included dietary advice based on Latino foods, including the customization of Latino recipes; targeting cultural beliefs and attitudes toward diabetes prevention and delivery of the intervention in Spanish by</p>	<p>Developed an inexpensive, culturally sensitive diabetes prevention program that resulted in weight loss, improved HbA1c, and improved insulin resistance in a high-risk Latino population.</p>	<p>It will be important to explore possible genetic underpinnings for such population sensitivity</p>

bicultural and bilingual.

<p>Author & Date: Seear et al. (2019)</p> <p>Title: Piloting a culturally appropriate, localized diabetes prevention program for young aboriginal people in a remote town</p> <p>Country: Australia</p>	<p>Design: mixed methods study</p> <p>Sample: $N = 10$</p> <p>Data collection: through semi-structure interviews</p>	<p>In this study, a locally adapted community-led diabetes prevention program with local young Aboriginal facilitators was created and trialed through the Derby Aboriginal Health Service (DAHS). The aim of this study was to report the process of piloting this program and its acceptability and feasibility.</p> <p>To deliver a culturally relevant diabetes education program to a Hispanic population at a migrant clinic</p>	<p>8-weeks program highlighted causes and consequences of diabetes, incorporated physical activity and healthy eating topics with a focus on practical activities, and included stress management to support healthy lifestyles.</p> <p>This educational program consisted of six, two-hour sessions delivered entirely in Spanish by Hispanic CHWs.</p>	<p>-Gained important new knowledge.</p> <p>-Made changes in behaviors including shopping choices, portioning and soft drink consumption.</p> <p>consequences of diabetes, incorporated physical activity and healthy eating topics with a focus on practical activities, and included stress management to support healthy lifestyles.</p> <p>-Improvement in community health workers diabetes-related knowledge.</p>	<p>Delivering this program multiple times annually is several years is required to build further community support, normal participation, overcome shame embarrassment.</p> <p>Future program should focus on community health workers outreach including improving confidence, leadership skills and satisfaction in addition to diabetes related knowledge</p>
<p>Author & Date: Valen et al. (2012)</p> <p>Title: An innovative approach to diabetes education for a Hispanic population utilizing community health workers</p> <p>Country: USA</p>	<p>Design: Mixed methods Quantitative descriptive/ survey based on data analyze them. Pretest and posttest.</p> <p>Descriptive analysis statistics used.</p> <p>Data collection: through 2 questionnaires and</p>	<p>To deliver a culturally relevant diabetes education program to a Hispanic population at a migrant clinic</p>	<p>This educational program consisted of six, two-hour sessions delivered entirely in Spanish by Hispanic CHWs.</p>	<p>-Improvement in community health workers diabetes-related knowledge.</p>	<p>Future program should focus on community health workers outreach including improving confidence, leadership skills and satisfaction in addition to diabetes related knowledge</p>

contained three open-ended questions regarding diabetes management strategies learned and 17 Likert scale items

Author & Date: Weber et al. (2020)
Title: Tailoring lifestyle programs for diabetes prevention for US South Asians
Country: USA

Design: mixed methods (pilot, pre-post study to test the feasibility and impact of delivering the culturally tailored program.
Sample: $N = 109$
Data collection through Focus group discussions
Descriptive analysis used

To develop and test the feasibility of a culturally tailored diabetes prevention program (DPP) for US South, a large population with high diabetes risk.

South Asian Health and Prevention Education (SHAPE) program included: (1) focus group discussions with South Asian adults to understand views of lifestyle behaviors and diabetes prevention; (2) modification of the US DPP for South Asians and (3) a pilot, pre-post study to test the feasibility and impact of

-Provide important information on the barriers faced by US South Asians in participating in 'standard' lifestyle change programs.
 -Show positive impact of a culturally tailored program for diabetes prevention in South Asian population.

Future work should focus on testing SHAPE intervention in a larger trial, collecting more formalized feedback on program acceptability and considering additional intervention models in a family-based program, for instance, to address the high risk of diabetes in this community.

delivering the culturally tailored program.

Author & Date: Yin et al. (2018)	Design: Quantitative-randomized controlled trials Sample: $N = 75$	To test the feasibility and effectiveness of an evidence-based diabetes prevention program in Yuci, Shanxi Province, China from 2012 to 2014.	Diabetes prevention program (DPP)	Prevent diabetes in at-risk women in community health centers in China is feasible and acceptable.	Future implementation studies are needed to test PATH effectiveness in a large RCT with refinement of the intervention based on feedback from this study.
Title: Cultural adaptation of an evidence-based lifestyle intervention for diabetes prevention in Chinese women at risk for diabetes: results of a randomized trial					
Country: China					

INNOVATION AND RESTRUCTURING OF LAB AND CLINICAL SIMULATION IN UNDERGRADUATE NURSING PROGRAMS AS A RESPONSE TO THE COVID-19 PANDEMIC: PROTOCOL FOR AN INTEGRATIVE REVIEW

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Abstract

The COVID-19 pandemic brought the world to a standstill, forcing businesses to close or adjust operations to online platforms. Nursing Educational Institutions (NEIs) were similarly affected by the implementation of public health measures to reduce the transmission of COVID-19, leading to abrupt lockdowns and campus closures, reduced or no face-to-face time in labs, and a sudden loss of clinical placement sites for students. To combat this problem, NEIs had to adjust their conventional practices and find alternative, novel approaches to fulfill the required hands-on lab teaching and clinical practice hours for their students. Many NEIs turned to simulation to close this gap for nursing students. Therefore, this integrative review seeks to explore what innovative simulation strategies were used during the pandemic era and the lessons that can be learned from these innovations.

Key Terms: COVID-19, simulation, innovative strategies, undergraduate nursing

Introduction

Nursing requires not only the acquisition of knowledge but also the capacity to apply the knowledge into practice. Skills such as conducting a thorough health assessment, inserting a urinary catheter, or making critical clinical decisions cannot be taught using didactic teaching methods. Simulation is a widely used pedagogical approach to allow students to engage in an immersive environment that mimics real clinical situations (Aebersold, 2018; Foronda et al., 2013; Kim et al., 2015; Lee & Peacock, 2020). One of the key advantages of using simulation in nursing education is to allow students to practice their skills in a low-risk environment.

The term fidelity in simulation refers to the realism of the simulation scenario (Karlsaune et al., 2023). The realism of the scenario can range from high fidelity to low fidelity. High-fidelity simulation involves the use of manikins that are technologically equipped to mimic human physiology or the use of human actors who can be trained in advance to play certain roles (Nehring & Lashley, 2011). Medium fidelity refers to the use of task trainers or equipment that is not as technologically advanced (Lapkin & Levett-Jones, 2011). Low fidelity simulation can be done with the use of teaching strategies such as role-playing and/or discussing case studies (Karlsaune et al., 2023).

Simulation-based education (SBE) has exploded in recent years to accommodate issues with clinical placement areas, and other factors that inhibit nursing students from practicing to full capacity. The Nursing and Midwifery Council (NMC) in the UK recently released an announcement that they are giving nurse educators flexibility in utilizing simulation to deliver up to 600 hours out of the 2300 practice hours (Nursing and Midwifery Council, 2023). This is double what the hours were prior to the announcement. Announcements like this show how simulation is taking the place of clinical practice hours and the need for Nursing Educational Institutions (NEI) to accommodate simulation in their curricula.

The COVID-19 pandemic was declared on 11 March 2020 by the World Health Organization (WHO, 2023). During the pandemic, public health measures led to reduced or lack of face-to-face time in labs. The other issue was a lack of clinical placement areas for students to complete clinical practice hours. To combat this problem, NEIs had to look at innovative solutions to fulfill lab teaching and clinical practice hours. One of the directions from nursing governing bodies was to increase simulation hours to ensure nursing students were able to successfully attain the learning objectives of the lab and clinical practice courses.

COVID-19 forced NEIs to pivot to strategic measures to complete the required lab and clinical hours. Therefore, this integrative review will seek to explore what innovative simulation strategies were used during the pandemic era and what we can learn from these innovations. The reason for choosing the topic is to explore what novel approaches emerged during this time to replace actual hands-on clinical and lab practice. The expectation of this integrative review is to provide direction for future research to demonstrate what novel approaches were delivered by nurse educators as they endeavour to meet practicum and lab expectations set forth by academic institutions.

Methods

An integrative review is being used to explore the topic in question. An integrative review is suitable when you wish to gain a deeper understanding of a phenomenon (Soares, 2014). This integrative review followed the guidelines from Whittmore and Knafl. These guidelines are divided into five sections: 1. the problem; 2. the literature; 3. the data evaluation; 4. the data extraction; and 5. the presentation of the results (Whittemore & Knafl, 2005).

Step 1: Problem Identification

To obtain a clear picture of the topic under study during the review of white and grey literature, the researchers developed some guiding questions.

1. What types of approaches were used to engage students learning to replace a clinical practicum?
2. What novel approach was used to engage students learning in labs?

Step 2: Literature Search

See Tables 1 and 2 below for the following databases that were included in this search and the terms used to guide the search of the literature.

Table 1: List of searched databases

For published articles	For grey literature
<ol style="list-style-type: none"> 1. Pubmed 2. CINAHL (EBSCO) 3. Academic Search Complete (EBSCO) 4. ERIC (EBSCO) 5. Embase (OVID) 6. Scopus 	<ol style="list-style-type: none"> 1. Google 2. Google Scholar 3. openGrey 4. ProQuest Dissertation and Thesis Global

Table 2: Search terms

Concepts	Search keywords
Undergraduate nursing students	baccalaureate*, bachelor*, nurs*, BSN, BN, BScN
Simulation	simulation-based, "Computer Simulation", "Patient Simulation", "High Fidelity Simulation", "Simulation Training", "Virtual Reality" OR simulat*, "Manikins", lab*
COVID-19	2019 novel coronavirus disease, COVID19
Innovation and restructuring	restructur*, innovat*, adapt*, supplemen*, replac*, augment*, modif*, and novel

Inclusion and exclusion of studies

A set of defined inclusion and exclusion criteria was developed by the research team, see Table 3. This review consists of both white and grey literature. Articles will be downloaded onto Rayyan platform and then screened by two of the researchers initially. All duplicates will be removed prior to screening. Screening will be blind, and title and abstract will be reviewed for inclusion in the review. Both reviewers will then meet to come to a congruence of selection, and those articles that meet the inclusion criteria will be screened for full-text review. In the event that there is a discrepancy, a third author will be called upon to resolve the discrepancy and to reach a mutual agreement.

Table 3: Inclusion/exclusion criteria

Inclusion Criteria	<ul style="list-style-type: none"> ● Studies: Original research with innovation or restructuring of simulation interventions during COVID-19 ● Populations: Undergraduate nursing students ● Nursing programs should be a 3- or 4-year undergraduate nursing program leading to an undergraduate degree in Nursing. ● Design: Any types of studies ● Outcomes: Includes but not limited to any innovations or restructuring of simulation to deliver clinical or lab teaching during COVID-19
Exclusion Criteria	<ul style="list-style-type: none"> ● Studies not describing innovation or restructuring of simulation for clinical and/or lab ● If the description of the simulation activity lacked detail such as this was an innovation or restructuring of a simulation ● No original studies, e.g., publications in the form of editorials, reviews, or opinion articles ● Studies not in English ● Undergraduate Nursing programs that are less than 3 or 4 years in length ● Undergraduate nursing programs that do not lead to an undergraduate nursing degree

Step 3: Data Evaluation

Data extraction will be done using a predefined tool which the team has determined. This tool will be piloted by two members of the research team with the use of five of the articles to come to an agreement for what data extraction headings are to be used. Two members of the team will perform data extraction to remove bias and ensure consensus.

Step 4: Data Analysis

To obtain an in-depth description of the data and the topic, we will utilize Ritchie & Spencer's (2002) five step process for coding the data. The steps consist of 1. Familiarizing ourselves with the data, 2. Identifying the framework to elucidate themes and ideas, 3. Indexing the data to apply the framework, 4. Charting the data into a matrix for visualization and 5. Mapping and interpreting the data into major characteristics for display.

Step 5: Presentation

In this step, the extracted data will be both analysed and synthesized to draw conclusions from the data. During this stage, all literature will be appraised using the Mixed Methods Appraisal Tool and the Authority, Accuracy, Coverage, Objectivity, Date, and Significance (AACODS) tool.

Outcomes

The purpose of this comprehensive integrative review is to identify and analyze the different innovative simulation strategies that were used during the COVID-19 pandemic to fulfill the lab and clinical hour requirements of the nursing degree program. With this study, we will be able to analyze these strategies in terms of their effectiveness and how they can be used to supplement or replace traditional lab and clinical practice in the future. Barriers, facilitators, and outcomes of the existing simulation strategies in nursing education will be identified as well. Through this study, we anticipate gaining insight into how nursing educators adapted to the limitations due to the pandemic and the benefits of doing so. This study will determine what types of simulation strategies may work for undergraduate nursing students.

Potential Impact

The findings from this integrative review will help nursing educators and institutions better respond to the changing landscape of the current lab and clinical practice. New simulation techniques could be useful in the training of future nurses. This review has the potential to inform the design and implementation of novel simulation methodologies, which in turn may enhance nursing curricula and produce more competent graduates. Further, our analysis has the potential to aid efforts to enhance nursing programs and ensure that students receive the support they need with regard to meeting the clinical requirements of their program even in the face of

challenging situations. Finally, this review may highlight the need for further research to develop and evaluate innovative simulation strategies in nursing education.

Strengths

Through the assistance of a librarian, this integrative review will employ a systematic and structured approach with specific inclusion and exclusion criteria and encompassing search terms to yield comprehensive results from multiple databases. The search will be inclusive of both original research and grey literature, forming a diverse and solid foundation to gain insight into the innovations in simulation that were used to fill in for lost face-to-face lab time and clinical placements during the COVID-19 pandemic. Valid tools will be used by two reviewers to appraise the literature independently to prevent bias.

Limitations

This integrative review will be limited to articles published only in the English language and to simulations used in undergraduate baccalaureate nursing programs, which may exclude relevant innovations outside of these parameters. Additionally, the wide range of included literature may result in less rigorous findings.

Knowledge Translation

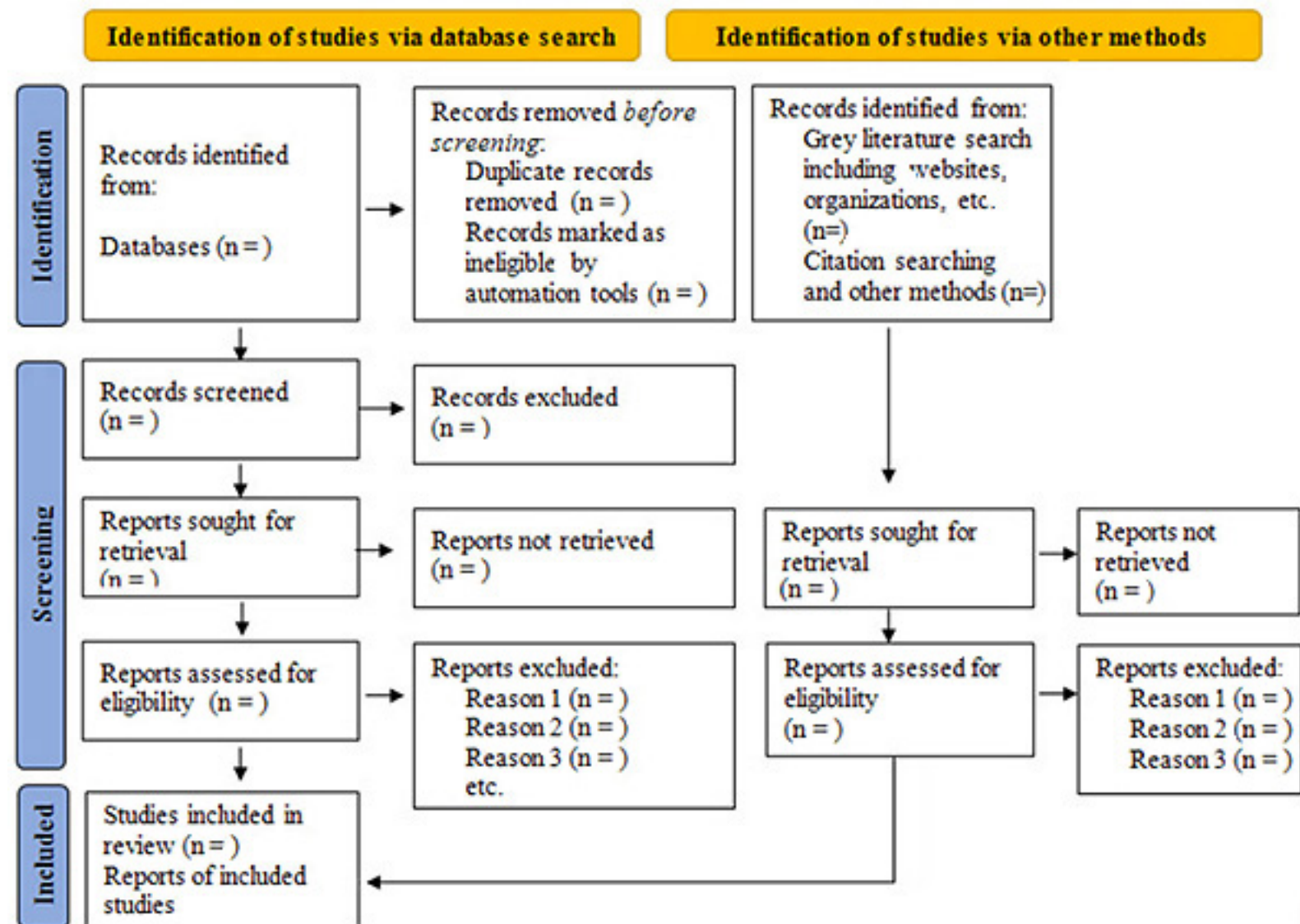
Knowledge translation plans include presenting to academic audiences both locally and globally. The researchers will also endeavour to present at both local and global conferences. The results of this integrative review will be submitted to an open-access journal for wider dissemination.

Declarations

All authors have nothing to declare and have received no financial support for this integrative review.

Appendices

Figure 1: Literature Search Flow Diagram



Note. Flow diagram of search and selection process for the integrative review
 (Adapted from "The PRISMA 2020 statement: An updated guideline for reporting systematic reviews," by Page et al., 2021).

Data Extraction Table

Extraction Table						
Author (year), Title, Country	Study Aim	Study Design	Sample Size & Undergraduate Year	Innovation / Restructuring - Lab or Clinical (Intervention)	Key Findings	Comments

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DEPRESSION CAUSES VARIOUS INFLAMMATORY PROCESSES IN HUMAN BODY

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Abstract

Background: We tried to understand whether or not there are some relationships between irritable bowel syndrome (IBS), chronic gastritis (CG), depression, and various inflammatory processes in the body.

Method: Consecutive patients with IBS and age and sex-matched control cases were included.

Results: The study included 936 patients with IBS (592 females) and 346 control cases. Mean age of the patients was 41.0 years, and 63.2% of them were female. Although gastric sample biopsies were taken just in suspected cases, CG was diagnosed nearly in all of the patients with the IBS (80.4% vs 15.0%, $p < 0.001$). Interestingly, prevalence of antidepressants use was also higher in the IBS cases, significantly (46.4% vs 16.1%, $p < 0.001$). Similarly, smoking (35.2% vs 20.8%, $p < 0.001$), hemorrhoids (37.1% vs 7.2%, $p < 0.001$), and urolithiasis (22.0% vs 9.5%, $p < 0.001$) were all higher in the IBS patients, again. Beside that the mean values of fasting plasma glucose (FPG) (111.9 vs 105.4 mg/dL, $p = 0.002$) and plasma triglycerides (167.0 vs 147.3 mg/dL, $p = 0.013$) were also higher in the IBS patients, significantly.

Conclusion: Because FPG and triglycerides are well-known acute phase reactants in the body, IBS and CG may be some low-grade inflammatory processes initiated with anxiety, depression, infection, inflammation, trauma, and cancer fear-like stresses of the body, and eventually terminate with hemorrhoids and urolithiasis. Due to the highly significant associations between IBS, CG, and depression, IBS and CG may actually be the two sides of the same paper, and just be two examples of depression-induced various inflammatory processes in human body.

Key words: Depression, irritable bowel syndrome, chronic gastritis, irritable gastrointestinal syndrome, smoking, fasting plasma glucose, triglycerides

Introduction

Recurrent upper abdominal discomfort may be the cause of nearly half of the applications to the Internal Medicine Clinics, and irritable bowel syndrome (IBS) and chronic gastritis (CG) may be the most commonly diagnosed disorders in such cases (1). Flatulence, periods of diarrhea and constipation, repeated toilet visits due to urgent evacuation or early filling sensation, excessive straining, feeling of incomplete evacuation, frequency, urgency, reduced feeling of well-being, and eventually disturbed social life are often reported with the IBS. A meaningful dietary role is doubtful, and psychological factors seem to precede onset and exacerbation of gut symptoms. Many potentially psychiatric disorders including anxiety, depression, sleep disorders, cancer fear, or death fear usually coexist with the IBS (2). For example, thresholds for sensations of initial filling, evacuation, urgent evacuation, and utmost tolerance recorded via a rectal balloon decreased by focusing the examiners' attention on gastrointestinal stimuli by reading pictures of gastrointestinal malignancies in the IBS (3). In other words, although IBS is described as a physical disorder according to Rome II guidelines, psychological factors may be crucial for triggering of these physical changes. IBS may have a more complex mechanism by affecting various systems of the body with a low-grade inflammatory process (4). Eventually, IBS may even terminate with CG, urolithiasis, and hemorrhoids (5-7). Similarly, some authors studied the role of inflammation in the IBS by means of colonic biopsies in 77 patients (8). Although 38 patients had normal histology, 31 patients demonstrated microscopic inflammation, and eight patients fulfilled criteria for lymphocytic colitis. However, immunohistology revealed increased intraepithelial lymphocytes as well as increased CD3 and CD25 positive cells in lamina propria of the group with "normal" histology. These features were more evident in the microscopic inflammation group who additionally revealed increased neutrophils, mast cells, and natural killers. All of these immunopathological abnormalities were the most evident in the lymphocytic colitis group who also demonstrated HLA-DR staining in the crypts and increased CD8 positive cells in the lamina propria (8). Some other authors demonstrated not only an increased mast cell degranulation in the colon but also a direct correlation between proximity of mast cells to neuronal elements and severity of IBS (9). In addition to the above findings, there are some evidences for extension of the inflammatory process behind the mucosa. Some authors addressed this issue in ten patients with the severe IBS by examining full-thickness jejunal biopsies, laparoscopically (10). They detected a low-grade infiltration of lymphocytes into the myenteric plexus of nine patients, four of whom had an associated increase in intraepithelial lymphocytes and six demonstrated evidence of neuronal degeneration (10). Nine patients had hypertrophy of longitudinal muscles, and seven had abnormalities in the number and size of interstitial cells of Cajal (10). The finding of intraepithelial lymphocytosis was consistent with some other reports in the colon and duodenum, too (8, 11). We tried to understand whether or not there are some significant relationships between IBS,

CG, depression, and various inflammatory processes in the body.

Material and methods

The study was performed in the Internal Medicine Clinic of the Dumlupinar University between August 2005 and March 2007. Consecutive patients with upper abdominal discomfort were taken into the study. Their medical histories including smoking, alcohol, urolithiasis, and already used medications including antidepressants at least for a period of six months were learned. Patients with devastating illnesses including eating disorders, malignancies, acute or chronic renal failure, cirrhosis, hyper- or hypothyroidism, or heart failure were excluded. Current daily smokers at least for the last six months and cases with a history of five pack years were accepted as smokers. Patients with regular alcohol consumption (one drink a day) at least for the last six months and cases with a history of five drink years were accepted as drinkers. A routine check up procedure including fasting plasma glucose (FPG), total cholesterol, triglycerides, high density lipoproteins (HDL), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, creatinine, thyroid function tests, hepatic function tests, markers of hepatitis A, B, C, and human immunodeficiency viruses, a urinalysis, a posterior-anterior chest x-ray graphy, an electrocardiogram, a Doppler echocardiogram in case of requirement, an abdominal ultrasonography, an abdominal x-ray graphy in supine position, a rectosigmoidoscopy just in patients symptomatic for hemorrhoids, and a questionnaire for the IBS was performed. IBS was diagnosed according to Rome II criteria in the absence of red flag symptoms including pain, nocturnal diarrhea, weight loss, fever, and any abnormal finding of the physical examination. An upper gastrointestinal endoscopy was performed, and sample biopsies were taken just in cases with suspicion. CG is diagnosed, histologically. Infiltrations of neutrophils and monocytes into the gastric mucosa is the hallmark of CG (12). An additional intravenous pyelography was performed according to the results of the urinalysis and abdominal x-ray graphy. So urolithiasis was diagnosed either by medical history or as a result of current clinical and laboratory findings. Body mass index (BMI) of each case was calculated by measurements of Same Physician instead of verbal expressions. Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already using antidiabetic medications were defined as diabetics (13). An oral glucose tolerance test with 75-gram glucose was performed in cases with FPG levels between 100 and 126 mg/dL, and diagnosis of cases with a two-hour plasma glucose level of 200 mg/dL or higher is diabetes mellitus (DM) (13). Office blood pressure (OBP) was checked after five minutes of rest in seated position with mercury sphygmomanometer on three visits, and no smoking was permitted during the previous two hours. Ten days twice daily measurements of blood pressure at home (HBP) were obtained in all cases, even in normotensives in the office due to the risk of masked hypertension after an education about proper blood pressure (BP) measurement techniques (14). The education included recommendation

of upper arm devices, using a standard adult cuff with bladder sizes of 12 x 26 cm for arm circumferences up to 33 cm in length and a large adult cuff with bladder sizes of 12 x 40 cm for arm circumferences up to 50 cm in length, and taking a rest for a period of five minutes in seated position before measurements (14). An additional 24-hour ambulatory blood pressure monitoring was not required due to the equal efficacy of the HBP measurements to diagnose hypertension (HT) (15). HT is defined as a mean BP of 140/90 mmHg or greater on HBP measurements, and white coat hypertension (WCH) is defined as an OBP of 140/90 mmHg or greater, but a mean HBP value of lower than 140/90 mmHg (14). Eventually, all patients with the IBS were collected into the first and age and sex-matched control cases were collected into the second 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 936 patients with the IBS (592 females) and 346 control cases, totally. Mean age of the patients was 41.0 years, and 63.2% of them were female. Although gastric sample biopsies were taken just in suspected cases, CG was diagnosed nearly in all of the patients with the IBS (80.4% vs 15.0%, $p < 0.001$). Interestingly, prevalence of antidepressants use was also higher in the IBS cases, significantly (46.4% vs 16.1%, $p < 0.001$). Similarly, smoking (35.2% vs 20.8%, $p < 0.001$), hemorrhoids (37.1% vs 7.2%, $p < 0.001$), and urolithiasis (22.0% vs 9.5%, $p < 0.001$) were all higher in the IBS patients, again. Beside that the mean values of FPG (111.9 vs 105.4 mg/dL, $p = 0.002$) and plasma triglycerides (167.0 vs 147.3 mg/dL, $p = 0.013$) were also higher in the IBS patients, significantly (Table 1). Due to the limited number of cases with alcoholism among the study cases, regular alcohol consumption was not included in comparison.

Table 1: Comparison of patients with irritable bowel syndrome and without

Variables	Patients with IBS*	p-value	Control cases
Number	936		346
<i>Mean age (year)</i>	<i>41.0 ± 14.7 (13-86)</i>	Ns†	41.4 ± 14.4 (15-82)
<i>Female ratio</i>	<i>63.2%</i>	Ns	63.0%
<i>CG‡</i>	<i>80.4%</i>	<i><0.001</i>	15.0%
<i>Antidepressants use</i>	<i>46.4%</i>	<i><0.001</i>	16.1%
<i>Hemorrhoids</i>	<i>37.1%</i>	<i><0.001</i>	7.2%
<i>Smoking</i>	<i>35.2%</i>	<i><0.001</i>	20.8%
<i>Urolithiasis</i>	<i>22.0%</i>	<i><0.001</i>	9.5%
Mean BMI‡ (kg/m ²)	27.2 ± 5.6 (15.0-51.1)	Ns	27.7 ± 5.9 (16.5-49.0)
WCH§	27.7%	Ns	31.4%
HT	12.8%	Ns	14.7%
DM**	8.3%	Ns	10.0%
<i>Mean FPG*** (mg/dL)</i>	<i>111.9 ± 42.8 (66-392)</i>	<i>0.002</i>	105.4 ± 32.9 (70-323)
Mean TC**** (mg/dL)	199.8 ± 43.9 (105-352)	Ns	196.5 ± 43.6 (110-296)
<i>Mean triglycerides (mg/dL)</i>	<i>167.0 ± 106.5 (20-622)</i>	<i>0.013</i>	147.3 ± 102.9 (27-857)
Mean LDL***** (mg/dL)	125.4 ± 35.8 (10-282)	Ns	124.0 ± 32.5 (54-231)
Mean HDL***** (mg/dL)	46.6 ± 13.5 (24-124)	Ns	45.0 ± 10.3 (26-72)

*Irritable bowel syndrome †Nonsignificant ($p > 0.05$) ‡Chronic gastritis ‡Body mass index

§White coat hypertension ||Hypertension **Diabetes mellitus ***Fasting plasma glucose

****Total cholesterol *****Low-density lipoprotein *****High-density lipoprotein

Discussion

IBS is a chronic low-grade inflammatory process affecting various organ systems of the body with an average world prevalence of 11.2% to 15.0% (16, 17). It is higher in females and under the age of 50 years (18). It has become a multifactorial disease that is characterized by visceral hypersensitivity, alteration of the gut microflora, an increased intestinal membrane permeability, a low-grade inflammation mainly affecting the gastrointestinal and genitourinary tracts, deterioration in gastroenteric physiology, gastrointestinal motor dysfunction, somatization, fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, interstitial cystitis, sexual dysfunction, sleep disturbance, increased colonic motility, increased colonic bile acid concentration, epithelial barrier dysfunction, neurohormonal up-regulation, activation of secretory processes in the epithelial layer, immune activation, disordered bile salt metabolism, abnormalities in serotonin metabolism, and alterations in brain functions (19-24). The interface of IBS and psychiatry is well established with psychiatric comorbidities approaching 20% to 60% in IBS cases (25). For example, patients with IBS who asked for medical help because of their symptoms presented emotional problems such as anxiety, depression, and expressed neurotic personality (26). In another study, patients with IBS had a three-fold increased odds of either anxiety or depression (27). Similarly, IBS was also common in patients seeking treatment for major depression in another study (28), and symptoms of major depressive disorders occur in up to 90% of patients with IBS in the other study (16). The life time prevalence of major depressive and anxiety disorders increased up to 76% and 54% in cases with IBS, respectively (29). Particularly in diarrhea predominant type of IBS, the major depression was considered to be strongly involved in the onset and the clinical course of IBS (30). Anxiety disorders, depressive disorders, and somatoform disorders were the more frequently detected comorbid disorders with IBS in the other study (25). Lower socioeconomic status was associated with an increased prevalence of comorbid anxiety and depression in IBS (31). Similarly, the prevalences of both depression and insomnia were higher with IBS compared to each individual occurrence (32). Prevalences of IBS and abdominal/belly pain were greater among a sample of veterans with posttraumatic stress disorder (33). Additionally, the prevalences of IBS and depressive symptoms were higher in the fibromyalgia patients (34). Fibromyalgia alone and patients with fibromyalgia plus IBS averaged greater disability than those with IBS alone, and disability was correlated with anxiety and depression (35). Prevalences of fibromyalgia (30% vs 3%, $p < 0.001$), anxiety-disorder (39.7% vs 10.2%, $p < 0.001$), and depression (8.1% vs 4.9%, $p < 0.001$) were higher with IBS in another study, again (36). Eventually, 54% to 100% of patients with IBS may have associated psychiatric illnesses and personality pathologies according to the some authors (26).

Primary bacterial gut disturbances may be important for the development and severity of IBS (37). Dysbiosis, or alteration in the normal intestinal flora, modulates

intestinal permeability, inflammation, and gut motility (37). The severities of psychological and gastrointestinal symptoms in IBS have been linked with a distinct intestinal microbiota signature (37). Similarly, various psychiatric disorders including depression and posttraumatic stress disorder are associated with unique gut microbiota profiles, which could differentially affect the onset and progression of coincident IBS (38). But efforts to modulate intestinal dysbiosis in IBS have shown little improvement in large systematic reviews which means that the intestinal dysbiosis may actually be the result instead of the cause of IBS (37). On the other hand, IBS patients with a depression score on the Zung Depression Self-Rating Scale of 50 or more had a significantly lower number of total and T lymphocytes than the rest of IBS patients (39). The results may suggest a possible association between depression and indices of cellular immunity in IBS (39). An emerging role has been attributed to the importance of immune factors in the pathophysiology of IBS with evidence of altered cytokine profiles and increased levels of mucosal immune cells (40). These factors have also been shown to have direct effects on neuronal signalling (40). Pro- and anti-inflammatory cytokines are important modulators of the immune response, and may also play a major role in IBS (41). Cytokine production is regulated genetically, and imbalances in cytokine secretion may affect disease susceptibility and clinical outcomes of various conditions (41). Psychological stress, anxiety, and depression may also be involved in the altered profiles of pro- and anti-inflammatory cytokines leading to IBS (41). On the other hand, a maladaptive stress response, probably mediated by corticotropin-releasing hormone (CRH), contributes to the initiation, persistence, and severity of symptom flares in IBS (40). CRH is the stress hormone of the body, and a major mediator of stress response in the brain-gut axis (42). IBS is presumed to be a disorder of the brain-gut link associated with exaggerated response to stress (42). The previous study findings suggest the major role of CRH in stress-related pathophysiology of IBS, and possibly in inflammation of the gastrointestinal and genitourinary tracts mucosae (42). This inflammatory infiltrate is mainly represented by increased numbers of T lymphocytes and mast cells lying in the lamina propria (43). The close apposition of immunocytes to gut nerves supplying the mucosa provides a basis for neuroimmune cross-talk, which may explain gut sensorimotor dysfunction and related symptoms in IBS (43). Similarly, some other authors have also supported the idea that a low-grade inflammation, particularly mast cell activation, may be a contributory factor in IBS (44). As a result, it is not a surprising that IBS was an independent predictor ($p = 0.025$) of greater high-sensitive CRP levels in the plasma (45).

The monolayer of endothelial cells that forms the inner lining of arteries, veins, capillaries, and lymphatics is called as the endothelium. Probably, the whole endothelium all over the body may act as a separate organ that may be the largest organ of the body. It may contract vasculature of the peripheral organs while relaxing the internal ones during cold, anxiety, and depression-like stresses. Because we measure the systolic and diastolic BPs of the

arms and legs, they may not show the actual BPs of the brain, heart, lung, liver, and kidney-like internal organs. The endothelium may be the main organ in the control of blood fluidity, platelets aggregation, and vascular tone all over the body. It may control vascular tone and blood flow by releasing nitric oxide, reactive oxygen species, and metabolites of arachidonic acid into the circulation. It may also be important for synthesizing of vasoactive hormones such as angiotensin II. An endothelial dysfunction-induced accelerated atherosclerosis all over the body may be the main cause of end-organ insufficiencies, aging, and death. Such a dysfunction may also be important in the development of cancers by preventing clearance of malignant cells by the natural killers in terminal points of the circulation. Similarly, physical inactivity, animal-rich diet, excess weight, higher BP and glucose levels, chronic inflammations, prolonged infections, cancers, smoking, and alcohol may be accelerating factors of the chronic endothelial inflammation and dysfunction terminating with the accelerated atherosclerosis-induced end-organ insufficiencies (46). The much higher BP of the afferent vasculature may be the major accelerating factor by inducing recurrent injuries on the vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the medical literature. Due to the chronic endothelial damage, inflammation, edema, fibrosis, and dysfunction, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood flow to the terminal organs, and increase systolic and decrease diastolic BPs further. Some of the irreversible consequences of the systemic inflammatory process are obesity, HT, DM, cirrhosis, peripheral artery disease, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, early aging, and premature death (47). Although early withdrawal of the accelerating factors may delay terminal consequences, endothelial changes can not be reversed, completely after development of the irreversible end-points due to their fibrotic natures. The accelerating factors and irreversible consequences are researched under the titles of the metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature, extensively (48).

Excess weight may be the most common cause of systemic vasculitis, and the major underlying cause of metabolic syndrome all over the world. Unfortunately, obesity may be one of the irreversible end-points of the metabolic syndrome. Although some transient successes can be achieved, nonpharmaceutical approaches provide limited benefit to reverse the obesity, permanently. Due to the excess weight-induced chronic low-grade inflammation on the vascular endothelium, the risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess weight in all age groups (49). The chronic low-grade inflammation may even cause genetic changes in the endothelial cells, and the systemic atherosclerosis may prevent clearance of malignant cells, effectively. The adverse effects of excess

weight on the BP were shown in the literature, extensively (50). For example, prevalences of sustained normotension (NT) were higher in the underweight than the normal weight (80.3% vs 64.0%, $p < 0.05$) and overweight groups (80.3% vs 31.5%, $p < 0.001$) (50), and 52.8% of patients with HT had obesity against 14.5% of patients with the sustained NT ($p < 0.001$) (51). So the major underlying cause of the metabolic syndrome appears as weight gain that may be the main cause of insulin resistance, hyperlipoproteinemias, impaired fasting glucose, impaired glucose tolerance, and WCH (52). Interestingly, weight gain before the development of an obvious overweight or obesity may even cause development of several components of the metabolic syndrome. For example, WCH alone may be a strong indicator of weight gain even before development of excess weight (50, 51). On the other hand, prevention of the weight gain with physical activity even in the absence of a prominent weight loss usually results with resolution of many parameters of the syndrome (53). According to our experiences, excess weight may actually be a result of physical inactivity instead of an excessive eating habit. In another word, there is a problem with burning of calories instead of getting them. Therefore prevention of weight gain can not be achieved by diet, alone (54). On the other hand, limitation of excess weight as an excessive fat tissue around abdomen under the heading of abdominal obesity may be meaningless, instead it should be defined as overweight or obesity by means of the BMI. Because adipocytes function as an endocrine organ, and they release leptin, tumour necrosis factor (TNF)-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines into the plasma (55). Eventual hyperactivities of sympathetic nervous system and renin-angiotensin-aldosterone system are probably associated with insulin resistance, elevated BP, and chronic endothelial inflammation and dysfunction. Similarly, the Adult Treatment Panel (ATP) III reported that although some people classified as overweight with larger muscular masses, most of them also have excessive fat tissue predisposing to the irreversible end-points of the metabolic syndrome (13).

Smoking may be the second common cause of systemic vasculitis all over the world. It is one of the major risk factors for the atherosclerotic end-organ insufficiencies (56). 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 up to now. Smoking may cause a moderate or severe inflammatory process in the vascular endothelium (57), and plasma triglycerides, low density lipoproteins (LDL), ESR, and CRP may be positive whereas HDL and FPG may be negative acute phase reactants (APRs) indicating such moderate or severe inflammatory effects in the plasma (58). Whereas FPG and plasma triglycerides were increased in the IBS cases in the present study, indicating that FPG may behave as a positive in mild but as a negative APR in moderate and severe inflammatory disorders in the body (59). In other words, IBS causes a mild, but smoking

causes a moderate or severe inflammatory process in the body. Beside the obvious atherosclerotic effects of smoking, some studies reported that smoking in human being and nicotine administration in animals are associated with the lower values of BMI (60). Some evidences revealed an increased energy expenditure during smoking both on the rest and light physical activity (61). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (62). According to an animal study, nicotine may lengthen intermeal time, and decrease amount of meal eaten (63). 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 (64). As the opposite findings to the above studies, the mean body weight and BMI were similar both in the smokers and non-smokers in the other study (58). Similarly, prevalences of smoking were similar in the normal weight (35.9%), overweight (32.9%), and obesity groups (33.7%, $p>0.05$ between all) in another study (65). 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 BMI, LDL, triglycerides, WCH, HT, and DM in females (66). 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 (67). In another words, smoking may be more dangerous for women about the atherosclerotic end-points probably due to the higher BMI and its consequences in them. Several toxic substances found in the cigarette smoke get into the circulation, and cause a vascular endothelial inflammation in all organ systems of the body. For example, smoking is usually reported together with depression, IBS, CG, hemorrhoids, and urolithiasis in the literature (5, 6). There may be several underlying mechanisms to explain these associations in the smokers (68). First of all, smoking may have some antidepressant properties and the most widely used antidepressant drug with several side effects in the body. Secondly, smoking-induced vascular endothelial inflammation may disturb epithelial functions for absorption and excretion in the gastrointestinal and genitourinary tracts. These functional problems may terminate with urolithiasis and hemorrhoids. Thirdly, diarrheal losses-induced urinary changes may even cause urolithiasis (5, 6). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the gastrointestinal and genitourinary tracts terminating with urolithiasis and hemorrhoids. 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 IBS and 11.6% of cases without in the other study ($p<0.01$) (5).

Alcohol may be the third common cause of systemic vasculitis in the world. It is addictive to human being, and can result in alcohol use disorder (AUD), dependence, and withdrawal. Similar to the smoking, alcohol may have some antidepressant properties, and may be the second most widely used antidepressant drug with several side effects in the body. Alcohol is causally associated with more than 200 different pathologies including cancers in whole body (69). Eventually, people hospitalized with AUD have an average life expectancy of 47-53 years in men and 50-58 years in women, and die 24-28 years earlier than the others (70). People with AUD have three-fold higher mortality in men and four-fold in women (71). Similar to smoking, alcohol may be more dangerous for women about the atherosclerotic end-points probably due to their lower body mass induced lower capacity to metabolize alcohol and higher body fat. It may even cause unconsciousness and sudden death if taken in high amounts. Hepatic alcohol dehydrogenase is the main enzyme to metabolize alcohol that requires the cofactor, nicotinamide adenine dinucleotide (NAD). Normally, NAD is used to metabolize fats in the liver but alcohol competes with these fats for the use of NAD. Eventually, prolonged exposure of alcohol causes fatty liver. Ethanol is the only alcohol that is found in alcoholic beverages. Ethanol crosses biological membranes and blood-brain barrier by means of the passive diffusion, easily. Alcohol works particularly by increasing effects of the gamma aminobutyric acid that is the main inhibitory neurotransmitter of the brain. Alcohol causes happiness and euphoria, decreased anxiety, increased sociability, sedation, generalized depression of central nervous system, and impairment of cognitive, memory, motor, and sensory functions. It may even cause fetal disorders in pregnancy. Regular alcohol consumption leads to cell death in the liver, scarring, cirrhosis, and hepatocellular carcinoma. Heavy alcohol consumption may even terminate with permanent brain damage. Alcohol is the major contributing factor of elevated triglycerides which are the sensitive APRs in the plasma (52). Although regular alcohol consumers were excluded, plasma triglycerides were higher in the smokers (163.1 vs 151.3 mg/dL, $p<0.05$), indicating the inflammatory effects of smoking (72).

The acute phase response occurs in case of infection, infarction, cancer, trauma, and burn-like inflammatory conditions of the body. Certain mediators known as APRs are increased or decreased during the response (73, 74). These markers are commonly used in the clinical practice as the indicators of acute and chronic inflammations in the body. The terms of acute phase proteins and APRs are usually used synonymously, although some APRs are polypeptides rather than proteins. Positive and negative APRs are those whose concentrations increase or decrease during the acute phase response, respectively. The response is predominantly mediated by the pro-inflammatory cytokines including TNF, interleukin-1, and interleukin-6 secreted by neutrophils and macrophages into the circulation. The liver and other organs respond to the cytokines by producing many positive APRs. ESR, CRP, fibrinogen, ferritin, procalcitonin, hepcidin,

haptoglobin, ceruloplasmin, complement proteins, and serum amyloid A are some of the well-known positive APRs. CRP is a useful indicator of the acute phase response, clinically. It is responsible for activation of the complement pathway. CRP reaches up to the maximum concentration within two days, and decreases with the resolution of the inflammation with a half-life of 6-8 hours, rapidly. It correlates with ESR, but not simultaneously since ESR is largely dependent upon elevation of fibrinogen with a half-life of one week, approximately. Thus ESR remains higher for a longer period of time despite the removal of the inflammatory stimulus. Similarly, white blood cells and platelet counts may also behave as some other positive APRs in the body (75). On the other hand, productions of the negative APRs are suppressed, simultaneously. Albumin, transferrin, retinol-binding protein, antithrombin, transcortin, alpha-fetoprotein, and hemoglobin are some of the well-known negative APRs in the body. Suppressions of such negative APRs are also used as the indicators of the acute phase response in the body. Suppressions of such negative APRs may actually be secondary to the protection of amino acids and polypeptides required for the production of positive APRs, sufficiently. As also observed in the smokers in the above study (72), production of HDL may also be suppressed in the liver during the acute phase response (76). Similarly, triglycerides, DM, and CHD were all higher in patients with plasma HDL values of lower than 40 mg/dL, significantly (76). So HDL may actually behave as negative whereas triglycerides positive APRs in the plasma. Similarly, the highest CHD of the group with HDL values of lower than 40 mg/dL can also be explained by the same hypothesis in the other study (52). Additionally, plasma triglycerides increased whereas HDL decreased during infections (77). On the other hand, a 10 mg/dL increase of plasma LDL values was associated with a 3% lower risk of hemorrhagic stroke (78). Similarly, the highest prevalences of HT and DM parallel to the elevated values of LDL and HDL, and the highest prevalences of COPD, CHD, and CRD in contrast to the lowest values of LDL and HDL may show initially positive but eventually negative behaviors of LDL and HDL as the APRs (79). Probably, HDL turn to the negative direction much more earlier than LDL in the plasma. Interestingly, the most desired values were between 80 and 100 mg/dL for LDL, between 40 and 46 mg/dL for HDL, and lower than 60 mg/dL for triglycerides in the plasma (52). Parallel to ESR and CRP, plasma triglycerides and LDL may behave as positive whereas FPG and HDL negative APRs in smokers in the above study (72). In another words, lower HDL values should alert clinicians for researching of any underlying pathology in the body (80, 81).

Cholesterol, triglycerides, and phospholipids are the major lipids of the body. They do not circulate in the plasma, freely instead they are bound to proteins, and transported as lipoproteins. There are five major classes of lipoproteins in the plasma. Chylomicrons carry exogenous triglycerides to the liver via the thoracic duct. Very low density lipoproteins (VLDL) are produced in the liver, and carry endogenous triglycerides to the organs. VLDL are converted into the intermediate density lipoproteins

(IDL) by removal of 90% of triglycerides by lipases in the capillaries of adipocytes and muscle tissues. Then the IDL are degraded into LDL by removal of more triglycerides. So VLDL are the main source of LDL in the plasma, and LDL deliver cholesterol from the liver to organs. Although the liver removes majority of LDL from the circulation, a small amount is uptaken by scavenger receptors of the macrophages migrating into the arterial walls, and become the foam cells of atherosclerotic plaques. HDL remove fats and cholesterol from cells including the arterial wall atheroma, and carry the cholesterol back to the adrenals, ovaries, and testes-like steroidogenic organs and liver for excretion, re-utilization, or disposal. All of the carrier lipoproteins are under dynamic control, and are readily affected by diet, drug, inflammation, infection, cancer, trauma, smoking, alcohol, and excess weight. Thus lipid analysis should be performed during a steady state, but the metabolic syndrome alone is a low-grade inflammatory process, and it may even cause abnormal lipoproteins levels in the plasma. HDL may normally show various anti-oxidative, anti-inflammatory, and anti-atherogenic properties including reverse cholesterol transport (82). However, HDL may become 'dysfunctional' in pathologic conditions which means that relative compositions of lipids and proteins, as well as the enzymatic activities of HDL are altered (82). For example, properties of HDL are compromised in patients with DM by means of the oxidative modification, glycation, and/or transformation of HDL proteomes into the proinflammatory proteins. Additionally, the drugs increasing HDL values such as niacin, fibrates, and cholesteryl ester transfer protein inhibitors can not reduce all cause mortality, CHD mortality, myocardial infarction, and stroke (83). In other words, HDL may just be some indicators instead of being the main actors of the health. Similarly, BMI, DM, and CHD were the lowest between the HDL values of 40 and 46 mg/dL, and the prevalence of DM was only 3.1% between these values against 22.2% outside these limits (84). Similar to the above study (72), HDL and FPG values were also suppressed in the sickle cell diseases (SCDs), probably due to the severe inflammatory nature of the diseases (85). Smoking may reduce HDL and FPG by means of the moderate or severe inflammatory effects on the vascular endothelium all over the body (58). On the other hand, triglycerides alone may be one of the most sensitive APRs indicating the metabolic syndrome (86). Although ATP II determined the normal plasma triglycerides as lower than 200 mg/dL in 1994 (87), World Health Organisation in 1999 (88) and ATP III in 2001 reduced the normal limits as lower than 150 mg/dL (13). Although these cutpoints, there are still suspicions about the safest values of triglycerides in the plasma (86). Beside that triglycerides are the only lipids which were not suppressed with the pathological weight losses (89). For example, plasma triglycerides increased in contrast to the suppressed body weight and BMI in the SCDs (89). Similarly, prevalences of excess weight, DM, HT, and smoking were all higher in the hypertriglyceridemia group (200 mg/dL and higher) in the other study (90). Interestingly, the greatest number of deteriorations of the metabolic parameters was observed with the triglycerides values of 60 mg/dL and higher (86).

The body's homeostatic mechanism keeps blood glucose levels within a narrow range with two groups of mutually antagonistic hormones. Glucagon, cortisol, and catecholamines are the catabolic hormones increasing the blood glucose, whereas insulin is the anabolic hormone decreasing the blood glucose levels. Glucagon is secreted from the alpha cells while insulin is secreted from the beta cells of pancreatic islets which are the bundles of endocrine tissues. When the blood glucose levels are too high, insulin tells muscles to take up excess glucose for storage as glycogen. When the blood glucose levels are too low, glucagon informs the tissues to produce more glucose from the stores of glycogen. Catecholamines prepare the muscles and respiratory system for a 'fight to fight' response. Cortisol prepares the body for the various stresses. A blood glucose level of four grams, or about a teaspoon, is critical for the normal function of millions of cells of a person with the weight of 70 kg (91). The constant blood glucose levels are maintained via the hepatic and muscular glycogen stores on fasting. The brain consumes about 60% of the blood glucose on fasting. FPG is the most commonly used indication of overall glucose homeostasis, and it is measured after a fasting period of 8 hours. Infection, inflammation, surgical operation, depression, alcohol, and smoking-like stresses may affect the blood glucose homeostasis. For example, smoking was negatively associated with the FPG and DM in Chinese men with the normal weight, but not in men with excess weight or in women (92). Similarly, smokers have a lower likelihood of newly-diagnosed DM in Chinese men with a lower BMI in the other study (93). Parallel to the above studies, FPG and DM were also lower in the smokers (102.3 vs 111.6 mg/dL, $p=0.007$ and 8.9% vs 14.3%, $p<0.05$, respectively), and although majority of the smokers were male again (70.0%), BMI was relatively higher (26.6 kg/m²) in contrast to the above studies (72).

As a conclusion, because FPG and triglycerides are well-known APRs in the body, IBS and CG may be some low-grade inflammatory processes initiated with anxiety, depression, infection, inflammation, trauma, and cancer fear-like stresses of the body, and eventually terminate with hemorrhoids and urolithiasis. Due to the highly significant associations between IBS, CG, and depression, IBS and CG may actually be the two sides of the same paper, and just be two examples of depression-induced various inflammatory processes in human body.

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CORTICOSTEROIDS DURING ACUTE PAINFUL CRISES OF SICKLE CELL DISEASES

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Abstract

Background: Sickle cell diseases (SCD) are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of hardened red blood cells (RBC) into the tissues.

Methods: All patients with the SCD were included.

Results: The study included 222 males and 212 females with similar ages (30.8 vs 30.3 years, $p>0.05$, respectively). Disseminated teeth losses (5.4% vs 1.4%, $p<0.001$), ileus (7.2% vs 1.4%, $p<0.001$), cirrhosis (8.1% vs 1.8%, $p<0.001$), leg ulcers (19.8% vs 7.0%, $p<0.001$), digital clubbing (14.8% vs 6.6%, $p<0.001$), coronary heart disease (18.0% vs 13.2%, $p<0.05$), chronic renal disease (9.9% vs 6.1%, $p<0.05$), chronic obstructive pulmonary disease (25.2% vs 7.0%, $p<0.001$), and stroke (12.1% vs 7.5%, $p<0.05$) were all higher but not acute chest syndrome (2.7% vs 3.7%), pulmonary hypertension (12.6% vs 11.7%), deep venous thrombosis and/or varices and/or telangiectasias (9.0% vs 6.6%), and mean age of mortality (30.2 vs 33.3 years) in males ($p>0.05$ for all).

Conclusion: Although the hardened RBC-induced capillary endothelial damage is present in whole body even at birth, severe exacerbations during additional stresses are called as acute painful crises. An increased basal metabolic rate, exaggerated sickling, diffuse capillary endothelial damage, exaggerated capillary endothelial inflammation and edema, generalized tissue hypoxia, and multiorgan insufficiencies may be the main causes of mortality during the crises. Although rapid RBC supports are the main treatment option, corticosteroids should also be added to decrease severity of endothelial inflammation and edema, and to prevent tissue hypoxia and multiorgan insufficiencies during such crises.

Key words: Sickle cell diseases, acute painful crises, capillary inflammation, capillary edema, corticosteroids, metabolic syndrome, atherosclerosis

Introduction

Chronic endothelial damage may be the main cause of aging and death by causing end-organ insufficiencies in human being (1). Much higher blood pressures (BP) of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelial cells. Probably, whole afferent vasculature including capillaries are mainly involved in the 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, those eventually reduce blood supply to the terminal organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, animal-rich diet, smoking, alcohol, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia-like end-organ insufficiencies, 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, PAD, mesenteric ischemia, osteoporosis, stroke, dementia-like end-organ insufficiencies, and aging, endothelial changes can not be reversed due to their fibrotic natures, completely. The accelerating factors and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the literature, extensively (4-6). On the other hand, sickle cell diseases (SCD) are chronic inflammatory and highly destructive process on vascular endothelium, initiated at birth and terminated with accelerated atherosclerosis induced end-organ insufficiencies in early years of life (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Probably loss of elasticity instead of shape is the main problem since sickling is rare in peripheral blood samples of the cases with associated thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammations, infections, and additional stresses. The hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with tissue hypoxia all over the body (9). As a difference from other causes of chronic endothelial damage, SCD keep vascular endothelium particularly at the capillary level (10, 11), since the capillary system is the main distributor of the hardened RBC into the tissues. The hardened RBC induced chronic endothelial damage builds up an advanced atherosclerosis in early years of life. Vascular narrowings and occlusions induced tissue ischemia and infarctions are the final consequences, so the mean life expectancy is decreased by 25 to 30 years for both genders in the SCD (8).

Material and methods

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

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

Results

The study included 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, $p>0.05$, respectively). Prevalence of associated thalassemia minors were similar in both genders, too (72.5% vs 67.9%, $p>0.05$, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9%

vs 0.4%) were higher in males ($p<0.001$ for both) (Table 1). Similarly, transfused units of RBC in their lives (48.1 vs 28.5, $p=0.000$), disseminated teeth losses (5.4% vs 1.4%, $p<0.001$), ileus (7.2% vs 1.4%, $p<0.001$), cirrhosis (8.1% vs 1.8%, $p<0.001$), leg ulcers (19.8% vs 7.0%, $p<0.001$), digital clubbing (14.8% vs 6.6%, $p<0.001$), CHD (18.0% vs 13.2%, $p<0.05$), CRD (9.9% vs 6.1%, $p<0.05$), COPD (25.2% vs 7.0%, $p<0.001$), and stroke (12.1% vs 7.5%, $p<0.05$) were all higher but not ACS (2.7% vs 3.7%), PHT (12.6% vs 11.7), DVT and/or varices and/or telangiectasias (9.0% vs 6.6%), and mean age of mortality (30.2 vs 33.3 years) in males ($p>0.05$ for all) (Table 2). Beside that the mean ages of ACS and PHT were 30.3 and 34.0 years ($p<0.05$), respectively (Table 3).

Table 1: Characteristic features of the study cases

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

*Sickle cell diseases †Nonsignificant ($p>0.05$)

Table 2: Associated pathologies of the study cases

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

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

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

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

*Acute chest syndrome †Chronic obstructive pulmonary disease ‡Pulmonary hypertension

§ Coronary heart disease ¶Deep venous thrombosis **Chronic renal disease

Discussion

The deaths seem sudden and unexpected events in the SCD. Unfortunately, most of the deaths develop just after the hospital admission, and majority of them are patients without hydroxyurea therapy (19, 20). Rapid RBC supports are usually life-saving for such cases but preparation of RBC units for transfusion usually takes time. Beside that RBC supports in emergencies become much more difficult in terminal cases due to the repeated transfusions induced blood group mismatch. Actually, transfusion of each unit of RBC complicates the following transfusions by means of the blood subgroup mismatch. Due to the significant efficacy of hydroxyurea therapy, RBC transfusions should be kept just for acute events and emergencies in the SCD (19, 20). According to our experiences, simple and repeated transfusions are superior to RBC exchange in the SCD (21, 22). First of all, preparation of one or two units of RBC 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 patients. Secondly, transfusions of one or two units of RBC suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their relatives since RBC transfusions probably have the strongest analgesic effects during the 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 RBC suspensions in each time by means of

the simple transfusions will decrease transfusion-related complications including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices.

Acute painful crises are the most disabling symptoms of the SCD. Although some authors reported that pain itself may not be life threatening, infections, medical or surgical emergencies, and emotional stress-like factors are the most common precipitating factors of the crises (23). The increased basal metabolic rate during such additional stresses aggravates the capillary endothelial damage, inflammation, edema, tissue hypoxia, and multiorgan failures. So the risk of mortality is significantly higher during such crises. The deaths in the SCD can not be explained by a solitary reason alone, instead they may have a multisystemic nature. Actually, each painful crisis may complicate with the following crises by leaving some sequelae on the capillary endothelial system. After a period of time, the sequelae may terminate with sudden end-organ insufficiencies. On the other hand, pain is the result of a complex and poorly understood interaction between RBC, white blood cells (WBC), platelets

(PLT), and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis of the crises by releasing cytotoxic enzymes is unknown. The adverse actions of WBC on endothelium are of particular interest with regard to the cerebrovascular diseases in the SCD. For example, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCD (24), and it was associated with the risk of stroke in a cohort of Jamaican patients (25). 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 (26), but according to our practice, simple and repeated RBC transfusions may be highly effective both to relieve pain and to prevent sudden death that may develop secondary to multiorgan failures on the chronic inflammatory background of the SCD.

Hydroxyurea may be the only life-saving drug for the treatment of the SCD. It interferes with the cell division by blocking the formation of deoxyribonucleotides by means of inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the suppression of leukocytosis and thrombocytosis by blocking the DNA synthesis in the SCD (27, 28). By this way, the chronic inflammatory and destructive process of the SCD 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 in the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' own WBC and PLT. So suppression of proliferation of them may limit the endothelial damage-induced edema, ischemia, and infarctions in whole body (29). Similarly, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels (30). 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 (31). The study particularly researched effects of hydroxyurea on painful crises, ACS, and requirement of blood transfusion. The outcomes were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was initiated for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations (31). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (31). 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 (31). Whereas we used all subtypes of the SCD 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, $p < 0.000$) in the previous study (20).

Parallel to our results, adult patients using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period (32). Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may also decrease severity of disease and prolong survival (32). The complications start to be seen even in infancy in the SCD. For example, infants with lower hemoglobin values were more likely to have a higher incidence of clinical events such as ACS, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them (33). Hydroxyurea therapy in early years of life may protect splenic function, improve growth, and prevent end-organ insufficiencies. Transfusion programmes can also reduce all of the complications, but transfusions carry many potential risks including infections, iron overload, and development of allo-antibodies causing subsequent transfusions much more difficult.

ACS is a significant cause of mortality in the SCD (34). It occurs most often as a single episode, and a past history is associated with a high mortality rate (34). Similarly, all of 14 cases with ACS had just a single episode, and two of them were fatal in spite of the immediate RBC and ventilation supports and antibiotic therapy in the present study. The remaining 12 patients are still alive without a recurrence at the end of the ten-year follow up period. ACS is the most common between two to four years of age, and its incidence decreases with aging (35). As a difference from atherosclerotic consequences, the incidence of ACS did not show an increase with aging in the present study, and the mean ages of the cases with ACS and SCD 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 SCD, and the incidence of ACS is higher in severe cases such as cases with SCA and higher WBC counts (34, 35). According to our experiences, the increased metabolic rate during infections accelerates sickling, thrombocytosis, leukocytosis, and capillary endothelial damage and edema, and terminates with end-organ insufficiencies. ACS may also be a collapse of the pulmonary vasculature during such infections, and the exaggerated immune response against the abnormal RBC-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 SCD indicating a significant reduction of episodes of ACS with hydroxyurea therapy suggests that a considerable number of episodes are exaggerated with the increased numbers of WBC and PLT (36). Similarly, we strongly recommend hydroxyurea therapy for all patients with the SCD that may also be the cause of the low incidence of ACS among our follow up cases (2.7% in males and 3.7% in females). Additionally, ACS did not show an infectious etiology in 66% of cases (34, 35), and 12 of 27 cases with ACS had evidence of fat embolism in the other study (37). Beside that some authors indicated that antibiotics do not shorten the clinical course (38). RBC support must

be given early in the course of ACS. RBC support has the obvious benefits of decreasing sickle cell concentration directly, and suppressing bone marrow for the production of abnormal RBC and excessive WBC and PLT. So they prevent further sickling, capillary endothelial damage, exaggerated capillary endothelial inflammation and edema, tissue hypoxia, and end-organ insufficiencies not only in the lungs but in whole body.

PHT is a condition of increased BP within the arteries of the lungs. Shortness of breath, fatigue, chest pain, palpitation, swelling of legs and ankles, and cyanosis are common symptoms of PHT. Actually, it is not a diagnosis itself, instead solely a hemodynamic state characterized by resting mean pulmonary artery pressure of 25 mmHg or higher. An increase in pulmonary artery systolic pressure, estimated noninvasively by the echocardiography, helps to identify patients with PHT (39). The cause is often unknown. The underlying mechanism typically involves inflammation, fibrosis, and subsequent remodelling of the arteries. According to World Health Organization, there are five groups of PHT including pulmonary arterial hypertension, PHT secondary to left heart diseases, PHT secondary to lung diseases, chronic thromboembolic PHT, and PHT with unknown mechanisms (40). PHT affects about 1% of the world population, and its prevalence may reach 10% above the age of 65 years (41). Onset is typically seen between 20 and 60 years of age (40). The most common causes are CHD and COPD (40, 42). The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy (43). 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 (43). In fact, all layers of the vessel wall appear to be involved with prominent intimal changes (43). 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 (43). On the other hand, PHT is also a common consequence of the SCD (44), and its prevalence was detected between 20% and 40% in the SCD (45). Whereas we detected the ratio as 12.2% in the present study. Although the higher prevalences of smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CRD, COPD, and stroke-like atherosclerotic risk factors or consequences in male gender, and the male gender alone is a risk factor for the systemic atherosclerosis, the similar prevalences of PHT and ACS in both genders also support nonatherosclerotic natures of PHT and ACS in SCD in the present study. Additionally, frequencies of DVT and/or varices and/or telangiectasias were similar in males and females parallel to ACS and PHT (9.0% vs 6.6%, $p>0.05$, respectively). Similarly, CHD is the other most common cause of PHT in the society (46), and although the higher prevalence of CHD in males in the present study (18.0% vs 13.2%, $p<0.05$), PHT was not higher in males, again. In another definition, PHT may have a hardened RBC-induced chronic thromboembolic whereas ACS may have an acute thromboembolic backgrounds in the SCD (47,

48), since the mean age of ACS is lower than PHT (30.3 and 34.0 years, $p<0.05$), and its mortality is much higher than PHT (34, 35, 40).

COPD is the third leading cause of death with various underlying etiologies in whole world (49, 50). Aging, smoking, male gender, and excess weight may be the major underlying causes. Probably regular alcohol consumption is also important for the pulmonary and systemic inflammatory process of the COPD. For example, COPD was one of the most common diagnoses in alcohol dependence (51). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (52). Probably an accelerated atherosclerotic process is the main structural background of functional changes that are characteristics of the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may actually be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD (53, 54). For example, there may be close relationships between COPD, CHD, PAD, and stroke (55). Furthermore, two-third of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (56). When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again (56). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (57). On the other hand, COPD may actually be the pulmonary consequence of the systemic atherosclerotic process caused by the hardened RBC in the SCD (49).

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 (58). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (59). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, and hepatic diseases and smoking which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect their functions in a short period of time. On the other hand, digital clubbing is also common in the SCD, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, $p<0.001$) may also show some additional role of male gender on the systemic atherosclerotic process.

Leg ulcers are seen in 10% to 20% of the SCD (60), and the ratio was 13.5% in the present study. Its prevalence increases with aging, male gender, and SCA (61). Similarly, its ratio was higher in males (19.8% vs 7.0%, $p < 0.001$), and mean age of the leg ulcer cases was higher than the remaining cases (35.3 vs 29.8 years, $p < 0.000$) in the present study. The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (60). As an evidence of their atherosclerotic nature, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow (60). The hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the major causes, again (61). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC induced venous insufficiencies may also accelerate the process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, probably pooling of blood is the cause of delayed wound and fracture healings in the lower extremities. Smoking and alcohol may also have some additional atherosclerotic effects on the ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCD (62). It is an orally-administered, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (11). Its main action may be the suppression of hyperproliferative WBC and PLT in the SCD (63). Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage (30). According to our experiences, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBC and PLT counts induced an 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 in 2001 (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 (64). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (64). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases (65). Authors reported independent associations between

NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (66). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCD (67). 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 (68). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with the systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious and inflammatory processes may also terminate with an accelerated atherosclerosis in whole body (69). 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 (69, 70). As a result, beside COPD, ileus, leg ulcers, clubbing, CHD, CRD, and stroke, cirrhosis may also be an atherosclerotic consequence of the SCD.

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 (71, 72). Aging, physical inactivity, excess weight, smoking, alcohol, and inflammatory or infectious processes may be the major causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged renal tissues, particularly 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 BP, and insulin resistance may cause tissue inflammation and immune cell activation (73). For example, age ($p = 0.04$), high-sensitivity C-reactive protein ($p = 0.01$), mean arterial BP ($p = 0.003$), and DM ($p = 0.02$) had significant correlations with the CIMT (72). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess weight (74). 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 (74). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (75). With prolonged weight excess, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in cases with excess weight, CRD progresses much more easily (74). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (76). The inflammatory

and atherosclerotic effects of smoking are much more prominent in the respiratory endothelium due to the highest concentrations of its metabolites there. Although some authors reported that alcohol was not related with the CRD (76), various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the renal vascular endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature (69). 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 (77). For example, the most common cause of death was the cardiovascular diseases in the CRD again (78). The hardened RBC-induced capillary endothelial damage in the renal vasculature may be the main cause of CRD in the SCD. In another definition, CRD may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCD, again (79).

Stroke is an important cause of death, and develops as an acute thromboembolic event on the chronic atherosclerotic background in most of the cases. Aging, male gender, smoking, alcohol, and excess weight may be the major underlying causes. Stroke is also a common complication of the SCD (80, 81). Similar to the leg ulcers, stroke is particularly higher in the SCA and cases with higher WBC counts (82). Sickling induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial inflammation, edema, and fibrosis (83). Probably, stroke may not have a macrovascular origin in the SCD, and disseminated capillary endothelial inflammation, edema, and fibrosis may be much more important. Infections, inflammations, medical or surgical emergencies, and emotional stresses may precipitate stroke by increasing basal metabolic rate and sickling. A significant reduction of stroke with hydroxyurea may also suggest the hypothesis that a significant proportion of cases is developed due to the increased WBC and PLT counts-induced exaggerated capillary inflammation, edema, and fibrosis (36).

The venous endothelium is also involved in the SCD (84). For example, varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. 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/or telangiectasias develop. DVT may also cause varicose veins. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus physical examination must be performed in upright position. Although the relatively younger mean ages of the patients and significantly lower body mass index of the SCD patients in the literature (10), the prevalences of DVT and/or varices and/or telangiectasias of the lower limbs were relatively higher in the present study (9.0% vs 6.6% in males and females, $p > 0.05$, respectively), indicating an additional venous involvement of the SCD.

Similarly, priapism is the painful erection of penis that can not return to its flaccid state within four hours in the absence of any stimulation (85). It is an emergency since 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 (85). It is seen with hematological and neurological disorders including SCD, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (86, 87). Ischemic (veno-occlusive), stuttering (recurrent ischemic), and nonischemic priapisms (arterial) are the three types of priapism (88). Ninety-five percent of clinically presented priapisms are the ischemic (veno-occlusive) disorders in which blood can not return adequately from the penis as in the SCD, and they are very painful (85, 88). The other 5% are nonischemic (arterial) type usually caused by a blunt perineal trauma in which there is a short circuit of the vascular system (85). Treatment of arterial type is not as urgent as the veno-occlusive type due to the absence of risk of ischemia (85). RBC support is the treatment of choice in acute phase whereas hydroxyurea should be the treatment of choice in chronic phase in the SCD (89). According to our experiences, hydroxyurea is an effective drug for prevention of attacks and consequences of priapism if initiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillary walls if initiated later in life.

As a conclusion, although the hardened RBC-induced capillary endothelial damage is present in whole body even at birth, severe exacerbations during additional stresses are called as acute painful crises. An increased basal metabolic rate, exaggerated sickling, diffuse capillary endothelial damage, exaggerated capillary endothelial inflammation and edema, generalized tissue hypoxia, and multiorgan insufficiencies may be the main causes of mortality during the crises. Although rapid RBC supports are the main treatment option, corticosteroids should also be added to decrease severity of endothelial inflammation and edema, and to prevent tissue hypoxia and multiorgan insufficiencies during such crises.

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PURPLE URINE BAG SYNDROME: THE ART OF PURPLISH MIX OF BLUE AND RED

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Abstract

Purple urine bag syndrome (PUBS) is an exceptional finding in the clinical setting and is featured by its distinctive purplish urine discoloration. It has been claimed to be due to many culprits, namely, long term indwelling catheterisation, dementia, and urinary tract infection with alkaline urine that is fully loaded with bacteria, bed or chair bound patients, female gender, constipation and chronic kidney disease (Sabanis et al, 2019). It is seen more in the geriatric words. It is said that it's related to tryptophan aberrant metabolism by-products in red and blue pigments, due to bacterial colonization in urinary catheter. Its distinctive colour is due to indigo-producing (bluish) and indirubin- producing (reddish) pigments which react with the plastic tube, to yield the striking purplish colour (Van Keer et al, 2015, Kalsi et al, 2017).

The Purple urine bag syndrome process starts with tryptophan metabolism by the intestinal bacteria such as proteus mirabilis, and will be converted into indoxyl sulfate in the liver then catalyzed by the bacterial phosphatases or sulfatases to indoxyl, and later in the urine it will be converted to two pigments namely indigo and indirubin, to give the distinctive purplish colour of the urine bag (Figure 1).

Differentials for this condition can be haematuria, haemoglobinuria, myoglobinuria, nephrolithiasis, UTIs, food dyes, drugs, poisons, porphyria, and alkaptonuria. Also, beets, carrots, and blackberries can cause urine discolouration (Kalsi et al, 2017). The lists can be endless.

Figure 1: Purple Urine Bag



Photo courtesy of Dr Milad [®]

There are multiple implicated bacteria in this condition (Figure 2) (Ribeiro et al, 2004, Hadano et al, 2012, and Carmo et al 2019).

Figure 2: the implicated bacteria

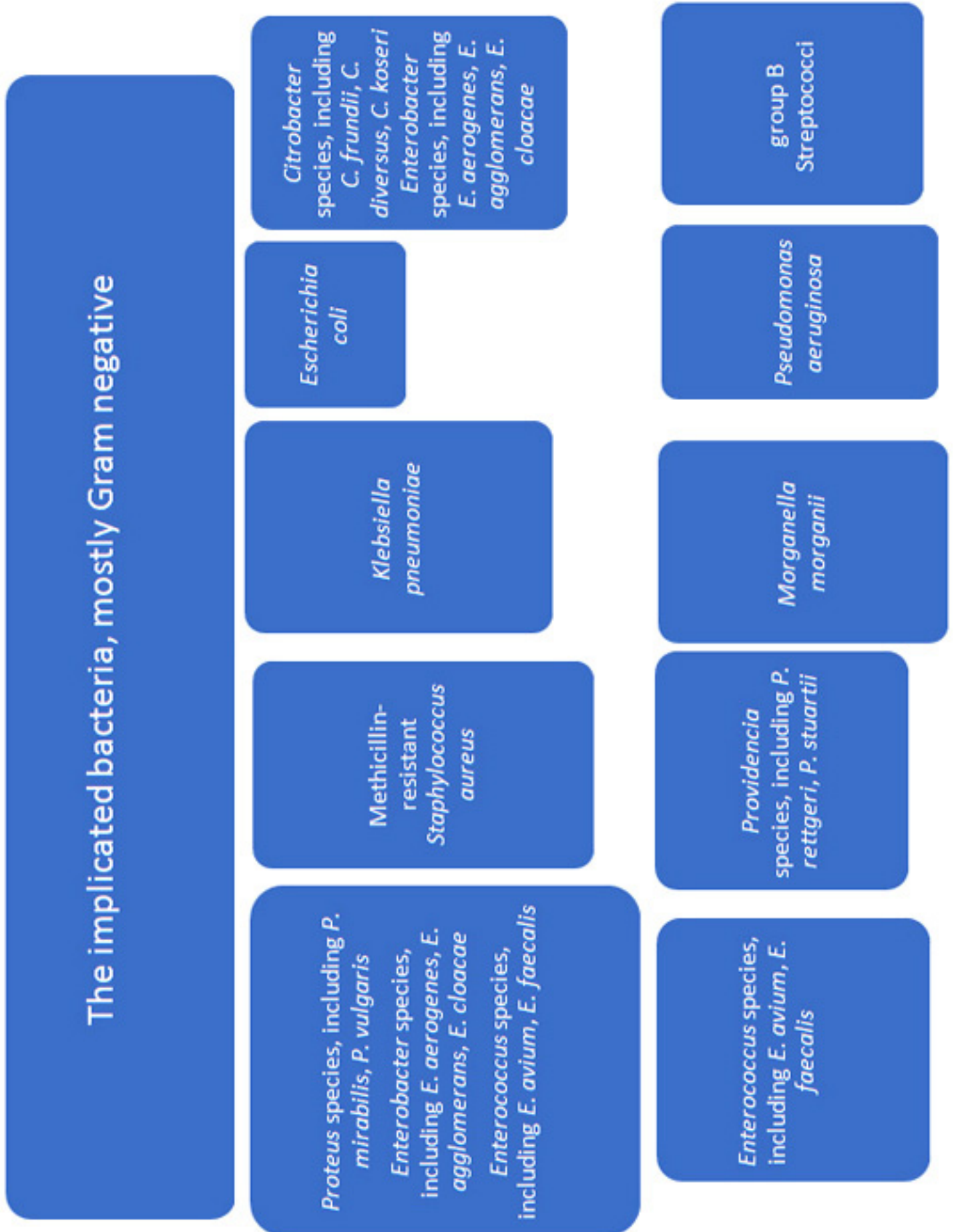
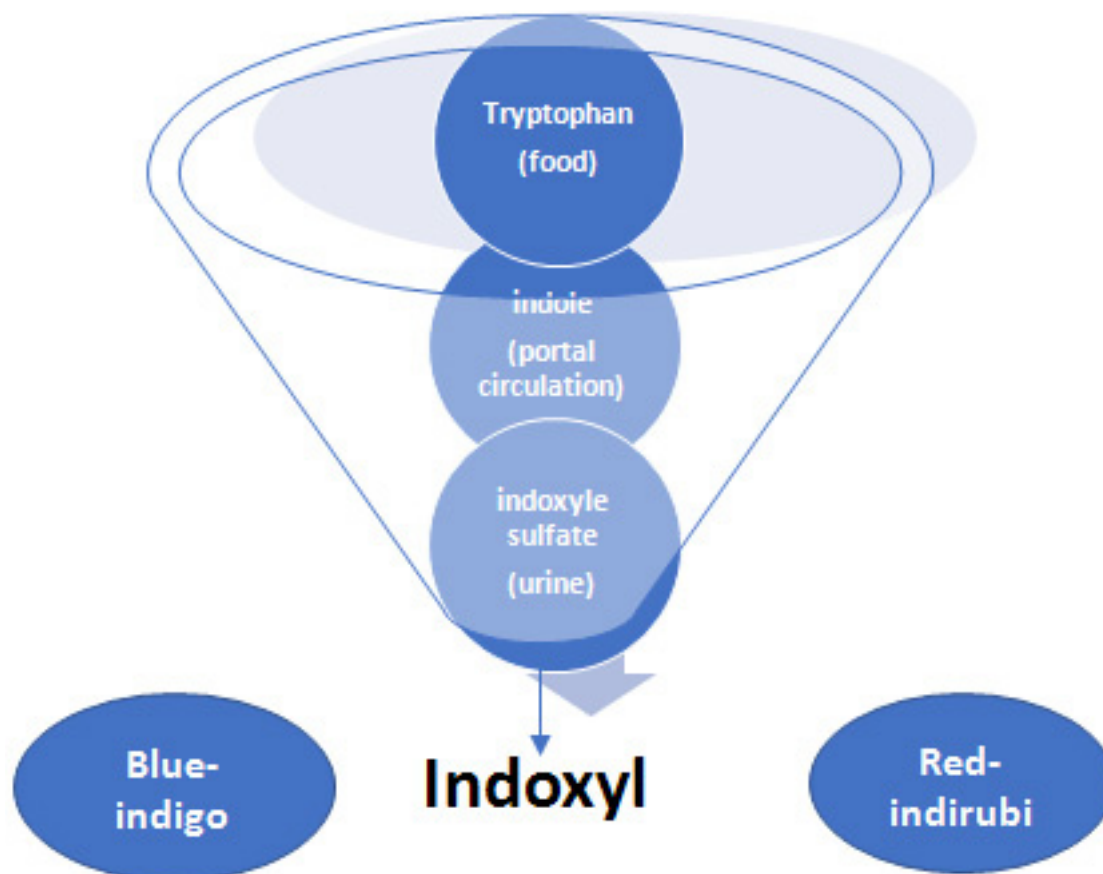


Figure 3: Process of purple urine production



Purple urine bag syndrome is a totally benign symptomless condition, but warrants attention to keep a close look at those cases. Nevertheless some health care professionals including doctors aren't aware of it and could lead to misdiagnosis of haematuria and hence over-management. Unnecessary catheters should not be kept in use for long as there is a claim they cause severe Fournier's gangrene in immunocompromised patients, plus the distress to the patients, and those surrounding the patient from the distinctive colour (Hadano et al, 2012). Therefore, reassure the patients that there is nothing to worry about. Also, it is advisable to change the catheter in those cases at least once per month to avoid this condition and lower the chance of urine bacterial infection.

The purpose of this short briefing is to create a better understanding of this condition among physicians and healthcare givers, and to serve as a reminder to remain watchful and vigilant to such cases, in order to receive a better outcome without exhausting the health resources unnecessarily (Saraireh et al, 2021), as in fact the current society is fledged of seniors who might be admitted for long time in hospitals for other ailments. The existing literature has reported around 174 cases. A few cases have died of septicaemia and aspiration pneumonia, and hence clinical assessment of each case is mandatory in order to not avoid a potential risky infection (Shin et al, 2018).

The first reported case was in 1978 in a geriatric hospital. Also, it has been said that King George III had this condition due to constipation as well.

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