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This is the first issue this year of the journal which include papers from various countries dealing with important issues.

Asiri., et al., did a quantitative cross-sectional study to evaluate nurses' perceived organizational support during the COVID- 19 pandemic in Aseer Region, Saudi Arabia.The study included 288 nurses working in 13 governmental hospitals. A self-administered questionnaire was designed by the researchers (in both English and Arabic versions), which included sociodemographic characteristics and the COVID Organizational Support Scale. Most participant were Saudi (79.5%), females (91.3%), aged 23-35 years (93.1%). About one two-thirds of nurses (61.8%) had 1-2 years of work experience in Saudi Arabia. Most nurses (87.2%) had a Bachelor degree. Most participants dealt with COVID-19 patients and had previous experience with previous outbreaks (77.8% for both). The majority of nurses agreed regarding having access to appropriate personal protective equipment (75.3%), and they can get tested for COVID-19 once they need to (70.8%). However, 90.3% of participants agreed that

they are exposed to the risk of getting COVID-19 at work and they may take the virus home to their families, while 22.2% agreed that they have access to childcare during increased work hours and school closure, and 46.5% lack access to up-to-date information and communication from healthcare system. Almost half of nurses (47.2%) perceived a poor organization support level, while 44.1% perceived good support level and only 8.7% perceived an excellent support level. Poor organizational support was most perceived by those aged 23-35 years (49.3%, p=0.044), while it was least perceived by female nurses (47.9%), non-Saudi nurses (50.8%), single nurses (48.8%), having no children (49.5%), with 1-2 years' experience in Saudi Arabia (50%), with Bachelor degree (48.6%), who deal with COVID-19 patients (50%) and with no previous experience with previous outbreaks. However, apart from nurses' age groups, differences in perceived organizational support according to nurses' personal characteristics were not statistically significant. The authors concluded that nurse perceived organizational support in Aseer Region during the COVID-19 pandemic is suboptimal. Therefore, training should be provided to nurses in order to handle and cope the increased workload during the COVID-19 pandemic, and to mitigate any experienced exhaustion.

Helvaci, et al., investigated the possibility that obesity may actually be a pre cirrhotic condition in adults. The authors followed consecutive patients with an umbilical hernia and/or a surgical repair history of the umbilical hernia were included. Although the prevalence of hypertension (HT) was also higher in the hernia group (50.0% versus 27.3%, p<0.01), mean values of triglycerides and low density lipoproteins and prevalence of white coat hypertension (WCH) were lower in them (p<0.05 for all). Although prevalences of diabetes mellitus (DM) and coronary heart disease (CHD) were also higher in the hernia patients, the differences were nonsignificant, probably due to the small sample size of the hernia group. The authors concluded that there may be some significant relationships between the umbilical hernia, obesity, cirrhosis, and other endpoints of the metabolic syndrome including HT, DM, and CHD, probably on the bases of prolonged inflammatory, atherosclerotic, and pressure effects of excessive fat tissue on abdominal wall muscles. The inverse relationships between obesity and hypertriglyceridemia and hyperbetalipoproteinemia may be explained by the hepatic fat accumulation, inflammation, and fibrosis induced relatively lost hepatic functions in obesity. Similarly, the inverse relationship between

obesity and WCH may be explained by progression of WCH into overt HT in obesity. So obesity may actually be a precirrhotic condition in adults.

Irritable bowel syndrome (IBS) is one of the frequent causes of recurrent upper abdominal discomfort in adults. Helvaci et al., looked at Acute phase reactants in irritable bowel syndrome. Consecutive patients with the IBS and age and sex-matched control cases were studied. IBS was diagnosed according to Rome II criteria in the absence of red flag symptoms including pain, diarrhea interfering with sleep, weight loss, fever, and any pathological finding in physical examination. The study included 473 patients with the IBS (308 females and 165 males) and 271 control cases. Mean age of the patients was 43.0 years. Interestingly, 65.1% of the patients with IBS were female. The authors concluded that probably IBS is a low-grade inflammatory process initiated by smoking, infections, inflammations, anxiety, depression, sleep disorders, illness fear, and cancer fear-like stresses, and eventually terminates with dysfunctions of the gastrointestinal and genitourinary tracts and elevations of ESR and CRP-like acute phase reactants (APR) in the plasma. The elevated APR will probably terminate with an accelerated atherosclerotic process all over the body and a shortened survival in both genders.

Baker, et al., reviewed the effect of regular exercise during pregnancy on duration of labor: a systematic review and meta-analysis Literature searches were undertaken; the following electronic databases were searched: PubMed, Cochrane, ProQuest Nursing, and MEDLINE. Also, the electronic database search was manual searching of reference lists in articles to locate any relevant related material that may not have been shown. The search included the late 2018 through 2022. The date of the search was 3rd of March 2022.A total of Three studies were included in the final synthesis of evidence. In this analysis, data from various other subjective were pooled together using the standardized mean difference statistic (SMD). The overall effect of regular exercise during pregnancy on duration of labor demonstrates a statistically significant difference between the intervention and control group (n=548, standardized mean difference (SMD) -1.75, 95% confidence interval (CI) -3.40 to -0.09, p = 0.04) when compared to control group. The authors stressed that the meta-analysis established that undertaking regular exercise throughout pregnancy has a positive effect on the duration of labor, and further clinical trials should be conducted to validate and replicate the findings.

NURSES' PERCEPTION OF ORGANIZATIONAL SUPPORT DURING COVID-19 PANDEMIC

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Abstract

Background: Nursing as a profession has been consistently challenging. As a result of the unstable conditions and continuous unpredictable changes in work environment due to the COVID-19 pandemic, nurses are experiencing twice the pressure than nurses who are recruited in normal circumstances. Organizational support is essential to assist nurses in reducing job-related stress.

Objective: To evaluate nurses' perceived organizational support during the COVID-19 pandemic in Aseer Region, Saudi Arabia.

Methods: A quantitative cross-sectional design was followed in Aseer Region, Saudi Arabia that included 288 nurses working in 13 governmental hospitals. A self-administered questionnaire was designed by the researchers (in both English and Arabic versions), which included sociodemographic characteristics and the COVID Organizational Support Scale.

Results: Most participant were Saudi (79.5%), females (91.3%), and aged 23-35 years (93.1%). About two-thirds of nurses (61.8%) had 1-2 years of work experience in Saudi Arabia. Most nurses (87.2%) had a Bachelor degree. Most participants dealt with COVID-19 patients and had previous experience with previous outbreaks (77.8% for both). The majority of nurses agreed regarding having access to appropriate personal protective equipment (75.3%), and getting tested for COVID-19 when they need to (70.8%). However, 90.3% of participants agreed that they are exposed to the risk of getting COVID-19 at work and they may take the virus home to their families, while 22.2% agreed that they have access to childcare during increased work hours and school closure, and 46.5% lack access to up-to-date information and communication from the healthcare system. Almost half of nurses (47.2%) perceived a poor organization support level, while 44.1% perceived good support level and only 8.7% perceived an excellent support level. Poor organizational support was most perceived by those aged 23-35 years (49.3%, p=0.044), while it was least perceived by female nurses (47.9%), non-Saudi nurses (50.8%), single nurses (48.8%), having no children (49.5%), with 1-2 years' experience in Saudi Arabia (50%), with Bachelor degree (48.6%), who deal with COVID-19 patients (50%) and with no previous experience with previous outbreaks. However, apart from nurses' age groups, differences in perceived organizational support according to nurses' personal characteristics were not statistically significant.

Conclusions: Nurses' perceived organizational support in Aseer Region during the COVID-19 pandemic is suboptimal. Therefore, training should be provided to nurses in order to handle and cope with the increased workload during the COVID-19 pandemic, and to mitigate any experienced exhaustion.

Key Words: Organizational Support; Nursing; COVID-19; Saudi Arabia.

Introduction

The global outbreak of COVID-19 in 2020 is a serious risk for healthcare providers, especially nurses. In the treatment and prevention of the disease's growing trend, nurses are vital first-line health-care providers (1).

Nursing as a profession has been consistently challenging. Taking into consideration the unstable conditions and continuous unpredictable changes in work environment due to the COVID-19 pandemic, nurses are experiencing twice the pressure than nurses who are recruited in normal circumstances (3).

During the time of COVID-19, challenges and factors causing stress that nurses face are likely to be exacerbated. Accordingly, there may be a noticeable impact on their psychological status, caused by the workplace stressors, lack of support, lack of personal protective equipment (PPE) availability and fear of being infected or to be the medium of the transmission of infection to family and loved ones (4). Additionally, several factors have separated nurses from their supportive social communities, such as work overload and social distancing (5).

Evidence has shown that the current pandemic of coronavirus has a negative impact on individual's psychological health (6-7). Although studies into the impact of the pandemic on health and well-being of nurses remains scarce, several recent publications revealed numerous stressing causes that may lead to psychological health issues (8). Consequently, organizational support is essential to assist nurses in reducing job-related stress. Literature has demonstrated that an advanced level of perceived organizational support could minimize the effect of various workplace stressors and may work as a factor protecting nurses from stress and anxiety caused by arising infectious diseases and pandemics (9).

Perceived organizational support refers to employees' perception regarding the extent to which their organization takes measures to protect their physical and psychological well-being. Additionally, perceived organizational support has many implications as it is related to job satisfaction, organizational performance and absenteeism (10).

Moreover, COVID-19, constituted a nerve-wracking factor to the nurses. Regarding COVID-19 context, recent studies have reported high levels of depressive and post-traumatic symptoms in up to 30% of healthcare workers. During this pandemic, most nurses were in urgent need of support and continued supervision until they were able to cope with their new environment and develop a sense of accountability to perform their assigned tasks (11).

The aim of this study was to evaluate nurses' perceived organizational support during the COVID- 19 pandemic in Aseer Region, Saudi Arabia.

Methodology

A quantitative cross-sectional design was followed to carry out this study in Aseer Region, Saudi Arabia. All nurses in 13 governmental hospitals were included, of which 3 hospitals were assigned as COVID-19 isolation centers, whereas the remaining hospitals were eligible for triaging COVID-19 patients and admitting them for a short-term period prior to transferring them to the center.

The estimated target sample size was determined to be 250 nurses, using purposive sampling technique G* power software, version 3.1.9.2, with the assumption that α= .05, effect size= 0.15 (medium), power level= 0.80, and number of predictors=8. However, this study included 288 nurses in the study settings to compensate for possible missing data.

Data collection instrument

A self-administered questionnaire was designed by the researchers (in English and Arabic versions), which included sociodemographic characteristics and the COVID organizational support scale (COVID-OS), which was used to assess the level of organizational support provided by the healthcare facility during the COVID-19 outbreak. It consists of eight statements with a grading scale containing 3-items to rate each of eight statements based on the level of agreement which varied between agreement, neutral or disagreement (12).

Pilot study

A pilot study was conducted on 30 nurses to test clarity of the data collection instrument and the necessary time to fill out the study questionnaire. The responses of nurses who participated in the pilot study were not included in the main study.

Data collection and Procedure:

After obtaining the ethical approval from the Research Ethical Committee at the General Directorate of Health Affairs, the researchers contacted the heads of nursing in the 13 study settings, seeking their support during data collection. Data were collected through an online version of the study questionnaire that was distributed to each targeted participant through E-mails or WhatsApp. Data collection took place during the period from July 2020 till June 2021.

Statistical analysis

Data entry and analysis were conducted using the Statistical Package for Social Sciences (IBM, SPSS, Chicago, IL, version 28). Data analyses included descriptive statistics (frequencies & percentages). For hypothesis testing, X^2 test of independence test was applied. A p-value less than 0.05 was considered as statistically significant.

Ethical considerations

An ethical clearance was given by the Ethical Committee of Aseer Directorate of Health. All participants nurses were asked for their consent before participation in the study. Moreover, anonymity and confidentiality of obtained data were completely fulfilled, as the personal identifying data (e.g., name, ID, phone number, etc.) were not requested.

Results

Table (1) shows that the majority of participant nurses were females (91.3%), and aged 23-35 years (93.1%). Most nurses (79.5%) were Saudi, single (59%), having no children (75.7%). About two-thirds of participant nurses (61.8%) had 1-2 years of work experience in Saudi Arabia. Most nurses (87.2%) had a Bachelor degree. Most participants dealt with COVID-19 patients and had previous experience with previous outbreaks (77.8% for both).

Table (2) shows that the majority of participant nurses agreed regarding having access to appropriate personal protective equipment (75.3%), and they can get tested for COVID-19 once they need to (70.8%). However, 90.3% of participants agreed that they are exposed to the risk of getting COVID-19 at work and they may take the virus home to their families. More than half of participants (58.3%) were uncertain that their organization would take care of their own needs if they get infected with COVID-19. Moreover, only 22.2% of nurses agreed that they have access to childcare during increased work hours and school closure, 30.9% can get support for other personal and family needs when work demands increase, 43% may receive competent medical care if they are deployed to a new area, and 46.5% lack access to up-to-date information and communication from the healthcare system.

Table (3) and Figure (1) show that almost half of nurses (47.2%) perceived a poor organization support level during COVID-19 pandemic, while 44.1% perceived good support level and only 8.7% perceived an excellent support level.

Table (4) shows that poor organizational support was most perceived by those aged 23-35 years (49.3%, p=0.044). Moreover, organizational support was least perceived (i.e., poor support) by female nurses (47.9%), non-Saudi nurses (50.8%), single nurses (48.8%), having no children (49.5%), with 1-2 years' experience in Saudi Arabia (50%), with Bachelor degree (48.6%), who deal with COVID-19 patients (50%) and with no previous experience with previous outbreaks. On the other hand, excellent organizational support was mostly observed among nurses aged 36-45 years, those with a Master degree (25%), and those who had no experience with similar past outbreaks (10.9%). However, apart from nurses' age groups, differences in perceived organizational support according to nurses' personal characteristics were not statistically significant.

Table 1: Personal characteristics of participant nurses

Personal characteristics	No.	%
Gender		
• Male	25	8.7
• Female	263	91.3
(Age groups (in years		
• 35-23	268	93.1
• 45-36	17	5.9
• 45<	3	1.0
Nationality		
• Saudi	229	79.5
• Saudi-Non	59	20.5
Marital status		
• Single	170	59.0
• Married	110	38.2
• Divorced/Widow	8	2.8
Having children		
• No	218	75.7
• Yes	70	24.3
Years of work experience in Saudi Arabia		
• year 1>	49	17.0
• years 2-1	178	61.8
• years 3≤	61	21.2
Qualification		
• Diploma	33	11.5
• Bachelor	251	87.2
• Master	4	1.4
Dealing with COVID-19 patients		
• Yes	224	77.8
• No	64	22.2
Experience with previous outbreaks		
• Yes	224	77.8
• No	64	22.2

Table 2: Participant nurses' responses regarding the COVID-19 perceived organizational support

Items of perceived organizational support	Disagree		Neutral		Agree	
	No.	%	No.	%	No.	%
I have access to appropriate personal protective equipment	47	16.3	24	8.3	217	75.3
I am exposed to the risk of getting COVID-19 at work and taking the virus home to my family	19	6.6	9	3.1	260	90.3
I can get tested for COVID-19 once I need to	56	19.4	28	9.7	204	70.8
I am uncertain my organization would take care of my own needs if I get COVID-19	56	19.4	64	22.2	168	58.3
People in my organization have access to child care during increased work hours and school closure	117	40.6	107	37.2	64	22.2
As work demands increase, I can get support for other personal and family needs	139	48.3	60	20.8	89	30.9
My organization can provide me with competent medical care if I am deployed to a new area	85	29.2	78	27.1	126	43.0
I lack access to up-to-date information and communication from the healthcare system	71	24.7	83	28.8	134	46.5

Table 3: Grades of available organizational support to nurses during the COVID-19 pandemic

Organizational support grades	No.	%
Poor	136	47.2
Excellent	25	8.7
Excellent	25	8.7

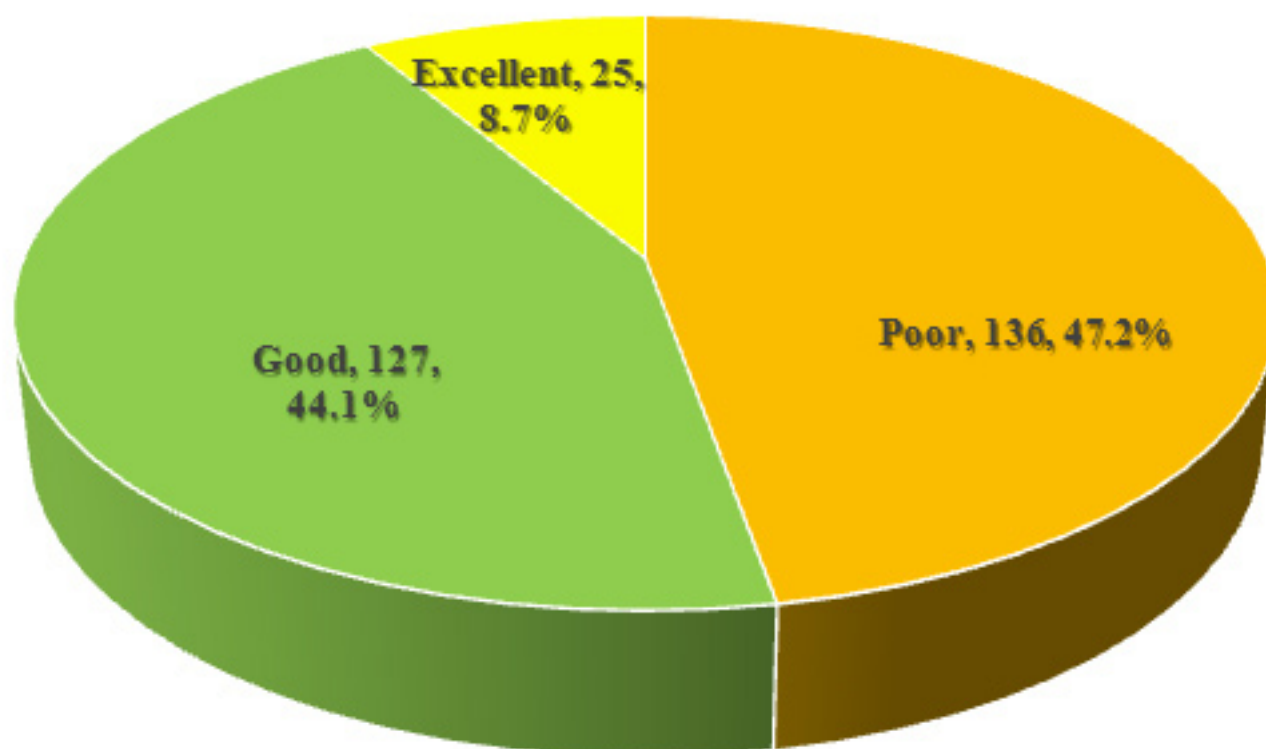**Figure 1: Grades of perceived organizational support among nurses during COVID-19 pandemic**

Table 4: Grades of received organizational support according to nurses' personal characteristics

Personal characteristics	Poor		Good		Excellent		P Value
	No.	%	No.	%	No.	%	
Gender							
• Male	10	40.0	13	52.0	2	8.0	
• Female	126	47.9	114	43.3	23	8.7	0.703
Age groups							
• years 35-23	132	49.3	114	42.5	22	8.2	
• years 45-36	4	23.5	10	58.8	3	17.6	
• years 45<	0	0.0	3	100.0	0	0.0	0.044
Nationality							
• Saudi	106	46.3	106	46.3	17	7.4	
• Saudi-Non	30	50.8	21	35.6	8	13.6	0.177
Marital status							
• Single	83	48.8	73	42.9	14	8.2	
• Married	50	45.5	50	45.5	10	9.1	
• Divorced/Widow	3	37.5	4	50.0	1	12.5	0.954
Having children							
• No	108	49.5	92	42.2	18	8.3	
• Yes	28	40.0	35	50.0	7	10.0	0.380
Work experience in Saudi Arabia							
• year 1>	21	42.9	25	51.0	3	6.1	
• years 2-1	89	50.0	72	40.4	17	9.6	
• years 3<	26	42.6	30	49.2	5	8.2	0.459
Qualification							
• Diploma	13	39.4	18	54.5	2	6.1	
• Bachelor	122	48.6	107	42.6	22	8.8	
• Master	1	25.0	2	50.0	1	25.0	0.492
Dealing with COVID-19 patients							
• Yes	112	50.0	92	41.1	20	8.9	
• No	24	37.5	35	54.7	5	7.8	0.149
Experience with similar past outbreaks							
• Yes	47	45.2	47	45.2	5	4.8	
• No	89	48.4	89	48.4	20	10.9	0.120

Discussion

Findings of the present study revealed suboptimal perceived organizational support among nurses in Aseer Region during the pandemic of COVID-19. Almost half of the nurses perceived a poor level of organizational support, while 44.1% perceived a good support level, while only 8.7% perceived excellent support.

Kurtessis et al. (13) noted that there are various ways of conveying to employees that their organization cares about their well-being and values their contributions. Supportive aspects of leadership, fairness, human resources practices, and working conditions were all related to better perceived organizational support. In addition, predictions, based on processes of organizational support theory involving social exchange, attribution, and self-enhancement, were generally successful in accounting for working conditions to perceived organizational support, as well as the relationship of this support with employees' positive orientation toward the organization, subjective well-being, and behaviors helpful to the organization. Taken as a whole, perceived organizational support plays a central role in the employee–organization relationship and has important implications for improving employees' well-being and favorable orientation toward the organization.

Several studies stressed that a challenging work environment, with increased work demands, associated with lack of organizational support can be linked to deterioration

of mental and physical health in healthcare workers (14-16). Moreover, mental and psychological distress among healthcare workers have been associated with poor quality of care, less productivity and increased risk for errors (17). Therefore, it is important for health organizations to identify the organizational needs of their healthcare workers and to ascertain the impact of organizational aspects on their employees' mental health (18).

Lilja et al. (19) emphasized the positive relationship between home and work conflict. This means that difficulties with balancing home and work life during the COVID-19 pandemic among professional, technical employees, and healthcare workers was related to higher levels of exhaustion. Moreover, increased workload is positively related to workers' exhaustion. This means that the greater the workload induced during the COVID-19 pandemic, the more exhaustion is experienced.

Several studies found an increase in workload was associated with subsequent negative aspects of employee well-being (20-22). Gudmundsdottir and Hathaway (23) added that this result may be related to workers' resilience and coping abilities during times of rapid transition and changing work practices.

Results of the present study showed that despite most nurses having access to appropriate personal protective equipment, and testing for COVID-19 once they need to, the majority expressed their fears toward being exposed to the risk of getting COVID-19 at work and that they may take the virus home to their families. Moreover, most nurses felt uncertain that their organizations would care about their own needs if they get infected with COVID-19. Access to childcare during increased work hours and school closure was limited to about one-fifth of nurses, about one-third of nurses can get supportfor other personal and family needs when work demands increase, 43% may receive competent medical care when deployed to a new area, and almost half of them lack access to up-to-date information and communication from the healthcare system.

It has been reported that organizational support, or the extent to which an organization commits to providing resources, reinforcing, encouraging, and communicating with its members, is a critical determinant of organizational success (24). Higher levels of organizational support may help to reduce the impact of multiple workplace stressors and protect employees from stress caused by disasters, catastrophes, and new diseases (9).

Several studies confirmed that fear of infection for COVID-19 is a straining job demand and constitutes one of the major stressors in nursing practice (21-22; 25-26). Galanis et al. (27) cautioned that nurse burnout is a major problem during the current COVID-19 epidemic. Therefore, nurses need better training to handle and cope with stressful situations during the pandemic.

Gualano et al. (28) argued that, since the initial outbreak of the COVID-19 pandemic, reports have highlighted the impact of the pandemic on healthcare workers' mental and psychological health. Nevertheless, only a few studies have explored organizational factors in relation to mental health outcomes during the pandemic, including dimensions of organizational support to HCWs (12; 29-30). These dimensions included education in self- protection, provision of protective equipment and psychological support and participation in decision making (14). A recent review pointed out the heterogeneity regarding the psychological and organizational measures used, as well as their cultural context; however, these findings support the association between organizational characteristics and mental health status of employees (31). Moreover, previous studies were conducted in a specific cultural context, thus jeopardizing the generalization of their findings (15-16).

Our study showed that, among nurses working in Aseer Region, poor organizational support was significantly most perceived by younger nurses (aged 23-35 years). Also, it was most perceived by nurses who are females, non-Saudi, single, having no children, with 3-4 years' experience in Saudi Arabia, with Bachelor degree qualification, who deal with COVID-19 patients and with no previous experience with similar epidemics. On the other hand, excellent organizational support was mostly observed among older nurses (aged 36-45 years), those with a Master degree, and those who had no experience with similar past outbreaks.

These findings are in accordance with those reported by several international studies. Naushad et al. (32) noted that nurses who provide care to patients infected with SARS-CoV-2 are at a high risk of developing psychological problems, as well as other mental health problems. They added that nurses may suffer from mental distress due to a variety of aspects, including personal protection equipment, an increasing number of confirmed and suspected cases, a lack of specific medications, burdensome workloads, extensive media coverage, and a sense of not being sufficiently supported.

In addition, an increased frequency of psychiatric symptoms has been reported in healthcare workers who dealt with previous relevant crises or outbreaks. A number of personal, work-related and organizational factors have been identified as risk factors for developing psychiatric symptoms in employees (33-34).

Consistent with organizational support theory's view that higher-level employees (e.g., older employees and those with postgraduate qualifications), who are usually senior supervisors, are more closely identified with the organization than lower-level employees and co-workers. Supervisors may vary in the degree to which they are identified with the organization and that favorable leadership by supervisors so identified is strongly linked to perceived organizational support (35-36).

Conclusions

Consistent with organizational support theory's view that higher-level employees (e.g., older employees and those with postgraduate qualifications), who are usually senior supervisors, are more closely identified with the organization than lower-level employees and co-workers. Supervisors may vary in the degree to which they are identified with the organization and that favorable leadership by supervisors so identified is strongly linked to perceived organizational support (35-36).

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EFFECT OF REGULAR EXERCISE DURING PREGNANCY ON DURATION OF LABOR: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: Many women decide to focus on and improve their lifestyle when they discover that they are pregnant and exercise is an effective tool for preventing pregnancy-linked illnesses. This systematic review set out to investigate whether taking regular exercise during pregnancy impacts on the length of a woman's labor.

Method: Literature searches were undertaken; the following electronic databases were searched: PubMed, Cochrane, ProQuest Nursing, and MEDLINE. Also, the electronic database search was manual searching of reference lists in articles to locate any relevant related material that may not have been shown. The search was conducted from late 2018 through to 2022. The search was completed on 3rd of March 2022.

Results: A total of three studies were included in the final synthesis of evidence. In this analysis, data from various other subjective studies were pooled together using the standardized mean difference statistic (SMD). The overall effect of regular exercise during pregnancy on duration of labor demonstrates a statistically significant difference between the intervention and control group (n=548, standardized mean difference (SMD) -1.75, 95% confidence interval (CI) -3.40 to -0.09, p = 0.04).

Conclusion: This meta-analysis established that undertaking regular exercise throughout pregnancy has a positive effect on the duration of labor, and further clinical trials should be conducted to validate and replicate our findings.

Keywords: Exercise, Labor duration, pregnancy

Introduction

Giving birth is a tense and traumatic event in every woman's life, and each pregnancy and labor differs. However, getting ready for delivery can be a positive way of minimizing undesirable responses during labor itself. A number of studies have examined how exercise effects pregnancy and have reached mixed conclusions, in relation to premature labor, intrauterine growth restriction, gestational diabetes (GDM), pregnancy-induced hypertension (PIH), levels of pain during labor, the length of labor and the possibility of Caesarean section (1,2).

The World Health Organization (3) has stated that lack of physical activity is one of the main reasons for global mortality, since a sedentary lifestyle places individuals at risk of developing cardiovascular disease as well as diabetes mellitus (4). Physical exercise is defined as scheduled physical and mental activities undertaken to increase physical fitness, and is an important element of having a healthy lifestyle and becoming more robust and thus healthier (5).

Pregnancy is a good time to start exercising, because women normally re-evaluate their lifestyle at this point and resolve to be healthier. In addition, one of the benefits of exercise is that it can help to forestall illnesses which are linked to pregnancy, namely gestational diabetes, excessive weight gain during pregnancy, hypertensive conditions, urinary incontinence, fetal macrosomia, pain in the lumbo-pelvic region, stress and prenatal depression (6). Pregnant women should be advised and encouraged to take part in physical activities, and provided with information on both the benefits and the risks of exercise during pregnancy (7).

Duration of labor is a term which is used to describe Stage 1 and Stage 2 of the process of giving birth, with Stage 1 being defined as the period when the cervix dilates from three to ten centimeters and uterine contractions are regular. Stage 2 refers to the time between the cervix being fully dilated and the delivery of the baby. A number of studies have shown that labor is shorter and has fewer complications when women who have never given birth are aerobically fit and healthy. Exercise during pregnancy is therefore beneficial for the health of the mother (8).

To the best of the authors' knowledge, no researchers have studied whether regular exercise during pregnancy has a direct effect on the duration of labor, and this systematic review sets out to fill this knowledge gap. The main research question which this meta-analysis paper addresses is: What are the reported effects of regular exercise in pregnancy on the duration of labor?

Materials and Methods

The present study used the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) as a guideline for reporting the findings (9).

Search strategy

The literature review was conducted by extensive searching of multiple databases in health sciences and nursing. Literature searches were undertaken; the following electronic databases were searched: PubMed, Cochrane, ProQuest Nursing, and MEDLINE. Also, the electronic database search involved manual searching of reference lists in articles to locate any relevant related material that may not have been shown. Multiple keywords were used, including the terms: "Pregnant women," "Labor," "duration of labor," " physical activity, " and "physical Exercise, ". Each of the keywords were used independently and in combination. The search included the late 2018 through 2022. The date of completion of the search was 3rd of March 2022.

Inclusion criteria

Studies were included if they were published in a peer-reviewed journal, written in English, published within the last five years between 2018 and 2022, and focused on the effects of regular exercise in pregnancy on the duration of labor, studies about the pregnant women without contraindication to exercise, and RCT only.

Exclusion criteria

Studies were excluded if they met any of the following criteria:

• Studies not involving pregnant women practicing regular exercise and its effects on the duration of labor.

• Discussion papers, dissertations, narratives, opinion articles, and editorials.

• Studies published in any language rather than English.

Validity assessment

The principal outcome of this review was to report the effect of regular exercise during pregnancy on duration of labor. Two authors independently carried out a review of titles and abstracts based on the inclusion/exclusion criteria.

Data Abstraction

Two authors performed the initial data abstraction in duplicate. Any discrepancies regarding study eligibility were discussed with the other authors to reach a consensus. To standardize the data abstraction, the following variables that were taken out for data analysis included the author, the year of study, location, as well as labor duration, the number of participants in each group, and the mean and standard deviation of labor duration. Extracted data were entered into Microsoft Excel Sheet for analysis.

Study characteristics

Two authors performed the data analysis. The obtained data were analyzed by Review Manager software, version 5.4.1 (RevMan), and the mean difference (MD) of labor duration, along with its 95% CI, which was calculated as summary measures. Furthermore, the chi-square test was applied based on Q-test and I2 statistics with a significance level of <0.00001 to evaluate the potential heterogeneity among the studies. The I2 statistics ranged from 0%-100%, and the high value indicated high inconsistency among the studies. Consequently, the random-effects model was utilized to estimate the pooled effect based on the rejection of the homogeneity hypothesis. The Z test determined the significance of the overall mean difference, and P<0.05 was considered statistically significant.

Critical appraisal of studies (quality assessment)

Quality assessment was conducted using the items in the Consolidated Standards of Reporting Trials checklist, including participants' eligibility criteria, the interventions for each group with sufficient essential details, completely defined outcome measures, the type of randomization, allocation concealment mechanism, statistical methods of group comparison for the outcomes, and the results for each group, along with the estimated effect size and its precision. The studies were grouped as high-quality data if they met all the required criteria or failed to meet only 1 or 2 items; otherwise, they were included in the low-quality group when not meeting more than two items. Then two researchers independently performed the quality assessment. Finally, the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement was used to report this study's findings which is presented in Table 1.

Results

Search strategy results

Figure 1 depicts the PRISMA flow diagram of the search strategy and the process of study selection. A total of 1,730 articles were retrieved from databases. After removing duplicate citation and screening for relevancy, 6 full-text articles were assessed for eligibility. Additionally, the three publications that reported the results separately were entered into meta-analysis as separate studies. The results of chi-square Q-test and I2 statistics revealed the heterogeneity between the studies (Tau2=2.08, Chi2=111.65, df=2 P<0.00001, and I2 =98.0%) duration of labor [Figures 2 and 3].

Literature search

One thousand, seven hundred and thirty articles were established through database searching via the following search engines—PubMed, yCochrane, ProQuest, and MEDLINE. Thirty-seven articles were removed due to duplication. The deleted records have the same title, author, and publication year. The remaining records (n=1693) were exported to an Excel file. The extensive screening by two independent reviewers using the inclusion and exclusion criteria resulted in the elimination of 1687 articles, leaving six full-text articles that were downloaded for consideration. Three articles were excluded for the following reasons: irrelevant to the aim of the study and lack of sufficient data.

Study characteristics and Risk of bias

The total number of participants in all of the studies was 548, with sample sizes ranging from 325 to 104. Two hundred and eighty-seven participants were included in the intervention groups, while 261 participants were enrolled in the control groups. The types of regular exercise included in the studies were moderate aerobic exercise programs throughout pregnancy (10), Pilates exercises (11), and Water Exercise during Pregnancy (12). One study provided aerobic exercise intervention from 9 weeks to the end of the third trimester (10). Another study provided the intervention of Pilates exercises from 26 to 28 weeks of gestation (11). Moreover, one study which provided the intervention of SWEP (Study of Water Exercise during Pregnancy) began in week 20 of gestation and ended in week 37 (12). The frequency of the regular exercise intervention ranged from two to three weekly sessions. One study performed a Pilates exercise program twice a week (11). Two studies performed an aerobic and Water Exercise of three sessions per week (10,12).

The Risk bias was conducted by using the Cochrane Collaboration's software RevMan 5.4. In terms of the randomization process, three studies described the process randomization. They assessed it as having a low risk of bias (10, 11, 12). One study did not provide the information on the allocation concealment and was judged to have a high risk of bias (18). In addition, one study failed to blind the participants and investigator with a detection bias considered a high risk (12); the remaining two studies had a low-risk bias (10,11). For attrition bias, all studies were rated as having a low risk of bias (10,11,12). Also, in terms of the reporting bias, all the studies were assessed as low risk (10, 11, 12). [Figure 4].

Quantitative data synthesis

In this analysis, data from various other subjective studies were pooled together using the standardized mean difference statistic (SMD). The overall effect of regular exercise during pregnancy on duration of labor demonstrates a statistically significant difference between the intervention and control group (n=548, standardized mean difference (SMD) -1.75, 95% confidence interval (CI) -3.40 to -0.09, p = 0.04) when compared to control group, with evidence of heterogeneity (p = 0.00001, I2 = 98%). The results of the meta-analysis in these subgroups show that regular exercise significantly reduces the duration of labor in the intervention group when compared to the control group among pregnant women.

Table 1: Characteristics of included studies in Meta- analysis regarding the effects of regular exercise on duration

Study	Year	Location	Intervention	Control	Quality
Barakat et al., 2018	2018	Madrid, Spain.	176	149	High
Rodríguez-Blanque et al., 2019	2019	Granada, Spain	60	60	High
Ghandali et al., 2021	2021	Iran	51	52	High

Figure 1: PRISMA Flow chart of the study. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta Analyses
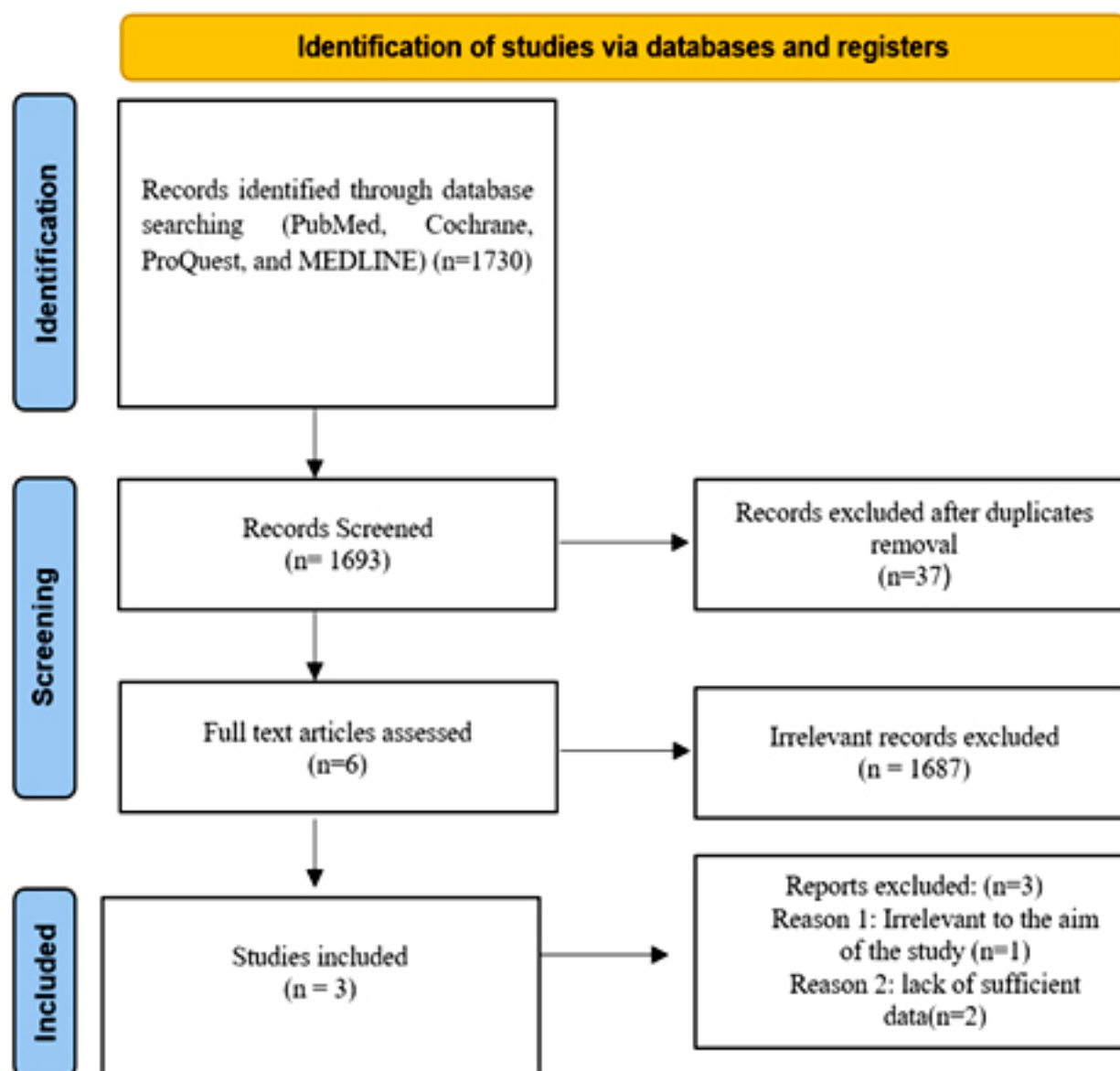
Figure 2: Forest plot depicting results from meta-analysis of three randomized controlled trials. Extensions from the boxes represent 95% confidence intervals. The sizes of the boxes represent the weight assigned to each study. The center diamond shows the pooled estimate of the effect size, and the width of the diamond indicates the 95% confidence interval for the pooled estimate.

| Study or Subgroup | Experimental | | | Control | | | Weight | Std. Mean Difference | Year |
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI	
Barakat et al., 2018	442.37	188.72	176	499.04	215.84	149	34.1%	-0.28 [-0.50, -0.06]	2018
Rodriguez et al., 2019	389.33	216.18	60	561.3	199.94	60	33.7%	-0.82 [-1.19, -0.45]	2019
Ghandali et al., 2021	170.42	15.2	51	247.54	20.29	52	32.2%	-4.26 [-4.97, -3.56]	2021
Total (95% CI)			287			261	100.0%	-1.75 [-3.40, -0.09]	

Heterogeneity: Tau^2 = 2.08; Chi^2 = 111.65, df = 2 (P < 0.00001); I^2 = 98%
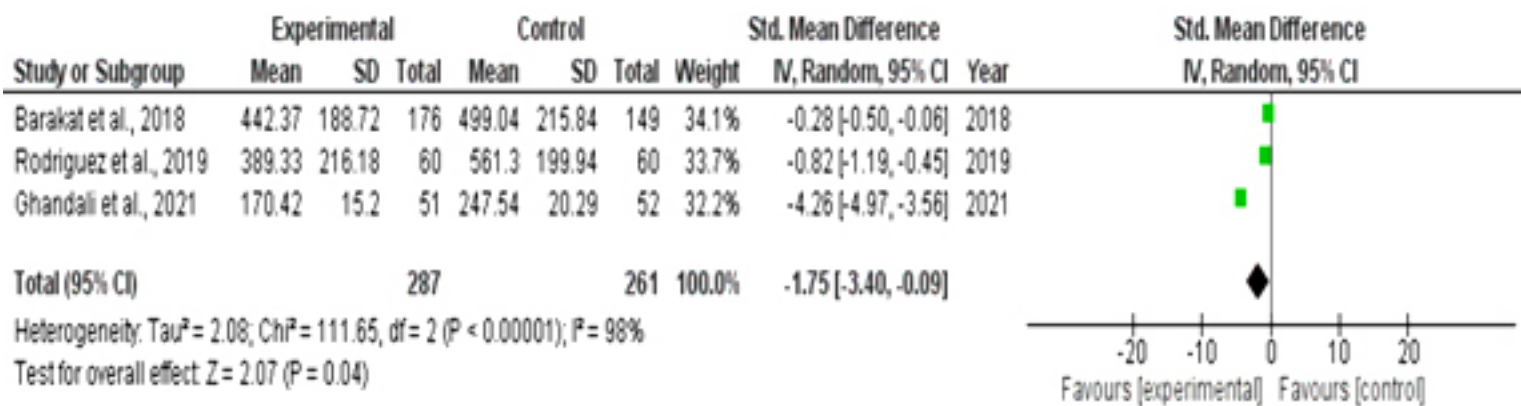Test for overall effect: Z = 2.07 (P = 0.04)

Figure 3: Funnel plot comparison of Physical Exercise on Duration of Labor.
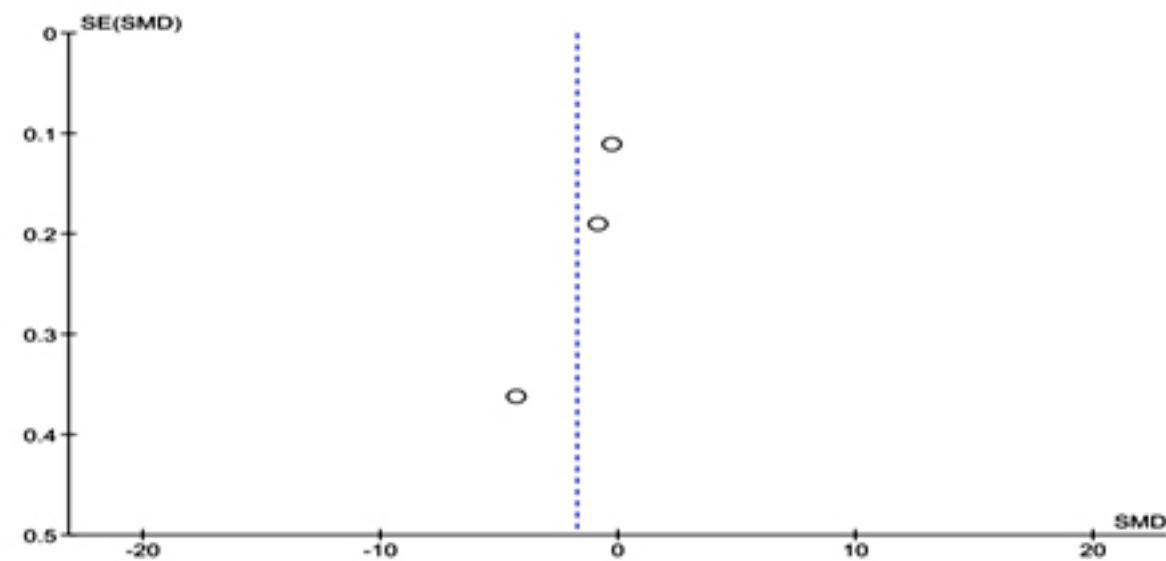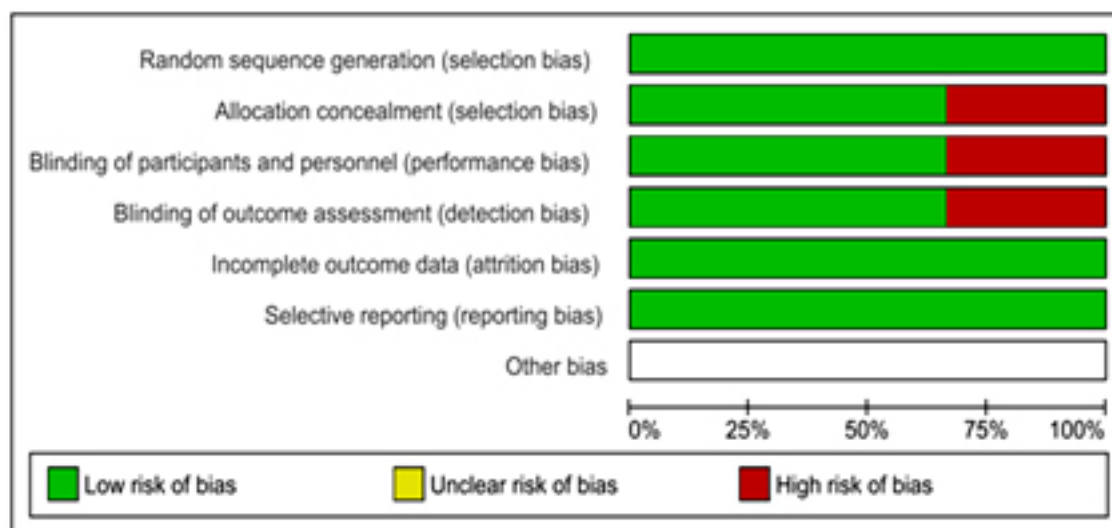
Figure 4. (a) Risk of bias graph: review authors' judgment about each item's risk of bias item presented as percentage across all included studies; (b) risk of bias summary: review authors' judgments about each item's risk of bias for each included study (+, low risk; ?, unclear; -, high risk)

(a) Risk of bias graph

(b) Risk of bias summary

Discussion

The findings of this meta-analysis, based on 548 participants in three RCTs, demonstrated that the intervention group, which took regular exercise during pregnancy, had statistically significant shorter labor than the control group, which did not exercise while pregnant. However, while the findings indicate that regular exercise during pregnancy has a major effect, there was a high degree of divergence in the results. This could be due to participants having different characteristics, ages, and their viewpoints, based on their geographical location. The exercises which were included in the studies were made up of: moderate aerobics throughout pregnancy (10), Pilates exercises (11) and water exercise during pregnancy (12). The conclusion mirrors those of Sandra et al. (13) in a combined analysis of 550 participants, which determined that women who were highly physically active in late pregnancy were less likely to have an emergency Caesarean delivery than women who had not been physically active. Makvandi et al. (14) added that it has been established that acupuncture shortens the length of the active phase of labor (95% CI –1.738 to –0.882; Pb0.001), as well as the second stage of labor (95% CI –1.615 to –0.807; Pb0.001).

A range of meta-analyses have established the positive effects of aquatic exercise programs, and found that they are helpful in controlling heart rate and blood glucose levels, preventing disproportionate weight gain, and improving balance and mobility in pregnant women. These exercise programs make it more likely that a healthy, pregnant woman will have a normal delivery (15,16).

Not all researchers agree, however, and Davenport et al. (17) for example, conducted a meta-analysis which concluded that there were no links between the regularity, intensity, volume and duration of exercise, and subsequent labor and delivery outcomes. Veisy et al. (18) also carried out a meta-analysis which found no statistically significant effect on a range of neonatal and maternal outcomes, including: the first, second and third stages of labor, gestational age at birth, Apgar scores taken at the first and fifth minute, the pH of the umbilical cord, neonatal weight, height and head circumference (p > .05). The current meta-analysis will have an effect on healthcare practice, since it argues that being physically active during pregnancy offers a number of key benefits. As a result, both nurses and nurse administrators should encourage pregnant women to be physically active, in order to improve both their own and their newborns' health outcomes. There are many benefits to exercising regularly during pregnancy, including the prevention of undesirable effects and complications during labor. Future research should focus on the long-term effects of regular exercise during pregnancy and determine how it impacts on the duration of labor.

This study has a number of limitations, since the search strategy only included studies which focused on singleton, low-risk, pregnant women. In addition, some of the studies had a clear selection and performance bias, which could have distorted or otherwise exaggerated the results. Finally, three of the included studies contained randomized control trials which met this meta-analysis' inclusion criteria.

In summary, our meta-analysis found that regular exercise during pregnancy has a positive effect on the duration of labor. Future clinical trials are now needed to establish the effects of taking regular exercise on the duration of labor.

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OBESITY MAY ACTUALLY BE A PRECIRRHOTIC CONDITION IN ADULTS

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Abstract

Background: There may be some significant relationships between the umbilical hernia, obesity, and cirrhosis during the process of metabolic syndrome in adults.

Method: Consecutive patients with an umbilical hernia and/or a surgical repair history of the umbilical hernia were included.

Results: There are 46 patients with the umbilical hernia with a mean age of 62.0 years, and 73.9% of them were female. Body mass index was higher in the hernia patients (33.6 versus 29.1 kg/m2, p= 0.000). Although the prevalence of hypertension (HT) was also higher in the hernia group (50.0% versus 27.3%, p<0.01), mean values of triglycerides and low density lipoproteins and prevalence of white coat hypertension (WCH) were lower in them (p<0.05 for all). Although prevalences of diabetes mellitus (DM) and coronary heart disease (CHD) were also higher in the hernia patients, the differences were nonsignificant, probably due to the small sample size of the hernia group.

Conclusion: There may be some significant relationships between the umbilical hernia, obesity, cirrhosis, and other endpoints of the metabolic syndrome including HT, DM, and CHD, probably on the bases of prolonged inflammatory, atherosclerotic, and pressure effects of excessive fat tissue on abdominal wall muscles. The inverse relationships between obesity and hypertriglyceridemia and hyperbetalipoproteinemia may be explained by the hepatic fat accumulation, inflammation, and fibrosis induced relatively lost hepatic functions in obesity. Similarly, the inverse relationship between obesity and WCH may be explained by progression of WCH into overt HT in obesity. So obesity may actually be a precirrhotic condition in adults.

Key words: Obesity, cirrhosis, metabolic syndrome, umbilical hernia, hepatosteatosis, atherosclerosis, end-organ insufficiency

Introduction

The endothelium is a monolayer of endothelial cells which constitutes the inner cellular lining of artery, vein, capillary, and lymphatics. It is the major player in the control of blood fluidity, platelets aggregation, and vascular tone. It may be the major actor in immunology, inflammation, and angiogenesis. It may also be important in the endocrinology. The endotelial cells control vascular tone and blood flow by synthesizing and releasing nitric oxide, metabolites of arachidonic acid, and reactive oxygen species. Additionally, they are also important for generation of vasoactive hormones such as angiotensin II. An endothelial dysfunction linked to an imbalance in the synthesis and/or release of these endothelial factors may explain the initiation of several cardiovascular pathologies including hypertension (HT) and atherosclerosis. On the other hand, chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in human being (1, 2). Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Therefore 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, sedentary lifestyle, excess weight, animal-rich diet, smoking, alcohol, chronic inflammations, and prolonged infections for the development of terminal consequences including obesity, HT, type 2 diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, end-organ insufficiencies, cancers, early aging, and premature death (3, 4). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, cancers, and aging, endothelial changes can not be reversed completely due to their fibrotic natures (5, 6). The accelerating factors and terminal endpoints are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature, extensively (7, 8). On the other hand, there may be some significant relationships between the umbilical hernia, obesity, and cirrhosis during the process of metabolic syndrome in adults.

Material and methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and January 2010. Consecutive patients with an umbilical hernia and/or a surgical repair history of the umbilical hernia were collected in the first, and age and sex-matched controls were collected into the second groups. Their medical histories including smoking habit, and already used medications were learnt, and a routine check up procedure including fasting plasma glucose (FPG), triglycerides, low density lipoproteins (LDL), and an electrocardiography was performed. Current daily smokers at least for the last six months and cases with a history of five pack-years were accepted as smokers. Insulin using diabetics and patients with devastating illnesses including malignancies, chronic renal failure, decompensated cirrhosis, uncontrolled hyper- or hypothyroidism, and congestive heart failure were excluded to avoid their possible effects on weight. Body mass index (BMI) of each case was calculated by the measurements of the Same Clinician instead of verbal expressions. Weight in kilograms is divided by height in meters squared (9). Office blood pressure (OBP) was checked after a five-minute of rest in seated position with the mercury sphygmomanometer on three visits, and no smoking was permitted during the previous two-hour. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in normotensives in the office due to the risk of masked hypertension after a 10-minute education about proper BP measurement techniques (10). A 24-hour ambulatory blood pressure monitoring (ABP) was not required due to its equal effectiveness with HBP measurements (11). Eventually, HT is defined as a BP of 135/85 mmHg or greater on HBP measurements (10). White coat hypertension (WCH) is defined as an OBP of 140/90 mmHg or greater but mean HBP of lower than 135/85 mmHg, and masked HT as an OBP of lower than 140/90 mmHg but mean HBP of 135/85 mmHg or greater (10). Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already taking antidiabetic medications were defined as diabetics. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 100 and 125 mg/dL, and diagnosis of cases with a two-hour plasma glucose level of 200 mg/dL or higher is DM (9). A stress electrocardiography was performed in suspected cases, and a coronary angiography was obtained only for the stress electrocardiography positive cases. Eventually, mean weight, height, BMI, triglycerides, and LDL values and prevalences of smoking, WCH, HT, DM, and CHD were detected in each group, and results were compared in between. Mann-Whitney U Test, Independent-Samples T Test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 46 patients in the umbilical hernia and 84 cases in the control groups. Mean age of the umbilical hernia patients was 62.0 years, and 73.9% of them were female. Prevalence of smoking was lower in the umbilical hernia group, nonsignificantly (13.0% versus 19.0%, p>0.05). Although the mean heights of the two groups were similar (157.4 versus 158.7 cm, p>0.05), the umbilical hernia patients were heavier than the control cases, significantly (85.1 versus 73.1 kg, p= 0.001). As a result, the BMI was also higher in the umbilical hernia patients, significantly (33.6 versus 29.1 kg/m2, p= 0.000). Interestingly, although the significantly higher mean weight and BMI of the patients with the umbilical hernia, the mean triglycerides and LDL values and prevalence of WCH were significantly lower in them (p<0.05 for all). On the other hand, prevalence of HT was significantly higher in the umbilical hernia group (50.0% versus 27.3%, p<0.01). Although the prevalences of DM and CHD were also higher in the umbilical hernia group, the differences were nonsignificant, probably due to the small size of the umbilical hernia group (Table 1).

Table 1: Characteristic features of the study cases

Variables	Cases with umbilical hernia	p-value	Control cases
Number	46		84
Female ratio	73.9%	Ns*	73.8%
Mean age (year)	62.0 ± 13.2 (29-82)	Ns	62.2 ±13.0 (29-83)
Prevalence of smoking	13.0%	Ns	19.0%
Mean weight (kg)	85.1 ± 20.8 (54-172)	0.001	73.1 ±13.1 (44-104)
Mean height (cm)	157.4 ±11.2 (134-191)	Ns	158.7 ±10.0 (138-181)
Mean BMI‡ (kg/m2)	33.6 ± 5.7 (21.0-47.1)	0.000	29.1 ±5.4 (17.2-42.9)
Mean triglycerides (mg/dL)	119.6 ±69.2 (49-361)	0.041	145.9 ± 76.9 (56-394)
Mean LDL‡ (mg/dL)	120.2 ±35.5 (49-193)	0.042	138.0 ± 42.1 (10-239)
Prevalence of WCH§	23.9%	<0.05	41.6%
Prevalence of overt HT‖	50.0%	<0.01	27.3%
Prevalence of DM¶	30.4%	Ns	28.5%
Prevalence of CHD**	17.3%	Ns	13.0%

*Nonsignificant (p>0.05) †Body mass index ‡Low density lipoproteins §White coat hypertension

‖Hypertension ¶Diabetes mellitus **Coronary heart disease

Discussion

The umbilical hernias are frequent anomalies of the abdominal wall muscles in both genders. Most of the umbilical hernias have an acquired origin, and only 10% of them have congenital causes in adults (12). They are more common in women both in children and adults (13). They are more common under the age of four and over the age of 50 years with unknown reasons, yet (13). They are especially common in premature babies (up to 84%), overweight children, and middle-aged multiparous women. According to the literature, their prevalences are around 2% in adults. As also observed in the present study, the umbilical hernias are frequently seen with terminal endpoints of the metabolic syndrome including obesity, HT, DM, cirrhosis, CHD, PAD, COPD, CRD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and cancers. There are not big differences in the frequency between the various ethnic groups in adults, supporting the possible acquired etiologies such as the metabolic syndrome (13). The umbilical hernias occur when a part of the intestine protrudes through a weak spot in the abdominal wall muscles at the site of umbilicus. Babies are prone to this malformation due to the process of fetal development during which abdominal organs develop outside the abdominal cavity, and then, they come into the abdominal cavity through an opening which will become the umbilicus later. Importantly, the umbilical hernias must be distinguished from paraumbilical ones, defects in one side of the midline at the umbilical region in adults, and from omphaloceles in newborns. Most umbilical hernias close on their own by the age of one year, although up to 10% may take longer to heal in infants. To prevent complications, the umbilical hernias those do not disappear by the age of four years or those appear during adulthood may need surgical repair operations. The umbilical hernias may become incarcerated or strangulated, but the risk is low, since the underlying defect of the abdominal wall muscles is larger than found in the inguinal ones. The risk of incarceration is half of the inguinal hernias, but three times higher than the femoral ones in the previous study (14). Up to 90% of incarcerated hernias of umbilicus occur in women with a mortality rate up to 25% (14). There is also a higher risk of incarceration in the cirrhotics receiving medical treatment for ascites, carrying an implant of a peritoneo-venous shunt, or getting an evacuating paracentesis (15). The higher prevalence of umbilical hernias in cirrhosis may also support the pressure effect of intra-abdominal fluid on abdominal wall muscles (16). Obesity, pregnancy, ascites, and peritoneal dialysis induced distensions of the abdominal wall may cause pulling of the muscles and deterioration of connective tissue over the umbilicus. The frequent association of the umbilical hernias with other abdominal wall defects may also support the possible etiologic role of the biophysical changes (13). In the previous study of umbilical hernias, 42% of them were associated with another hernia, and 5% of them were associated with more than two hernias (13). Abnormal dispositions of the umbilical fascia may be one of the factors contributing to herniations (17). Tendinous fibers coming from the muscles of both sides of the abdominal wall decussate obliquely at the linea alba, acquiring different levels of complexity (18). Simpler decussations may be found in cases with umbilical hernias in which the sac protrudes at the midline. Obesity, pregnancy, ascites, and peritoneal dialysis induced excess pressure on abdominal wall muscles may facilitate rupture of the fibers which decussate in a simple fashion at the linea alba on the umbilicus. In contrast, patients with more complex (triple) decussations may present with paraumbilical hernias in the above conditions. On the other hand, recanalized umbilical veins and deterioration of connective tissue secondary to the accelerated atherosclerotic process of the metabolic syndrome may also facilitate the herniations in cirrhosis.

Obesity may be one of the major terminal endpoints of the metabolic syndrome, since after development of obesity, nonpharmaceutical approaches provide limited benefit either to improve obesity or to prevent its complications. Overweight and obesity probably lead to a chronic and low-grade inflammation on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess weight in all age groups (19). The low-grade chronic inflammation may also cause genetic changes on the epithelial cells, and the systemic atherosclerotic process may decrease clearance of malignant cells by the immune system, effectively (20). Overweight and obesity are associated with many coagulation and fibrinolytic abnormalities suggesting that they cause a prothrombotic and proinflammatory state (21). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (22, 23). For example, elevated C-reactive protein (CRP) levels in serum carry predictive power for the development of major cardiovascular events (24, 25). Overweight and obesity are considered as strong factors for controlling of CRP concentration in serum, since adipose tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines (26, 27). On the other hand, individuals with excess weight will have an increased circulating blood volume as well as an increased cardiac output, thought to be the result of increased oxygen demand of the excessive fat tissue. The prolonged increase in circulating blood volume may lead to myocardial hypertrophy and decreased compliance, in addition to the common comorbidity of atherosclerosis and HT. In addition to systemic atherosclerosis and HT, FPG and serum cholesterol increased and high density lipoproteins decreased with increased BMI (28). Similarly, the prevalences of CHD and stroke, particularly ischemic stroke, increased with elevated BMI values in another study (29). Eventually, the risk of death from all causes including cardiovascular diseases and cancers increased throughout the range of moderate and severe excess weight for both genders in all age groups (19). The female predominance of the umbilical hernias in adults may also be explained by pregnancies and the higher prevalence of obesity in females. But hormonal status of females

and some other factors should take additional roles in the process to be able to explain the high prevalence of umbilical hernias even in the period of infancy in females. Similarly, varicous dilatations in the lower extremities are much more common in females, and most of them develop during labors, probably due to vasodilatory effects of estrogen. These vasodilatation may also disturb the abdominal wall muscles in women in the process of umbilical hernias.

Cirrhosis may actually be a systemic inflammatory process prominently affecting the hepatic vasculature. The origin of the inflammation is unclear but aging, smoking, alcohol, local and systemic inflammatory or infectious processes, and excess weight may be the major underlying causes. The inflammation is enhanced by release of various chemicals by lymphocytes to repair the damaged hepatic tissues, especially endothelial cells of hepatic arteriols (30). Due to the continuous irritation process of the endothelial cells in case of aging, smoking, alcohol, local and systemic inflammatory or infectious processes, or excess weight, prominent changes develop in the architecture of the hepatic tissue, since the chronic inflammatory process of the endothelial cells terminates with atherosclerosis, tissue hypoxia and infarcts, and fibrosis. Metabolic abnormalities such as dyslipidemia, hyperglycemia, and insulin resistance cause various cellular responses that induce tissue inflammation and immune cell activation, which in turn exacerbate the systemic atherosclerotic process (31). Although cirrhosis is mainly be an accelerated atherosclerotic process of the hepatic vasculature, there are several evidences about coexistence of a systemic endothelial inflammation all over the body. For instance, there may be close relationships between cirrhosis and CHD, COPD, PAD, CRD, and stroke-like other terminal endpoints of the metabolic syndrome, probably due to the underlying systemic atherosclerotic process (32). Similarly, most of the mortality cases in cirrhosis may actually be caused by cardiovascular diseases, and CHD may be the most common one among them (33). On the other hand, nonalcoholic fatty liver disease (NAFLD) is a term used to define a spectrum of disorders characterized by macrovesicular steatosis which occurs in the absence of consumption of alcohol in amount considered to be harmful to the liver. Since the risk of NAFLD is directly proportional to the BMI, and there is a high prevalence of excess weight in the society, NAFLD is also becoming a significant health problem all over the world. According to the literature, sustained hepatic injury will lead to progressive fibrosis and cirrhosis in up to 25% of cases with NAFLD (34). Excessive fat accumulation in hepatocytes is called as hepatosteatosis. It progresses to NAFLD, steatohepatitis, fibrosis, cirrhosis, hepatocellular carcinoma, and eventually hepatic failure. There are two histologic patterns of NAFLD including fatty liver alone and nonalcoholic steatohepatitis (NASH). NASH represents a shift from simple steatosis to an inflammatory process. Excess weight may be the major cause of exacerbation of hepatic inflammation and fibrogenesis in the NASH. NAFLD

affects up to one third of the world population, and it is the most common cause of chronic liver disease even in children and adolescents in the world (35, 36). The recent increase in the prevalence of excess weight likely explains the NAFLD epidemic, worldwide (32). NAFLD is combined with a low-grade chronic inflammatory state, which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (32). NAFLD shares many features of the metabolic syndrome as a highly atherogenic condition, and it may cause hepatic inflammation and cellular injury, particularly at the endothelial level. Beside terminating with cirrhosis, NAFLD is associated with a higher overall mortality and an increased prevalence of cardiovascular diseases (36). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased intima-media thickness of the carotid artery as the reliable markers of subclinical atherosclerosis (32). So NAFLD may also be a predictor of cardiovascular diseases (37). NAFLD may actually be considered as a hepatic component of the metabolic syndrome since hepatic fat accumulation is highly correlated with the components of the metabolic syndrome (38). Similar to the present study, although the prevalence of dyslipidemia was significantly lower in the normal weight than the overweight groups (25.0% versus 45.2%, p<0.001), there was a nonsignificant difference between the overweight and obesity groups (45.2% versus 37.5%, p>0.05) (39). These findings may be explained by the hepatic fat accumulation, inflammation, and fibrosis induced relatively lost hepatic functions in obesity.

WCH is a condition characterized by elevated BP in medical settings combined with normal ABP or self-measured HBP. As already detected in the literature (11, 40), the both methods are equally effective for diagnosis of the WCH. Similarly, recent HT guidelines propose self-measurement of HBP as an important technique to evaluate response to antihypertensive therapy, to improve compliance with the therapy, and as an alternative to ABP to confirm or refute WCH (41). We detected very high prevalences of WCH in the society, 33.3% in the second, 46.6% in the third, 50.0% in the fourth, 48.9% in the fifth, 36.9% in the sixth decades of life (11). Prevalence of HT initially started to be higher than 40% in the sixth decade, and it reached up to 75% in the eighth decade of life (11). On the other hand, the prevalences of HT were detected as 3% in the third, 8% in the fourth, and 21% in the fifth decades of life (11). The high prevalences of WCH in the society were also shown in some other studies, too (42, 43). Eventually, we come to the result that all HT cases, 75% in the eighth decade, may develop from the previous WCH cases, but WCH may actually be an acute phase reactant (APR) for several consequences instead of being a precursor sign of overt HT alone (11). Although the patients with WCH are characterized by absence of target organ damage induced by HT, absence of risk of cardiovascular diseases related to HT, and absence of lowering of BP with the antihypertensive therapies in a recent review (44), we evaluated WCH not just as a precursor sign

of overt HT alone but as an APR mainly alarming the excess weight and several consequences of it in the future (45). When we compared the underweight, normal weight, and overweight groups, beside decreased prevalences of sustained normotension (NT) from the underweight towards the normal weight and overweight groups, the prevalences of WCH increased in the same direction, significantly (45). Eventually, the prevalence of WCH reached up to 68.1% in the overweight group, and only 31.8% of the overweight cases have sustained NT although the relatively younger mean age of them. Similarly, although the lower prevalences of overweight and obesity in the early decades, we detected the prevalences of WCH as 33.3% even in the second and 46.6% in the third decades of life (11). On the other hand, when we compared the sustained NT, WCH, and overt HT groups (40), WCH cases were found in between according to frequencies of nearly all of the following disorders including obesity, impaired glucose tolerance, DM, hypertriglyceridemia, hyperbetalipoproteinemia, and dyslipidemia. Nearly all of the disorders showed a gradual progression in frequency from the sustained NT towards the WCH and HT groups (40). On the other hand, 20.0% and 35.5% of WCH cases in the underweight and the normal weight groups, respectively, may indicate that WCH may be an APR influenced by several factors instead of BMI alone (45).

As a conclusion, there may be significant relationships between the umbilical hernia, obesity, cirrhosis, and other terminal endpoints of the metabolic syndrome including HT, DM, and CHD in adults, probably on the bases of prolonged inflammatory, atherosclerotic, and pressure effects of excessive fat tissue on abdominal wall muscles. The inverse relationships between obesity and hypertriglyceridemia and hyperbetalipoproteinemia may be explained by the hepatic fat accumulation, inflammation, and fibrosis induced relatively lost hepatic functions in obesity. Similarly, the inverse relationship between obesity and WCH may be explained by progression of WCH into overt HT in obesity. So obesity may actually be a precirrhotic condition in adults.

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ACUTE PHASE REACTANTS IN IRRITABLE BOWEL SYNDROME

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Abstract

Background: Irritable bowel syndrome (IBS) is one of the frequent causes of recurrent upper abdominal discomfort in adults.

Method: Consecutive patients with the IBS and age and sex-matched control cases were studied. IBS was diagnosed according to Rome II criteria in the absence of red flag symptoms including pain, diarrhea interfering with sleep, weight loss, fever, and any pathological finding in physical examination.

Results: The study included 473 patients with the IBS (308 females and 165 males) and 271 control cases. Mean age of the patients was 43.0 years. Interestingly, 65.1% of the patients with IBS were female. Prevalence of smoking was higher in the patients with IBS, significantly (38.4% versus 18.8%, p<0.001). Although the mean height, weight, body mass index, hematocrit value, and systolic and diastolic blood pressures were similar in both groups, erythrocyte sedimentation rate (ESR) (14.6 versus 12.3 mm/h, p=0.02) and C-reactive protein (CRP) (2.9 versus 2.0 mg/L, p<0.001) values were higher in the IBS group, significantly.

Conclusion: Probably IBS is a low-grade inflammatory process initiated by smoking, infections, inflammations, anxiety, depression, sleep disorders, illness fear, and cancer fear-like stresses, and eventually terminates with dysfunctions of the gastrointestinal and genitourinary tracts and elevations of ESR and CRP-like acute phase reactants (APR) in the plasma. The elevated APR will probably terminate with an accelerated atherosclerotic process all over the body and a shortened survival in both genders.

Key words: Irritable bowel syndrome, erythrocyte sedimentation rate, C-reactive protein, chronic endothelial damage, atherosclerosis, smoking, metabolic syndrome

Introduction

Recurrent upper abdominal discomfort may be a frequent cause of applications to the Internal Medicine Polyclinics (1). Although gastroesophageal reflux disease, esophagitis, duodenal and/or gastric ulcers, erosive gastritis and/or duodenitis, celiac disease, chronic pancreatitis, and malignancies are found among possible causes, irritable bowel syndrome (IBS) and chronic gastritis (CG) may be the most common diagnoses. 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 by patients with the IBS. Although many patients relate onset of symptoms to intake of food, and often incriminate specific food items, a meaningful dietary role is doubtful in the IBS. According to literature, nearly 20% of general population have IBS, and it is more common in female gender with unknown reasons, yet (2). Psychological factors seem to precede onset and exacerbation of gut symptoms, and many potentially psychiatric disorders including anxiety, depression, sleep disorders, illness fear, or cancer fear usually coexist with the IBS (3). For example, thresholds for sensations of initial filling, evacuation, urgent evacuation, and utmost tolerance recorded via a rectal balloon significantly decreased by focusing the examiners' attention on gastrointestinal stimuli by reading pictures of gastrointestinal malignancies in patients with the IBS (4). 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 in the body. IBS is actually defined as a brain-gut dysfunction according to the Rome II criteria, and it may have more complex mechanisms affecting various systems of the body via a low-grade inflammatory process on vascular endothelium (5). Eventually, IBS may even terminate with CG, urolithiasis, and hemorrhoids (6-8). Similarly, some authors studied the role of inflammation in the IBS via colonic biopsies in 77 patients (9). 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 killer cells. 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 (9). A direct link between the immunological activation and IBS symptoms was shown by some other authors, too (10). They demonstrated not only an increased mast cell degranulation in the colon but also a direct correlation between proximity of the mast cells to neuronal elements and severity of pain in the IBS (10). In addition to above findings, there are some evidences for extension of the inflammatory process behind the mucosa. Some authors addressed this issue in ten patients with severe IBS by examining full-thickness jejunal biopsies obtained via laparoscopy (11). They detected a low-grade infiltration of lymphocytes in myenteric plexus of nine patients, four of whom had an associated increase in intraepithelial lymphocytes and six demonstrated evidence of neuronal degeneration (11). Nine patients had hypertrophy of longitudinal muscles, and seven had abnormalities in number and size of interstitial cells of Cajal (11). The finding of intraepithelial lymphocytosis was consistent with some other reports in the colon and duodenum, too (9, 12). On the other hand, smoking is a well-known cause of chronic endothelial inflammation terminating with an accelerated atherosclerosis-induced end-organ insufficiencies all over the body (13). We tried to understand whether or not there are some significant relationships between smoking, IBS, and acute phase reactants (APR) including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the present study.

Material and methods

The study was performed in the Internal Medicine Polyclinic 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 habit, alcohol consumption, urolithiasis, and already used medications were learned. Patients with devastating illnesses including eating disorders, malignancies, acute or chronic renal failure, cirrhosis, hyper- or hypothyroidism, and heart failure were excluded. Current daily smokers at least for six-month and cases with a history of five pack-year were accepted as smokers. Patients with regular alcohol consumption (one drink a day) were accepted as alcoholic. A routine check up procedure including hemogram, ESR, CRP, albumin, creatinine, thyroid function tests, hepatic function tests, markers of hepatitis A, B, C, and human immunodeficiency viruses, urinalysis, a posterior-anterior chest x-ray graphy, an electrocardiogram, a Doppler echocardiogram in case of requirement, an abdominal ultrasonography, 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, diarrhea interfering with sleep, weight loss, fever, and any pathological finding in physical examination. Body mass index (BMI) of each case was calculated by measurements of the Same Physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared (14). Office blood pressures (BP) were checked after a 5-minute of rest in seated position with mercury sphygmomanometer. Eventually, all patients with IBS were collected into the first and age and sex-matched controls were collected into the second groups. Mean values of height, weight, BMI, hematocrit, ESR, CRP, and systolic and diastolic BP and prevalence of smoking were detected in each group 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 473 patients with the IBS (308 females and 165 males) and 271 control cases. Mean age of the patients was 43.0 ± 13.6 (17-76) years. Interestingly, 65.1% of the patients with IBS were female. Prevalence of smoking was higher in the patients with IBS, significantly (38.4% versus 18.8%, p<0.001). Although the mean height, weight, BMI, hematocrit value, and systolic and diastolic BP were similar in both groups, ESR (14.6 versus 12.3 mm/h, p=0.02) and CRP values (2.9 versus 2.0 mg/L, p<0.001) were higher in the IBS group, significantly (Table 1). Due to the limited number of cases with alcoholism, regular alcohol consumption was not included in comparison.

Table 1: Comparison of patients with irritable bowel syndrome and control cases

Variables	Patients with IBS*	p-value	Control cases
Number	473		271
Female ratio	*65.1%*	Ns†	66.0%
Mean age (year)	*43.0 ± 13.6 (17-76)*	Ns	43.1 ±12.3 (13-66)
Smoking	*38.4%*	*<0.001*	*18.8%*
Weight (kg)	74.5 ±15.2 (42-122)	Ns	74.6 ±15.6 (44-129)
Height (cm)	163.8 ±9.3 (142-194)	Ns	164.4 ±9.3 (138-187)
BMI‡ (kg/m2)	27.7 ±5.8 (15.0-51.1)	Ns	27.6 ±5.6 (17.8-49.0)
Systolic BP§ (mmHg)	128.7 ±25.0 (80-240)	Ns	131.5 ±27.5 (80-220)
Diastolic BP (mmHg)	89.1 ±12.9 (50-130)	Ns	90.1 ±12.9 (60-140)
ESR‖ (mm/h)	*14.6 ± 11.6 (1-87)*	*0.02*	*12.3 ± 10.0 (1-61)*
*CRP** (mg/L)*	*2.9 ± 3.4 (0-22)*	*0.001*	*2.0 ± 2.3 (0-12)*
Hematocrit (%)	39.8 ±4.5 (30-57)	Ns	39.7 ±4.5 (21-52)

*Irritable bowel syndrome   †Nonsignificant (p>0.05)   ‡Body mass index   §Blood pressures
‖Erythrocyte sedimentation rate   **C-reactive protein

Discussion

Just after the excess weight, smoking may be the second common cause of vasculitis all over the world. It is a major risk factor for the development of atherosclerotic end-organ insufficiencies including coronary heart disease (CHD), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), cirrhosis, and stroke (13, 15). Its atherosclerotic effect is the most obvious in Buerger's disease. Buerger's disease is an obliterative vasculitis characterized by inflammatory changes in small and medium-sized arteries and veins, and it has never been reported in the absence of smoking in the literature. Although the well-known atherosclerotic effects of smoking, some studies reported that smoking in human being and nicotine administration in animals are associated with lower BMI values (16). Some evidences revealed an increased energy expenditure during smoking both on rest and light physical activity (17), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (18). According to an animal study, nicotine may lengthen intermeal time, and simultaneously decrease amount of meal eaten (19). Additionally, the BMI seems to be the highest in the former, the lowest in the current, and medium in never smokers (20). Smoking may be associated with a postcessation weight gain, but evidences suggest that risk of the weight gain is the highest during the first year after quitting, and decreases with the following years (21). Similarly, although the CHD was detected with similar prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher BMI, low density lipoproteins (LDL), triglycerides, white coat hypertension (WCH), hypertension (HT), and diabetes mellitus (DM) in females (22). This result may indicate both the atherosclerotic and weight decreasing roles of smoking (23). Similarly, the incidence of myocardial infarctions is increased six-fold in women and three-fold in men who smoked at least 20 cigarettes per day (24). In another word, smoking may be more harmful for women about the atherosclerotic end-points probably due to the higher BMI and its consequences in them. Similarly, smoking is consistently higher in men in the literature (15). So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite. On the other hand, smoking-induced weight loss may be related with the vascular endothelial inflammation all over the body, since loss of appetite is one of the major symptoms of disseminated inflammation in the body. Clinicians can even understand healing of their patients by means of normalizing appetite. Several toxic substances found in cigarette smoke get into the circulation via the respiratory tract, and cause a vascular endothelial inflammation until their clearence from the circulation. But due to the repeated smoking habit of the individuals, the clearence process never terminates. So the patients become ill with loss of appetite, permanently. In another definition, smoking-induced weight loss is an indicator of being ill instead of being healthy (18-20). After smoking cessation, appetite normalizes with a prominent weight gain but the returned weights are their physiological weights, actually. On the other hand, there may be several underlying mechanisms terminating with

the IBS in smokers. First of all, 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 the symptoms and components of the IBS including loose stool, diarrhea, constipation, and urolithiasis. Secondly, diarrheal losses-induced urinary changes may even cause urolithiasis (6, 7). Thirdly, smoking-induced sympathetic nervous system activation may cause motility disorders in the gastrointestinal and genitourinary tracts. Fourthly, smoking-induced loss of appetite may terminate with obstipation. Finally, immunosuppression secondary to smoking-induced vascular endothelial inflammation may even terminate with gastrointestinal and genitourinary tract infections causing loose stool, diarrhea, and urolithiasis since some types of bacteria can provoke urinary supersaturation and modify the environment to form crystal deposits in the urine. In fact, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infection with bacteria that possess the enzyme, urease. Similarly, urolithiasis was detected in 17.9% of cases with the IBS, whereas this ratio was 11.6% in cases without the IBS (p<0.01) (6).

Chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in human being (25). Much higher BP of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on 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 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, sedentary lifestyle, animal-rich diet, excess weight, smoking, alcohol, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, HT, DM, cirrhosis, PAD, COPD, CHD, CRD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, early aging, and premature death (26). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and aging, endothelial changes can not be reversed completely due to their fibrotic natures. The accelerating factors and terminal consequences are researched under the headings of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the literature, extensively (27, 28).

Obesity may be one of the terminal consequences of the metabolic syndrome since after development of the obesity, nonpharmaceutical approaches provide limited benefit either to heal obesity or to prevent its

complications. Excess weight may cause a chronic low-grade inflammation on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess weight in all age groups (29). The low-grade chronic inflammatory process may even cause genetic changes on the epithelial cells, and the systemic atherosclerotic process may decrease clearance of malignant cells by the immune system. The effects of excess weight on BP were shown in the literature, extensively (30). For example, incidence of sustained normotension (NT) was higher in the underweight (80.3%) than the normal weight (64.0%, p<0.05) and overweight groups (31.5%, p<0.05), significantly, and 52.8% of cases with HT had obesity against 14.5% of cases with the NT (p<0.001) (31). So the dominant underlying cause of the metabolic syndrome appears as weight gain, which is probably the main cause of insulin resistance, hyperlipoproteinemias, impaired fasting glucose, impaired glucose tolerance, and WCH via the prolonged low-grade inflammation on vascular endothelium all over the body (32). Prevention of the weight gain with physical activity, even in the absence of a prominent weight loss, will probably result with resolution of many parameters of the syndrome (33-36). According to our experiences, excess weight may actually be a consequence of physical inactivity instead of an excessive eating habit, thus prevention of weight gain can not be achieved by diet, alone (37). Additionally, limitation of excess weight as an excessive fat tissue around abdomen under the title of abdominal obesity is meaningless, instead it should be defined as overweight or obesity via the BMI since adipocytes function as an endocrine organ, and they produce a variety of cytokines and hormones all over the body (32). The eventual hyperactivities of sympathetic nervous system and renin-angiotensin-aldosterone system are probably associated with chronic endothelial inflammation, insulin resistance, and elevated BP. Similarly, the Adult Treatment Panel III reported that although some people classified as overweight with larger muscular masses, most of them also have excessive fat tissue predisposing to HT, DM, CHD, and stroke-like terminal end-points of the metabolic syndrome (14).

The acute phase response is a facet of the innate immune system that occurs in response to infections, infarctions, foreign bodies, autoimmune disorders, allergies, neoplasms, traumas, or burns-like stresses of the body. Certain mediators known as APR are increased or decreased during the acute phase response (38, 39). These markers are commonly measured in clinical practice as indicators of acute illnesses. The terms of acute phase proteins and APR are usually used synonymously, although some APR are polypeptides rather than proteins. An acute phase reaction classically presents with fever, tachycardia, and leukocytosis. Positive and negative APR are those whose concentrations increase or decrease during an acute phase response, respectively. The acute phase response is predominantly mediated by the pro-inflammatory cytokines including TNF, IL-1, and IL-6 secreted by the immune cells. In case of inflammations, infections, and tissue damages, neutrophils and macrophages release such cytokines into the circulation. The liver and some other organs respond by producing many positive APR to the cytokines. Some of the well-known positive APR are ESR, CRP, fibrinogen, ferritin, procalcitonin, hepcidin, haptoglobin, ceruloplasmin, complement proteins, and serum amyloid A. CRP is involved in innate immunity, and responsible for activating the complement pathway. Serum CRP rises rapidly, with a maximal concentration reached within two days, and falls quickly once the inflammation has resolved. Measurement of CRP is a useful indicator of inflammations in the clinics. It correlates with ESR, but not always directly. This is due to the ESR being largely dependent on 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. Whereas CRP rises with a half-life of 6-8 hours, rapidly, and then returns to normal in case of a successful treatment, quickly. On the other hand, productions of the negative APR are suppressed at the same time. Some of the well-known negative APR are albumin, transferrin, retinol-binding protein, antithrombin, transcortin, and alpha-fetoprotein. The suppression of such proteins is also used as an indicator of inflammations. Suppression of the synthesis of such proteins may be due to the protection of amino acids for the production of positive APR, sufficiently. Due to the same reason, productions of high density lipoproteins (HDL) and LDL may also be suppressed in the liver during the acute phase responses (40). For example, although the similar mean age, gender distribution, smoking, and BMI in both groups, triglycerides, DM, and CHD were higher whereas LDL were lower in patients with plasma HDL values of lower than 40 mg/dL, significantly (40). So HDL and LDL may actually behave as negative APR in the plasma. Similarly, although the lower mean age, BMI, fasting plasma glucose, and LDL, the highest CHD of the group with HDL values of lower than 40 mg/dL can also be explained by the same hypothesis (41). Beside that although the mean triglycerides, fibrinogen, CRP, and glucose values were higher in cases with ischemic stroke, the oxidized LDL values did not correlate with the mean age, stroke severity, and outcome in another study (42). Additionally, significant alterations occurred in the lipid metabolism and compositions of the lipoproteins, and plasma triglycerides increased whereas HDL and LDL decreased during infections (43). Furthermore, a 10 mg/dL increase of plasma LDL values was associated with a 3% lower risk of hemorrhagic stroke in another study (44). Similarly, the highest prevalences of HT and DM parallel to the increased 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 APR natures of LDL and HDL in the plasma (45). So 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 (41).

As a conclusion, probably IBS is a low-grade inflammatory process initiated by smoking, infections, inflammations, anxiety, depression, sleep disorders, illness fear, and cancer fear-like stresses, and eventually terminates with dysfunctions of the gastrointestinal and genitourinary tracts and elevations of ESR and CRP-like APR in the plasma. The elevated APR will probably terminate with an accelerated atherosclerotic process all over the body and a shorthened survival in both genders.

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