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The Trend of Four Consultation Models in Four Specialties at Four Tertiary Care Hospitals

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This issue of the journal is rich with papers with different topic from the region of interest to primary care. Abdulghani, et al., looked at the trend of four consultation models in four specialties at four tertiary care hospitals. Out of 263, most clinicians (n=121, 46.0 %) were found to practice a blended consultation approach while dealing with patients. The 2nd most common adopted consultation model was the Deliberative model (n= 109, 41.4%). Other consultation (Informative and Interpretive) models were the least practiced models (1.5%). The authors concluded that the blended consultation is found to be the most practiced consultation model. A clinician should adopt an attitude that is flexible and empathetic towards patients' needs and expectations. Consideration should be given to assisting physicians in adapting their roles for interpersonal styles to the preferences of various patients. This expanded role will result in improved health outcomes for diverse populations utilizing health care.

Andijani , et al., did a cross-sectional study was conducted on patients receiving chemotherapy to assess the effect of COVID-19 pandemic on gynecological cancer patients receiving chemotherapy. A total of 84 patient were identified. The most diagnosis was ovarian cancer (41.7%) followed by uterine cancer (33.3%). Of studied patients, 17.9%, 19.1%, 27.4 and 33.3% had I, II , III and IV cancer stages respectively. Patients with recurrent disease had a significantly higher percentage of patients detected with COVID-19, and all cases detected with COVID-19 died with respiratory failure. Patients who had their chemotherapy delayed had a significantly higher mean number of cycles. The authors concluded that improved communication and management programs are required to keep cancer patients and their healthcare providers connected, as well as to allow cancer patients to survive a pandemic.

Albaqami et al., a descriptive cross-sectional study that was conducted to study the impact of COVID-19 on asthmatic patients which was conducted using prepared questionnaire which was distributed online among 300 patients with asthma. In this study, we were able to collect data from 311 asthmatic patients in response to our questionnaire. Most of asthmatic patients were females (67.2%) with ratio of females: males of 2:1. The prevalence of COVID-19 in asthmatic patients was 64.3 % where third of patients needed to go to hospital because of their bad conditions, 12.6 % needed to be hospitalized in ICU and 56.4 % needed oxygen. The authors concluded that the prevalence of COVID-19 in asthmatic patients was much higher than general population especially in female patients who aged between 31-40 years old. Moreover, COVID-19 had more severe outcomes on asthmatic patients including higher prevalence of ICU admission and oxygen need. Poorer outcomes of COVID-19 were associated with poor control of asthma.

El-Gamal, et al., did a cross section study, include 2501 patients, visited the outpatient clinics at two private general hospitals in Jeddah during the years 2018 through 2019. The aim is to study gender differences of the burden of type 2 diabetes and complication risk among Saudi subjects visiting the outpatient clinics. Out of all the visits to the outpatient clinics, DM constituted 5.5%. Type 2 DM was common in those aged 40 years and above, while Type 1 DM was common in those aged 18 years and younger. The authors concluded that DM is a common chronic disorder, which imposed burden on the primary health care in Saudi Arabia. It is more common in males than females, however, the pattern of cardiovascular complications and health care management were similar in both genders.

Alhajaji, et al., did a cross-sectional study was conducted among 236 type-1 diabetics in Makkah Al-Mukarramah City. The aim is to assess magnitude of diabetic ketoacidosis (DKA) among type-1 diabetics and to identify associated risk factors. 70.8% reported past history of DKA. The main causes of DKA were "first presentation of the disease" (40.9%), and "discontinued treatment" (37%). The HbA1c among 53.6% was above 9%. Almost all cases who experienced DKA were hospitalised (98.8%). The authors concluded that most type-1 diabetics experience DKA, mainly with their first presentation of disease or due to discontinuation of treatment. DKA tends to occur more frequently among female patients, those with less educated parents or when their parents are relatives.

Arain, et al , did a comparative cross sectional study conducted on the 3rd, 4thand 5th year medical students in Taif Medical College of Taif University KSA, to determine the association of test anxiety on OSCE performance of medical students in taif medical college. A total of 518 students participated in the survey. The authors concluded that test anxiety is experienced by a large number of undergraduate medical students of Taif Medical University .anxiety has a negative effect on overall academic performance , female students were also more affected as compared to their male counterparts.

Mark Spigelman says the Covid-19 virus leads to a rapid loss of protection in many patients within 6 months. Thus the need for a 3rd injection has been found to be mandatory for continuing protection, as well as to highlight the need to monitor immune compromised patients and those with comorbidities particularly in indigenous populations where co-morbidities may be present preventing an adequate response to the initial vaccination.

Al-Amri et al., did a descriptive cross sectional study to determine the level of knowledge and awareness and the factors affecting the corneal donation. A total of 641 participants were involved. The study revealed low level of knowledge of corneal donation in Aseer Region. Approximately one quarter of the participants reported willingness to donate their cornea. Lacl of knowledge was the main barrier reported by two thirds of the particiapnts.

Khan, et al., did a parallel, two-arm, cluster randomized controlled trial. 768 mother-child pairs ('dyads') attending any of the 24-public health centers in two districts of Pakistan will be recruited, with an average of 32 participants per cluster. In intervention arm, ECD based counselling sessions will be delivered to mothers-child dyads by trained staff at public health care centers. Our primary outcome is reduction in prevalence of two or more developmental delays among children, from 38% to 23% in intervention arm. Unit of randomization will be public health care center. 24 eligible clusters recruited will be randomized into intervention and control arms, using 1:1 allocation. The authors concluded that the integrated model of child care into primary health care has the potential to provide a feasible and sustainable model for improving child developmental at scale.

Kanwal, et al., did a cross sectional study among 60 polycystic ovarian syndrome patients. The aim of current study was to appraise the relationship between women body image perception and depression in case and controls. 55% of PCOS patients with depression while 36.7% were found with depression in control group. In PCOS group 65% of patients were found with positive body image while 98.3% of patients were found with positive body image. The authors concluded that there was significant association of study group with body image perception and depression. Therefore, health of the patients with the set of symptoms is essential to be acknowledged more fully, predominantly in relation to the despair and poor body image. The outcomes of this study foster implications for clinical practice and propose that a multidisciplinary team should be involved in treatment of PCOS.

Alshareef , et al., did a retrospective chart review of growth hormone deficient (GHD) patients was done at the security force hospital in Riyadh, Saudi Arabia. The data was collected from the medical records of the patients. The aim is to examines the chances of developing growth hormone disruption and Diabetes Mellitus in patients diagnosed with Congenital Hypothyroidism at the Security Forces Hospital in Riyadh, Saudi Arabia. At the beginning of the research, 287 growth hormone-deficient (GHD) children ranging in age from 1 to 15 years old were evaluated for diabetes. The authors concluded that levothyroxine therapy has no discernible effect on blood sugar level fluctuations in males and females.

Mandoura, et al., did a descriptive cross-sectional study was conducted in the primary healthcare centers` clinics and outpatient pediatric clinics of Abha maternity and children hospital. The aim is to assess the prevalence of breastfeeding and determinants of not continuing initiated breast feeding among Saudi females. The study included 276 mothers. Majority of them (88.1%) aged between 20 and 39 years and Saudi nationals (90.2%). The authors concluded that initiation of breastfeeding was very highly practiced by mothers in Abha city, Saudi Arabia. However, its discontinuation before the recommended time is also a highly reported practice.

A number of review papers discussed important topics in practice. Dr. Abdalla, reviewed Malignant Melanoma. He stressed that Malignant melanoma is cancerous neoplasm of the melanocytes. It is the most aggressive type of skin cancer as it tends to metastasize early. Melanoma is the 5th commonest cancer in the UK. It affects adult of any age but extremely rare in children. Excessive sun exposure in childhood and early adult life is the most dominent risk factor in most cases of MM. Other risks include those with skin type 1 (always burn and never tan), People with red or blond hair, freckles, high numbers of naevi >50, and strong family Dr. Daud, looked at the clinical Efficacy and Cholesterol-Lowering Effects of Inclisiran. Inclisiran, a drug developed by Novartis, is a recent medication designed to alleviate cardiovascular disease symptoms through improving low-density lipoprotein cholesterol levels. Positive, large-scale clinical trials on the use of inclisiran demonstrate the drug's efficacy in reducing LDL cholesterol levels in patients afflicted with cardiovascular disease. However, despite the promising clinical trials on inclisiran as well as its use in the UK, the U.S. Food and Drug Administration (FDA) has yet to approve the drug as a treatment strategy for cardiovascular disease. Dr. Abdalla, reviewed Non-surgical options to treat androgenic alopecia. He stressed that Androgenic alopecia (AGA) is the commonest cause of hair loss in men and women. It isattributed to genetic and hormonal factors. A major factor identified, so far, is the effect of Dihydrotestosterone (DHT) on the scalp hair follicles. DHT is formed by the conversion of Testosterone to DHT when it is activated by the enzyme 5?? reductase which is found in type 2 receptors on the scalp hair follicles. The result of this activation is miniaturization (thinning) and shortening of the growth phase (anagen) in the hair cycle.

The Trend of Four Consultation Models in Four Specialties at Four Tertiary Care Hospitals

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Abstract

Background and Aim: Multiple consultation models exist in medical practice. A comprehensive doctor-patient relationship serves as a foundation to bring about a positive outcome in terms of patient health. However, evidence of doctors' impact on improving patients' mental and physical health through a specific model is sparse. This study aimed to identify the most common consultation models adopted in four different specialties at four hospitals in Riyadh, Saudi Arabia.

Methods: From four tertiary care hospitals of Riyadh, clinicians (n=263) with clinical experience >3 years from Internal Medicine, Surgery, Family Medicine, and Psychiatry departments participated in this observational study. A 27-items questionnaire describing five consultation models was carried out in hard copy and a soft copy using the Snowball sampling method to receive the responses that were analyzed by using SPSS version 23.0 in the form of descriptive results.

Results: Out of 263, most clinicians (n=121, 46.0 %) were found to practice a blended consultation approach while dealing with patients. The 2nd most common adopted consultation model was the Deliberative model (n= 109, 41.4%). Other consultation (Informative and Interpretive) models were the least practiced models (1.5%).

Conclusion: The blended consultation is found to be the most practiced consultation model. A clinician should adopt an attitude that is flexible and empathetic towards patients' needs and expectations. Consideration should be given to assisting physicians in adapting their roles for interpersonal styles to the preferences of various patients. This expanded role will result in improved health outcomes for diverse populations utilizing health care.

Key words: Deliberative model, Doctor Behavior, Family Medicine, Interpretive Model, Paternalistic Model, Informative Model, Psychiatry

Introduction

In the debate for doctor-patient relationships, different consultation models have been suggested over the years. One of the theories implies that people, once in distress or illness, unwillingly look for a wiser, older, and more experienced character [1]. Another model is patient-centred care that focuses on patients through their personal needs and expectations. A different approach called "treat to target" has substantiated vast influence in many areas of medicine [2,3]. This approach is used to monitor long-term chronic disease that requires adjustments to therapy during the treatment process to keep up with the disease progression.

All these models elucidate the patient's role in medical decision-making and the nature of the doctor-patient relationship. Emanuel and Emanuel discussed the doctor-patient relationship models based on different circumstances [4]. These models are a) Paternalistic, b) Informative, c) Interpretive, and d) Deliberative).

The Paternalistic model (PM) is also known as the parental or priestly model [5-7]. As the name suggests, and while using the paternalistic approach, the physician acts as a parent. Their opinion is imposed on the patient, and some information regarding the disease is given to the patient to encourage them to follow the physician's opinion. This approach ensures that the best interventions are made available to the patient. This model safeguards what is best for the patient, yet with their negligible involvement in decision-making. The Informative model (Inf M) is also recognized as a scientific, engineering, or consumer model [4,6]. While using the informative approach, the patient is provided with detailed information about their health and lets them choose what is best. Patients' values are well known and what is lacking is the health information, and hence, the doctor plays a crucial role in providing this missing information. Whereas, in the Interpretive model (Int M), all information is given to the patient [8]. The physician as a counsellor also helps clarify the values for the patient and choose the treatment option that best achieves these values. Therefore, the interpretive doctor aims to bring coherence between the patient's values and priorities. Moreover, in the Deliberative model (DM), the physician acts as a teacher or friend and provides the patient with all information regarding the disease. Both determine through negotiation what medical values are most important to the patient; a compulsion is typically avoided with this model [7,9].

Despite an ever-increasing number of treatment options, patients' relationships with their doctors are still unsatisfactory due to communication problems [10]. The persistence of patient discontent, despite rising medical knowledge and capacity, suggests that the problem is not with the quality of medical therapy, but with how it is conveyed, delivered and communicated while debating the patient's utility; there is an ongoing debate about whether paternalism is still relevant or to be avoided. Some argue that it is only suitable for a mentally compromised patient and should be used in emergency cases. On the other hand, we have the Inf M, which may be justified in a walk-in clinic where minimal patient-physician interaction exists, i.e., the patient is diagnosed on the spot and given all the treatment options to choose whatever suits their medical values [9]. In Eastern communities, including the Chinese context, the physicians tend to hold a more directive approach to make the decision, and, even so, it is still up to the patients to make the final decision [11,12].

After an extensive literature review, we could not find any study that reported on what type of model was most frequently used in the Arab community of doctors. We initiated this study to investigate the physician-patient relationship in Saudi Arabia, demonstrate which models are most frequently occurring in Saudi healthcare practice, and the factors affecting the choices of these models among different specialties of physicians. Therefore, this study intended to explore the most common consultation models used by clinicians in Saudi Arabia as: 1) It highly affects patient satisfaction, which in turn affects compliance positively and results in fewer malpractice complaints, 2) It helps doctors reach a correct diagnosis, 3) It also encourages patients to give information with confidence and trust.

Material and Methods

Study design and setting

A snowball sampling method was adopted for a quantitative observational study that was carried out at four tertiary care hospitals, namely, King Khalid University Hospital (KKUH), King Fahad Medical City (KFMC), Prince Sultan Military Medical City (PSMMC), and King Saud Medical City (KSMC) located in Riyadh, Saudi Arabia. Data were collected from December 2017 to April 2018.

Study subjects and data collection

Both male and female clinicians having a minimum of three years of clinical experience from any four specialties, Internal Medicine, Surgery, Family Medicine, and Psychiatry, participated in this study.

A snowball non-probability sampling technique was used. Before the actual data collection, a pilot study was done to calculate the time required to complete the questionnaire and check its appropriateness. The pilot study also helped ensure content validity. The study sample size was calculated using a one-way proportion equation (N= (Z2α) (P (1- P)/D2) and collected 297 samples as estimated with 95% confidence level and 4% precision.

Study Instrument

After an extensive literature review, we developed the questionnaire to quantify the Paternalistic model (PM), the Informative model (Inf M), the Interpretive model (Int M), and the Deliberative model (DM)[12,13]. Initially, a set of 39 items were created by a team of experts from the department of family and community medicine. Subsequently, two meetings were held to finalize the survey items. These meetings were attended by 3 experts from the department of family and community medicine who had initially created the 31 items and 4 experts from

the department of medical education. These experts discussed and agreed to delete 4 items as they were duplicated or challenging to understand. The final questionnaire consisted of 27 items. All items (related to the models) have a five-point Likert (1-5) scale, where 1 stands for strongly disagree, 2 disagree, 3 neutral, 4 Agree, and 5 strongly agree. We combined the answers 1 and 2 as Disagree, 3 remained neutral, and 4 and 5 were combined as Agree. We calculated the mean score of each model. The participants scoring 3.5 or above were considered a user for that model.

Ethical Consideration

The institutional Review Board of the College of Medicine, King Saud University, approved the study (IRB # E-20-4535). All participants were informed of the study purpose, and advantages and disadvantages were explained before starting data collection. Verbal and written consents were obtained, and the personal information of participants was kept confidential.

Analysis

Data entry was carried out using Excel Microsoft and analysis by SPSS software, version 23 (SPSS Inc., Chicago, Illinois, USA). The chi-square test was used to compare all variables. All analyses were carried out at a significance level of 0.05. Physicians with the high or low mean across 4 different models were labelled as adopting the 'blended approach'. Physicians with a high mean in one particular model and low in the other models were labelled as advocates and users of that particular model.

Results

The collected responses were N=263, among 184 (69.96%) were males, and 79 (30.03%) were females. The highest response rate was from King Khalid University Hospital (n=151, 57.4%). Regarding the nationality of the clinicians, Saudi candidates were 139 (52.85), and non-Saudis were 124 (47.14%). Most of the responses were from clinicians of internal medicine and surgery in all four hospitals (Table 1). The candidates, n=87 (56.61%), had greater than 3 years but less than five years of working experience. There were 62 respondents (22.4%) having experience between 5 to 10 years and (n=73, 60.83%) were the clinicians who had more than 15 years of experience (Table 2).

From Table 2, it is apparent that of the consultation models being practiced by respondents, the blended approach was the most popular model (n=121, 46%). The second most commonly used model was the deliberative model (n=109, 41.4%). The Interpretive and informative models were the least adopted models by clinicians (n=4, 1.93%). The deliberative model (DM) was the second most commonly adopted model by clinicians (Table 2).

Paternalistic model approach

The overall acceptance rate of PM = 2.28 by the different specialty doctors. Participants n=190 (72.2%) agreed that 'The doctor is the expert and should make the decision in most conditions.' Most participants, n=184 (70%), agreed with the statement, 'The doctor should share the information with the patient in a way that they agree to follow the advice given' (mean 2.59 (0.67). In the paternalistic model, most doctors (65.0%) disagree about the "patient should not be involved in decision making." Most of the doctors (73.8%) believe that 'all information should be shared with the patient' and difference of opinion found in the doctors about "the doctor should not criticize the patient's beliefs, even if these might harm the patient" (P=0.008) (Table 3a).

Informative model approach

The overall acceptance rate of the Informative model (IM) was mean = 2.75 by the different specialty doctors. Most of the physicians from various age groups agreed with the statements, 'doctor should explain to the patient all the advantages and disadvantages of the treatment options' (91.3%, mean (SD) 2.87(0.41)). More than 80% of doctors agree that "the patient should be involved in making the decision." Similarly, 80.2% of doctors agreed on an informative approach to "the doctor should respect the choice of the treatment that the patient prefers". Moreover, most doctors agreed (mean 2.85) that the "doctor and patient should together weigh all the different treatment options available thoroughly" (Table 3a).

Interpretive model approach

The overall acceptance rate of IntM = 2.50 by the different specialty doctors. Statistically significant (P=0.02) responses were reported in the interpretive model, about the "doctor provides all information to the patient about his health status and or disease". Most of the doctors (59.3%) agreed that the "Doctor helps the patient choose the treatment option that best achieves their value". About "Doctor helps the patient choose the treatment option that best achieves their value", significant responses were reported (P=0.02). Moreover, 84.4% of doctors reported, "doctor doesn't disapprove patients' values" (Table 3b).

Deliberative model approach

The overall acceptance rate of DM = 2.46 by the different specialty doctors. Significant response (P=0.01) was found when "Patients will appreciate it later on when physicians stick to their clinical opinion, even though they disagreed initially". We received not very clear responses from the doctor's side (agree-47.95; neutral-30.4; disagree-21.7) about "Patients, when given total autonomy, may harm themselves because of their limited knowledge" and almost similar responses received from the doctor's side (agree-44.5; neutral-33.5; disagree- 22.1), about "The patient is entitled to complete control of the medical decision, given the actual situational limits." Most of the doctors (88.6%) reported about "Informed consent has a crucial role in medical treatment" (Table 3b).

Consultation models utilized by faculty with different specialties

The most accepted paternalistic model by the different specialties is internal medicine, where the mean score was 17.68, with F=1.18; P=0.31. Similarly, family medicine doctors recognize it most as an informative model with a mean score of 21.92 followed by internal medicine (mean score 21.63), Interns (mean score 21.25), Surgery doctor (mean score 21.19), and psychiatry doctor (mean score 20.71). Moreover, most Intern doctors like (mean score 19.20) the deliberative model approach with F=1.55; P=0.18. Surgery doctors like the interpretive model most (mean score 19.27) (Table 4).

Table 1. Demographic characteristics of participants from four tertiary care hospitals in Riyadh (N= 263)

Hospital N (%)	Gender		Nationality		Work Exp.		Speciality*			
	M	F	Saudi	Non-Saudi	<10	≥10	IM	S	FM	P
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
King Khalid University Hospital 151 (57.4)	113 (74.83)	38 (25.16)	79 (52.31)	72 (47.68)	87 (57.61)	64 (42.38)	61 (40.39)	39 (25.82)	41 (27.15)	10 (6.62)
King Saud Medical City 47 (17.9)	28 (59.57)	19 (40.42)	26 (55.31)	21 (44.68)	31 (65.95)	16 (34.04)	18 (27.65)	13 (27.65)	14 (29.78)	2 (4.25)
King Fahad Medical City 33 (12.5)	24 (72.72)	9 (27.27)	19 (57.57)	14 (42.42)	11 (33.33)	22 (66.66)	13 (39.39)	9 (27.27)	8 (24.24)	3 (9.09)
Prince Sultan Military Medical City 32 (12.2)	19 (59.37)	13 (40.62)	15 (46.87)	17 (53.12)	14 (43.75)	18 (56.25)	11 (34.37)	10 (31.25)	7 (21.87)	4 (12.5)
Total N (%)	184 (69.96)	79 (30.03)	139 (52.85)	124 (47.14)	143 (54.37)	120 (45.62)	103 (39.16)	71 (26.99)	70 (26.61)	19 (7.22)

*Specialty (IM = Internal Medicine, S= Surgery, FM = family Medicine, P= Psychiatry

Table 2: The models illustrated according to hospital, department, and working experience of clinicians

Consultation models		N	Blended Model n (%)	Deliberative Model n (%)	Paternalist Model n (%)	Informative Model n (%)	Interpretive Model n (%)
Total Response		(n=263)	121 (46.0)	109 (41.4)	25 (9.50)	4 (1.93)	4 (1.93)
Hospitals							
King Khalid University Hospital		(n=151)	68 (56.19)	67 (61.46)	12 (48.0)	2 (50.0)	2 (50.0)
King Saud Medical City		(n=47)	24 (19.83)	16 (14.67)	4 (16.0)	1 (25.0)	2 (50.0)
King Fahad Medical City		(n=33)	14 (11.57)	12 (11.0)	6 (24.0)	1 (25.0)	0 (0.0)
Prince Sultan Military Medical City		(n=32)	15 (12.4)	14 (12.84)	3 (12.0)	0 (0.0)	0 (0.0)
Departments							
Internal medicine		(n=93)	46 (49.46)	36 (38.70)	9 (9.67)	0 (0.0)	2 (2.15)
Surgery		(n=68)	27(39.70)	23(33.82)	11(16.17)	3(4.41)	4(5.8)
Family medicine		(n=25)	13 (52.0)	11 (44.0)	1 (4.0)	0 (0.0)	0 (0.0)
Psychiatry		(n=07)	3(42.85)	3(42.85)	0 (0.0)	0(0.0)	1 (14.28)
Gender	Female	(n=79)	35 (44.30)	36 (45.56)	7 (8.8)	1 (1.26)	0 (0)
	Male	(n=184)	85 (46.19)	72 (39.13)	18 (9.78)	3 (1.63)	6 (3.26)
Work experience	3 >5	(n=81)	34 (57.02)	27 (59.6)	12 (48.0)	3 (75.0)	2 (50)
	5 to 10	(n=62)	23 (37.09)	26 (41.93)	8(12.90)	3 (4.83)	2(3.22)
	11 to 14	(n=47)	17 (5.78)	8 (9.17)	11 (12.0)	7 (25.0)	4(0.0)
	≥15	(n=73)	21 (28.76)	16 (21.91)	13 (17.80)	15 (20.54)	8 (10.95)

Table 3a: Model analysis by Likert scale

Model	Items	Mean (SD)	Categories	N (%)	χ2 (P-value)
Paternalistic	The doctor being the expert should decide most conditions.	2.60(0.69)	Agree	190(72.2)	15.87(0.04)
			Neutral	42(16.0)	
			Disagree	31(11.8)	
	The doctor should share the information with the patient in a way that they agree to follow the advice given.	2.59(0.67)	Agree	184(70.0)	8.75(0.36)
			Neutral	51(19.4)	
			Disagree	28(10.6)	
	If the doctor involves the patient in decision-making, it creates difficulties for the patient.	1.49(0.74)	Agree	39(14.8)	14.92(0.06)
			Neutral	53(20.2)	
			Disagree	171(65.0)	
	The doctor should consider the patients as "consumers" and all the available information about the treatment should be shared with them.	2.61(0.70)	Agree	194(73.8)	6.00(0.64)
			Neutral	36(13.7)	
			Disagree	33(12.5)	
	The doctor should not criticize the patient's beliefs, even if these might harm the patient.	2.12(0.83)	Agree	111(42.2)	20.8(0.008)
			Neutral	74(28.1)	
			Disagree	78(29.7)	
Informative	The doctor should explain to the patient all the advantages and disadvantages of the different treatment options available.	2.87(0.41)	Agree	240(91.3)	8.41(0.39)
			Neutral	14(5.3)	
			Disagree	9(3.4)	
	The doctor should find exactly how the patient wants to be involved in making the decision.	2.73(0.59)	Agree	212(80.6)	1 0.52(0.23)
			Neutral	31(13.3)	
			Disagree	17(6.5)	
	The doctor should respect the choice of the treatment that the patient prefers.	2.73(0.56)	Agree	211(80.2)	11.57(0.17)
			Neutral	35(13.3)	
			Disagree	17(6.5)	
	The doctor and patient should together, weigh thoroughly all the different treatment options available.	2.85(0.45)	Agree	236(89.7)	12.25(0.14)
			Neutral	16(6.1)	
			Disagree	11(4.2)	
	The doctor should provide proper information to the patient and give freedom to choose the treatment that better fits patients' medical beliefs.	2.60(0.70)	Agree	193(73.4)	7.58(0.47)
			Neutral	37(14.1)	
			Disagree	33(12.5)	

Overall mean of Paternalistic model=2.28; Informative model= 2.75; interpretive model=2.50; and deliberative model=2.46

Table 3b. Model analysis by Likert scale (Interpretive, Deliberative)

Interpretive	The doctor provides all information to the patient about his health status and or disease	2.25(0.83)	Agree	132(50.2)	17.20(0.02)
			Neutral	65(24.7)	
			Disagree	66(25.1)	
	The doctor brings coherence between the patient's values and priorities	2.27(0.80)	Agree	131(49.8)	11.03(0.20)
			Neutral	73(27.8)	
			Disagree	59(22.4)	
	The doctor helps the patient choose the treatment option that best achieves their values	2.45(0.72)	Agree	156(59.3)	17.33(0.02)
			Neutral	71(27.0)	
			Disagree	36(13.7)	
	The doctor doesn't disapprove of patients' values	2.76(0.58)	Agree	222(84.4)	6.27(0.61)
			Neutral	20(7.6)	
			Disagree	21(8.0)	
	Patients' values are essential to be considered while selecting treatment options	2.78(0.55)	Agree	226(85.9)	8.33(0.40)
			Neutral	18(6.8)	
			Disagree	19(7.2)	
Deliberative	Patients will appreciate it later on when physicians stick to their clinical opinion, even though they disagreed at the beginning	2.19(0.82)	Agree	120(45.6)	19.74(0.01)
			Neutral	74(28.1)	
			Disagree	69(26.2)	
	Patients, when given total autonomy, may harm themselves because of their limited knowledge	2.26(0.79)	Agree	126(47.9)	11.28(0.18)
			Neutral	80(30.4)	
			Disagree	57(21.7)	
	The patient is entitled to complete control of the medical decision, given the actual situational limits	2.22(0.78)	Agree	117(44.5)	11.56(0.17)
			Neutral	88(33.5)	
			Disagree	58(22.1)	
	Informed consent has a crucial role in medical treatment	2.83(0.49)	Agree	233(88.6)	7.31(0.50)
			Neutral	16(6.1)	
			Disagree	14(5.3)	

Table 4: Preference of consultation model by specialities

Model	Speciality	N	Mean (SD)	F	*P*-value
Paternalistic Model	Internal Medicine	93	17.68 (3.17)	1.18	0.31
	Surgery	68	17.30 (2.82)		
	Family medicine	25	17.2 (4.01)		
	Psychiatry	7	16.14 (4.63)		
Informative Model	Internal Medicine	93	21.63 (2.90)	0.37	0.82
	Surgery	68	21.19 (3.75)		
	Family Medicine	25	21.92 (4.10)		
	Psychiatry	7	20.71 (4.53)		
Interpretive Model	Internal Medicine	93	18.96 (2.38)	1.24	0.29
	Surgery	68	19.27 (2.62)		
	Family Medicine	25	18.42 (2.14)		
	Psychiatry	7	18.08 (3.13)		
Deliberative Model	Internal Medicine	93	18.97 (2.32)	1.55	0.18
	Surgery	68	18.98 (2.51)		
	Family Medicine	25	17.84 (3.27)		
	Psychiatry	7	18.57 (2.07)		

Internal Medicine, Surgery, Family Medicine, Psychiatry

Discussion

This study was about health care needs through a partnership between the doctor and patient because expectations from both sides play a vital role in the patients' physical and mental health. Our study found that most doctors practice the blended model. This is consistent with a previous study, in which (36.7%) of their respondents preferred a similar approach [7]. A possible explanation for this finding is that most doctors do not practice the same approach with all their patients. Results of another study showed that the intermingling in terms of individual aptitude and physicians' standpoint was also found to enhance the patient-centred approach [14]. Another finding was that 3 out of 10 physicians aged above 55 years old practiced PM; in a similar study performed in 2001, it was found that 38.42% of physicians aged above 51 years old practised paternalism as well [15]. Age might be the factor affecting choosing the PM. This model is about decision power, and the experienced clinicians attempt to overrule patients' expectations because of their experience. The majority of the respondents agreed with the statement 'the doctor is the expert and should make the decision in most conditions', which measures paternalism.

Additionally, many physicians (73.7%) agreed that 'the doctors should consider the patients' as consumers' - as in the Informative model" and all the available information about the treatment should be shared with them', which measures consumerism. Determining how physicians perceive the relationship between them and their patients is challenging, rendering this relationship complicated. Many factors intervene in producing the final encounter, and what is measured by observation is rarely what happens inside clinics. A study found that the most common single model practiced by physicians in Saudi Arabia was the DM. In contrast, a previous study found that the single most model practiced by the physician was the Inf M [16]; that difference might be due to the cultural and religious differences between the Middle Eastern and Western countries. In a cultural context, physicians from the United States of America (USA) and other European countries support a more consumerist style. It is highly advocated, and it is expected from the physicians to give complete and total control of the decision to the patient (7). Therefore, being a religious and conservative country Saudi Arabia will influence physicians to limit consumerism [17-19]. Additionally, a study on patients in Riyadh, Saudi Arabia, found that 57% of patients prefer a deliberative doctor [20]. This is also consistent with the global trend.
Besides, the DM was the model recommended by Emanuel and Emanuel as the ideal physician-patient relationship arguing that the other models are also needed as aforementioned for the PM and Inf M [3]. A study in the Saudi community reported that the patients overall prefer an approach in which the patient decides with the help of the physician (DM) with shared decision-making, followed by the directive approach (PM). Finally, the physician (Inf M) providing detailed information and letting the patient select what he assumes is best [21]. This relationship, or perhaps the agreement between the doctor and patient on how it should occur, is also essential to achieve patient-centred care, the most advocated approach in modern practice [22].

Effective consultation is equally important for doctors of both genders. Adopting a consultation approach that facilitates addressing the patients' agenda or sickness does lead to

higher levels of patient' satisfaction. The study found that female physicians practiced a less directive approach than their male counterparts did, which is consistent with the findings of another study[16,17]. Cultural context could be the primary cause of this discrepancy in the ratio between male and female doctors working in the Arab world. This trend would be reduced in the future as females are taking more and more opportunities in the Saudi community activities. This study also found no association whatsoever between age or specialty with the consultation model being used. This might be because a global trend which is leaning towards Deliberation has also reached Saudi Arabia.

Limitations

This study didn't include the qualitative aspect of the data. The participants could have been interviewed to seek the depth of their views to choose a particular consultation model. Furthermore, they could have informed the pros and cons of different models. To further deepen the impact of the study, patients could also be included. Therefore, it is suggested that future studies could focus on the qualitative aspect of these consultation models.

Conclusions

The most accepted paternalistic model by the different specialties is internal medicine. Concerning the consultation models being practiced by respondents, the blended approach was the most popular model. The second most commonly used model was the deliberative model. The Interpretive model was the least practiced by clinicians. The novice clinicians preferred the Informative model, whereas the experienced doctors had adopted the blended model. In summary, preferably, a physician should adopt different consultation models according to the varying needs of their patients. This ensures an attitude that is flexible and empathetic, fulfilling patients' expectations and needs.

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Prevalence and Associated Factors of Diabetic ketoacidosis among Patients Living with Type 1 Diabetes in Makkah Al-Mukarramah City

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Abstract

Objective: To assess magnitude of diabetic ketoacidosis (DKA) among type-1 diabetics and to identify associated risk factors.

Methods: A cross-sectional study was conducted among 236 type-1 diabetics in Makkah Al-Mukarramah City, Saudi Arabia.

Results: Among participants, 59.3% were males, 44.1% were diabetic for more than 5 years, while 70.8% reported past history of DKA. The main causes of DKA were “first presentation of the disease” (40.9%), and “discontinued treatment” (37%). The HbA1c among 53.6% was above 9%. Almost all cases who experienced DKA were hospitalised (98.8%). Out of them, 9 (5.4%) suffered complications. Female patients were more likely to suffer from episodes of DKA than males (76% and 68.3%, respectively). Most patients whose parents’ highest education was primary level had DKA more frequently than those whose parents’ had postgraduate education. Patients with unemployed fathers had significantly higher frequency of DKA (p=0.004). Ketoacidosis was significantly more frequent among patients with parents’ consanguinity (p<0.001). Patients who had their current HbA1c level exceeding 9% had positive history of DKA compared to those with HbA1c level ≤7% (87.9% and 28.6%, respectively, p<0.001).

Conclusion: Most type-1 diabetics experience DKA, mainly with their first presentation of disease or due to discontinuation of treatment. DKA tends to occur more frequently among female patients, those with less educated parents or when their parents are relatives.

Key words: Type 1 diabetes, diabetic ketoacidosis, magnitude, risk factors.

Advances in Knowledge

1. This study rang a warning bell towards parents' consanguinity among type-1 diabetics as a risk factor for diabetic ketoacidosis.
2. The current search revealed the lack of public's awareness about type-1 diabetes and its complications as well as their low compliance towards its treatment, since diabetic ketoacidosis occurred mainly at the first presentation of the disease among diabetics, or due to treatment discontinuation.

Application to Patient Care

1. This study indicated the importance of raising the public's awareness regarding early symptoms of diabetes among their children so as to be ready to seek medical advice as early as possible before the occurrence of complications.
2. Health education messages should be repeatedly broadcast via mass media explaining the hazards associated with consanguineous marriages.
3. Health care providers should stress to diabetic patients and/or their caregivers the importance of compliance to treatment.

Introduction

During childhood and adolescence, type-1 diabetes mellitus (T1DM) is considered the most common endocrine-metabolic disorder and one of the major threats to human health (1-2). Almost one in 300 youths develop T1DM (3). Worldwide, it has been reported that the incidence of T1DM is increasing by 3-4% per year (4).

Diabetic ketoacidosis (DKA) usually occurs as a result of insulin deficiency. It is a serious acute complication of diabetes mellitus (DM), which accounts for most hospitalizations due to severe insulin deficiency (5). It consists of the biochemical triad of ketonaemia, hyperglycaemia and acidaemia (6). Among children, the criteria for diagnosis of DKA includes blood glucose above 11 mmol/L, venous pH less than 7.3, or bicarbonate less than 15 mmol/L, and ketonaemia with ketonuria (7).

Although major advances have been achieved in the fields of care for diabetic patients, DKA continues as a significant cause of morbidity and mortality (8). It is frequently the main presenting symptom for new-onset cases in 25% to 30% of T1DM cases (9).

The incidence of DKA is difficult to establish, but it continues to increase, accounting for about 140,000 hospitalizations in the US in 2009 and more than 500,000 hospital days annually (10). Even with the promising statistics and raised awareness, the occurrence of DKA continues to be as high as 30% in children with T1DM (11).

The clinical presentation of DKA usually develops rapidly, over a period of less than 24 hours. Several days before development of DKA, several symptoms may develop, i.e., polyuria, polydipsia, and weight loss. The presenting symptoms usually include vomiting and abdominal pain (12). Physical examination of a patient with DKA shows signs of dehydration, e.g., loss of skin turgor, dry mucous membranes, tachycardia, and hypotension. Patient's level of consciousness varies from being full alert to loss of consciousness (13).

Although the diagnosis of DKA can be suspected on clinical grounds, confirmation is usually based on results of laboratory tests. The most widely used diagnostic criteria for DKA in the past was a blood glucose level more than 250 mg/dL, a moderate degree of ketonaemia, serum bicarbonate less than15 mEq/l, arterial pH less than 7.3, and an increased anion gap metabolic acidosis (13).

It is possible to prevent DKA by the establishment of better access to medical care, proper health education, and ensuring effective communication with health care providers during an intercurrent illness. It is also essential that family members become involved. Therefore, they should be educated on insulin regimen and patient's blood glucose assessment. Moreover, a written care plan should be provided to diabetic patients and/or their caregivers, as this is essential to enhance their understanding of the importance of diabetes self-management (14).

The use of ketone-meters that detect blood β-hydroxy-butyrate has also been shown to help early detection and management of ketosis, which may decrease the need for specialised care. Short-acting insulin may be administered with fluids, early on for the prevention of DKA (15).

The incidence of T1DM in Saudi Arabia total number of cases of T1DM in children under the age of 12 years was 22 with an estimated prevalence of 106.7/100,000 (16). The incidence rate of T1DM is growing in Saudi Arabia(17).

DKA is the most severe health problem among diabetic children and adolescents (5). It is typically caused by treatment non-compliance, i.e., shortage of insulin and may be precipitated by several factors, e.g., infections. Although DKA can be a life-threatening event for type-1 diabetics, it is a preventable condition. Recent advances in diabetes management could not minimize prevalence of DKA among children with T1DM (11). Despite the severity of DKA, research examining the event is limited in the empirical literature. Therefore, the identification of prevalence of DKA and its associated risk factors is a pressing necessity (18).

This study aimed to assess prevalence of DKA and to identify risk factors associated with it among Saudis with T1DM in Makkah Al-Mukarramah City.

Methodology

A cross-sectional study design was followed at the Diabetes and Endocrine Unit in the Maternity and Children's Hospital, and the Diabetes and Endocrine Center in Herra General hospital in the Holy City of Makkah Al-Mukarramah, Saudi Arabia. This study received the approval of the Ethical Research Committee of Makkah Al-Mukarramah Region on May 31st, 2018. The study was conducted between

January 2018 and July 2018 and included 236 Saudi type-1 diabetic patients aged 1-19 years.

Based on relevant literature, a study questionnaire was designed in simple Arabic Language by the researcher. It comprised the following:

• Personal data: Age, gender, duration of diabetes, parents' education, parents' employment status, consanguinity between parents and family history of diabetes.
• DKA data: Number of DKA incidents, expected cause(s) for DKA, hospitalization, complications, receiving health education at the Diabetes Clinic.
• Laboratory findings: HbA1c level.

Parents' consanguinity was classified according to Rohde et al. (19), as follows:

• First degree consanguinity: If parents share grandparents but have different parents (i.e., first degree cousins);
• Second degree consanguinity: If parents share great grandparents but have different grandparents (i.e., second degree cousins).

The study questionnaire validity (face and content) was assessed by three academic professors of Community Medicine.

A pilot was conducted on 22 diabetics, aiming to test the clarity and wording of the study questionnaire. Moreover, test-retest reliability of responses for included statements was assessed by applying the study questionnaires twice to the same participants, one week apart and the correlation coefficients for each response was calculated. Moreover, internal consistency of study questionnaire was assessed by applying the Cronbach's alpha coefficient.
The study settings were visited by the researcher during June and July 2018. All type-1 diabetic patients attending the Endocrine Clinic (and their caregivers) were briefed regarding the objectives of the study and were then invited to participate in the study. During data collection, participants were consecutively included in the study. The researcher then distributed the self-administered questionnaire sheet to each participant (or his/her caregiver). The questionnaire sheets were then collected immediately after being filled. The researcher repeated the daily visits till the required sample size was fulfilled.

The Statistical Package for Social Sciences (SPSS), version 25, was used for data entry and statistical analysis. Descriptive statistics (e.g., number, percentage, mean, range, standard deviation) and inferential statistics, using chi-square "$\chi 2$" test was applied. P-values <0.05 were considered as "statistically significant".

All necessary official permissions were secured by the researcher before the start of the data collection. Before the data collection, all patients and their caregivers were verbally informed about the study objectives, and a written form (informed consent) was fulfilled. Confidentiality and privacy were fully secured for all patients.

Results

Characteristics of the study group:
Most patients were males (59.3%), their mean age was 10.7±4.3 years. Regarding parental characteristics, Table 1 demonstrates that almost two thirds of the fathers had either secondary level of education (34.9%) or university qualifications (32.1%) in addition to 7.6% who had postgraduate degrees, with comparable percentages in mothers where 28.1% had secondary level of education and 35.5% had university qualifications and 2.3% had postgraduate degrees. While the majority of fathers (66.8%) had jobs; only 27.3% of the mothers indicated that they had jobs. Consanguinity was identified in almost one half of the parents (51.1%), out of them 34.9% shared the same grandparents.

Regarding clinical characteristics of the patients, Table 2 shows that most patients (84.5%) had been diagnosed with diabetes mellitus more than one year earlier. Almost one half of the patients (48.3%) had positive family history of diabetes mellitus; out of them, 12.7% in first degree and 4.7% in both first and second degree relatives. Respecting the last reading of HbA1c level, it was found that the overwhelming majority of the patients (91%) had HbA1c level exceeding 7%, out of whom, there was 53.6% who had HbA1c level more than 9%.

History of Ketoacidosis:
Figure 1 shows that most patients (70.8%) experienced ketoacidosis before. Out of them, there were 30.9% who had it once, 17.4% had it twice, and a total of 22.3% who had three or more episodes of ketoacidosis before.

Figure 2 shows that among 167 patients who experienced ketoacidosis before, for 41.9% it was their first presentation of diabetes mellitus. In 37.7%, ketoacidosis was attributed to discontinuation of treatment, and in 10.8%, it was attributed to non-adherence to diet.

It is to be noted that almost all cases who experienced DKA were admitted to hospitals (165; 98.8%). Out of them, only 9 (5.4%) suffered from complications.

Factors associated with ketoacidosis:
Table 3 demonstrates that, although female patients were more likely to suffer from episodes of DKA than males (76%, 68.3%, respectively), this difference is not statistically significant. Also, despite the apparent difference in the frequency of DKA according to education levels of the fathers, where 92.9% of the patients whose fathers had primary level of education had history of ketoacidosis compared to only 52.9% of patients whose fathers had postgraduate degrees, this difference was not statistically significant. The same was also observed with regards to mothers' educational levels, where the highest frequency was recorded in patients with illiterate mothers (89.5%), while the lowest was observed in patients whose mothers were university qualified (59.7%). Moreover, no statistically significant difference was observed according

Table 1: Demographic characteristics of the patients (n=236)

Characteristics	No.	Percentage
Gender:		
• Male	140	59.3
• Female	96	40.7
Father's education level (n=218):		
• Primary	14	6.4
• Intermediate	41	18.8
• Secondary	76	34.9
• University	70	32.1
• Postgraduate	17	7.8
Mother's education level (n=217):		
• Illiterate	19	8.8
• Primary	21	9.7
• Intermediate	34	15.7
• Secondary	61	28.1
• University	77	35.5
• Postgraduate	5	2.3
Father's job (n=208):		
• Jobless	69	33.2
• Teacher	54	26.0
• Military	27	13.0
• Physician	8	3.8
• Others	50	24.0
Mother's job (n=209):		
• Jobless	152	72.7
• Teacher	26	12.4
• Others	31	14.9
Consanguinity among parents (n=229):		
• Yes with same grandparents	80	34.9
• Yes with different grandparents	37	16.2
• No	112	48.9

Table 2: Clinical characteristics of the patients (n=236)

Characteristics	No.	Percentage
Duration of diabetes mellitus:		
• < one year	37	15.7
• 1-5 year	95	40.3
• >5 years	104	44.1
Family history of diabetes mellitus:		
• Yes	114	48.3
• First degrees relative	30	12.7
• Second degree relative	73	30.9
• Both first and second degree relatives	11	4.7
• No	122	51.7
HbA1c level (n=233):		
• ≤ 7	21	9.0
• >7-9	87	37.3
• >9	125	53.6

Table 3: Characteristics of ketoacidosis among type 1 diabetics

Characteristics	No.	%
History of ketoacidosis		
• Absent	69	29.2
• Present	167	70.8
Frequency of ketoacidosis		
• Once	73	30.9
• Twice	41	17.4
• Three times	24	10.2
• Four times	14	5.9
• Five times	15	6.4
Predisposing factors for ketoacidosis		
• First presentation	70	41.9
• Treatment discontinuation	63	37.7
• Non-adherence to diet	18	10.8
• Infectious diseases	11	6.6
• Others	5	3.0

Figure 1: History of ketoacidosis among T1DM patients

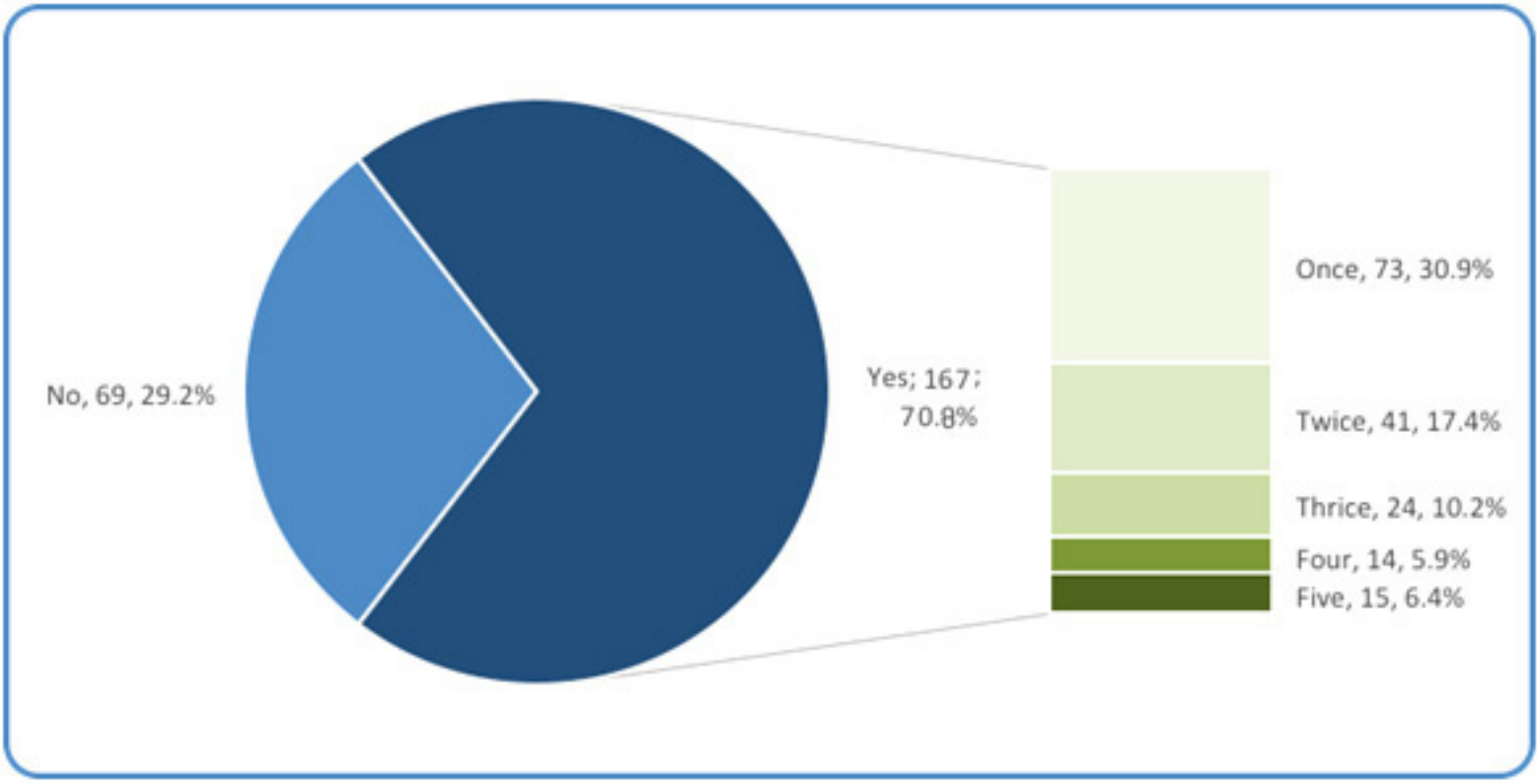
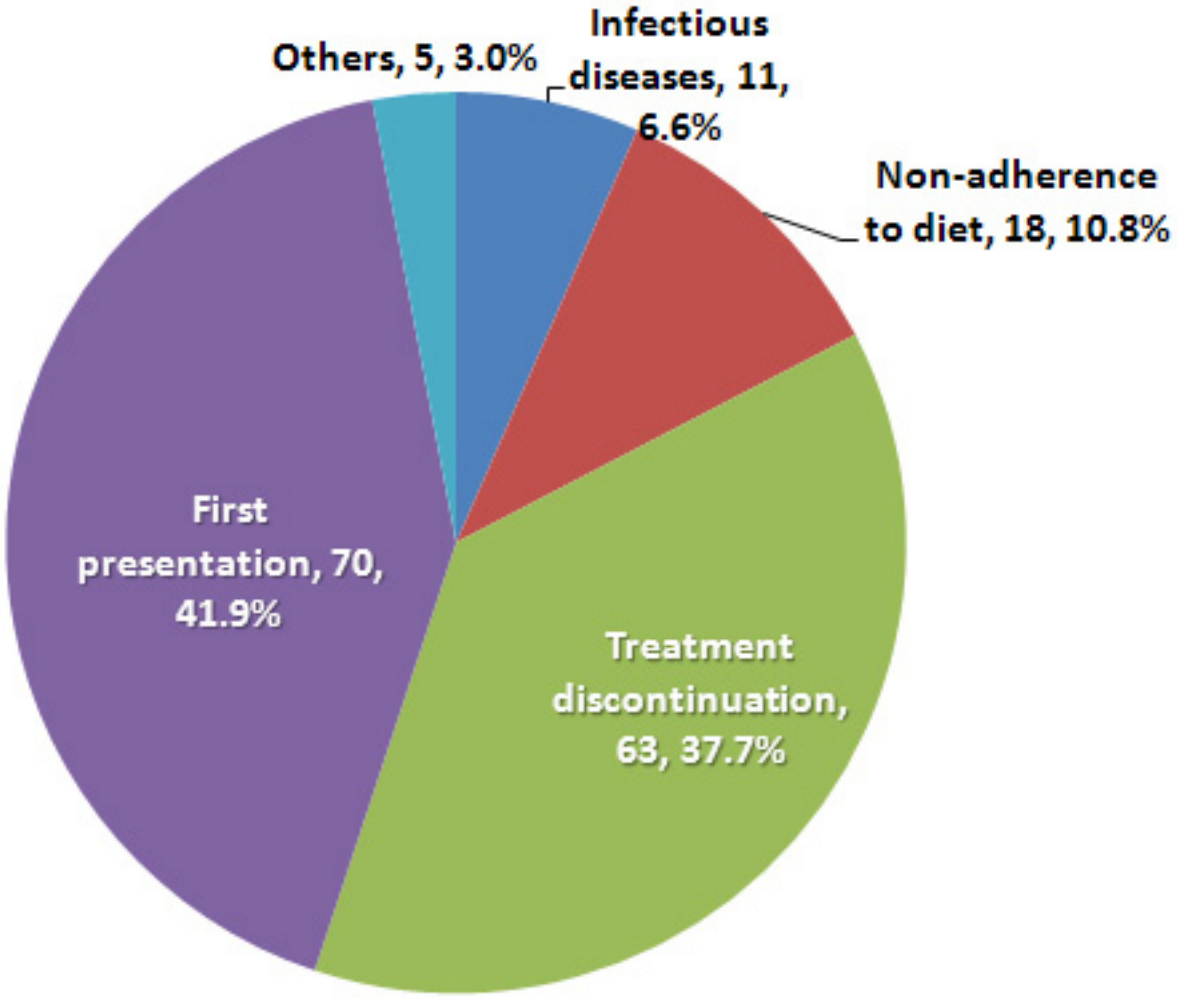


Figure 2: Predisposing factors of ketoacidosis among T1DM patients (n=167)



Frequency of DKA was significantly higher among patients with jobless fathers (79.7%), compared to patients whose fathers were employed (p-0.004). Moreover, ketoacidosis was significantly higher in presence of consanguinity of the parents, whether with same grandparents (86.5%) or with different grandparents (86.2%), compared to only 55% where there is no consanguinity (p<0.001).

As shown in Figure 3, there was no significant difference in age of those who had history of DKA and those who did not have DKA (Mean±SD: 10.5±4.6 and 11.1±3.6, respectively).

Table 4 shows that when patients were compared according to age groups, being children (≤12 years) or adolescents 13-18 years old. Moreover, there was no statistically significant differences between children and adolescents regarding frequency of diabetic ketoacidosis and possible predisposing factors, nor the last reading of HbA1c.

Table 5 illustrates that there was no statistically significant difference between the patients regarding history of DKA and duration since diagnosis of DM. Nevertheless, it was noted that DKA was significantly less among patients who had family history of DM than among those who did not have family history of DM (59.3% and 82.1%, respectively, p<0.001). Further analysis showed that there was no statistically significant difference within those who had familial history of diabetes mellitus according to the relation with the member who had the disease. Moreover, while the great majority of patients who had current HbA1c level above 9% (87.9%) had positive history of DKA compared to only 28.6% of patients who had their current HbA1c level ≤7%. This difference was statistically significant (p<0.001).

Figure 3: History of diabetic ketoacidosis according to age of the T1DM patients

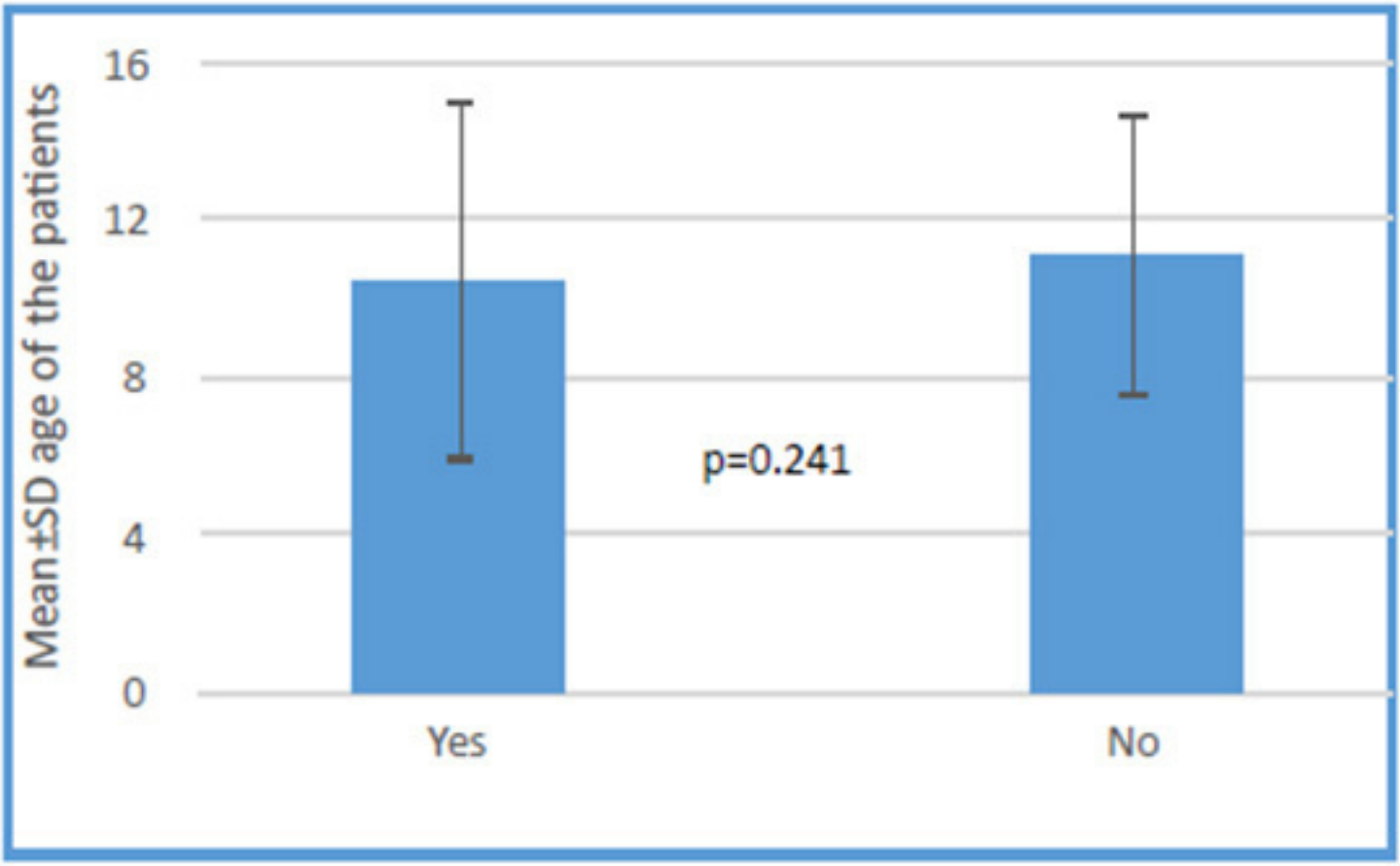


Table 4: Differences in occurrence of ketoacidosis according to demographic characteristics of the patients

Characteristics	History of ketoacidosis					P Value
	Yes		No			
	No.	%	No.	%	χ^2	
Gender						
• Male	95	68.3	44	31.7		
• Female	73	76.0	23	24.0	1.650	0.199
Fathers' education						
• Primary	13	92.9	1	7.1		
• Intermediate	28	68.3	13	31.7		
• Secondary	58	76.3	18	23.7	8.144	0.086
• University	45	65.2	24	34.8		
• Postgraduate	9	52.9	8	47.1		
Mothers' education						
• Illiterate	17	89.5	2	10.5		
• Primary	17	81.0	4	19.0		
• Intermediate	23	67.6	11	32.4		
• Secondary	45	75.0	15	25.0	9.586	0.088
• University	46	59.7	31	40.3		
• Postgraduate	4	80.0	1	20.0		
Fathers' job						
• No job	55	79.7	14	20.3		
• Teacher	39	72.2	15	27.8		
• Military	21	77.8	6	22.2	15.460	0.004*
• Physician	5	62.5	3	37.5		
• Others	24	48.0	26	52.0		
Mothers' job						
• No job	55	79.7	14	20.3		
• Teacher	16	61.5	10	38.5	0.992	0.609
• Others	21	67.7	10	32.3		
Parents' consanguinity						
• Yes, with same grandparents	69	86.2	11	13.8		
• Yes, with different grandparents	32	86.5	5	13.5	27.253	<0.001*
• No	61	55.0	50	45.0		

* Statistically significant

Table 5: Clinical characteristics of the patients according to their age category

Characteristics	Age category of patients				χ^2	P value
	No.	%	No.	%		
History of ketoacidosis						
• Yes	107	70.9	61	72.6		
• No	44	29.1	23	27.4	27.4	0.775
Frequency of ketoacidosis						
• Once	51	47.7	22	36.7		
• Twice	24	22.4	17	28.3		
• Thrice	16	15.0	8	13.3	4.460	0.347
• Four times	6	5.6	8	13.3		
• Five times	10	9.3	5	8.3		
Predisposing factors						
• First presentation of disease	49	45.8	21	35.0		
• Infectious cause	7	6.5	4	6.7		
• Discontinuation of treatment	37	34.6	26	43.3	3.021	0.554
• Non-adherence to diet	10	9.3	8	13.3		
• Others	4	3.7	1	1.7		
HbA1c:						
• ≤7	2	1.9	4	6.7		
• >7-9	34	32.1	17	28.3	2.480	0.289
• >9	70	66.0	39	65.0		

Discussion

Results of this study showed that more than two thirds of the participants experienced DKA at least once. Moreover, 41.9% attributed their DKA incidents to their first presentation of the disease, while 37% attributed their incidents to discontinuation of the treatment.

This prevalence is higher than what has been reported in a Polish study, (20) which reported that one-quarter of T1DM children presented with DKA at their first diagnosis, while in New-Zealand, the rate was reported to be 27% (21). Nevertheless, it is lower than that reported in a Nigerian study, where about three-quarters of diabetics presented with DKA (22).

Al-Hayek et al. (23), in Saudi Arabia, reported all their 103 adolescent T1DM patients had DKA, where 54.4% experienced one episode, and the main reason was the discontinuation of insulin treatment.

An American study reported stability in the rate of DKA among youth with T1DM, even though it is still high (more than third). This indicates the importance and the need for increasing awareness of signs and symptoms of diabetes and providing better access to health care. However, this rate was lower among youth with T1DM (11).

Essential health education to patients and their guardians in PHCCs is essential and is considered as an effective method to decrease DKA episodes. Consequently, every consultation at a health care facility should be used ideally so that DM patients can get the maximum benefits from the health care providers. Knowledge related to “DM & DKA” must be repeated at every visit (20).

The present study showed that, from the 168 DKA cases, 165 were admitted to the hospital, and only 9 reported complications with no death.

Globally, prevalence of case fatality due to DKA ranges from 0.3% to 1%, and it is mainly due to cerebral edema (24).

The present study showed a significant association between DMK episodes and both consanguinity and family history.

This finding is consistent with that reported by the Satti et al. study in Al-Baha, Saudi Arabia, (1) and the Zayed study, (25) where consanguineous marriages ranged from 27.3% to 67.8%.

It is to be noted that, due to cultural factors, consanguineous marriage is a common practice in the Arab world, mainly first-cousins marriage. This habit is responsible for the spread of genetic diseases (25).

Several studies reported that DKA is higher among female than male adolescents. This could be explained by several factors (22;25). The first is attributed to puberty-associated hormonal changes, especially the raising of serum levels of some counter-regulatory hormones, e.g., estrogen, which is, by far, higher in girls than boys at puberty (22). The second factor is related to body-image psychiatric problems, including eating problems, since adolescent diabetic girls often miss insulin injections for the sake of losing weight. Moreover, girls with DKA may have more behavioral problems, lower social competence, and higher levels of family struggle (25).

However, in the current study, there was an association between gender and DKA episodes, but the result was not statistically significant. This is similar to the results of the Al-Hayek et al. study, where DKA was higher among females than males (23).

Several studies, including our study, stated that patients with poorer glycemic control had higher risks of DKA, particularly those with HbA1c ≥10% (25-27).

Results of the present study showed no significant association between age category and DKA episodes, etiology, hospitalization, and HbA1c, even though the rate was higher among children than adolescents regarding episodes, etiology, hospitalization, and HbA1c.

Conclusion

More than two thirds of T1DM cases aged below 20 years, experience DKA. The main risk factors for DKA include first presentation of disease, and discontinuation of treatment. Most DKA cases become hospitalised, while less than one-tenth become complicated. Female patients are more likely to suffer from episodes of DKA than male patients. Most cases with history of DKA have uncontrolled HbA1c. DKA is higher among patients with less educated parents and among those with unemployed fathers. DKA is significantly higher among patients with consanguineously married parents.

Therefore, primary health care providers should provide the necessary health education on DKA for all T1DM patients and/or their caregivers. Health education messages should cover the main points of knowledge gaps, especially how to identify and manage sudden hyperglycaemia and raising the public’s awareness regarding DM and DKA through mass media. Patients and their caregivers should be encouraged to talk about DM with their physicians and to pay regular follow up visits for diabetes control. Further nation-wide prospective studies are needed to assess incidence of DKA and its associated risk factors.

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Gender differences of the clinical aspects and complication risks of diabetes mellitus among outpatient clinic visits, Jeddah, Saudi Arabia

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Abstract

Background: Gender differences are important in epidemiology, pathophysiology, treatment, and outcomes in Type 2 DM,

Objectives: To study gender differences of the burden of type 2 diabetes and complication risk among Saudi subjects visiting the outpatient clinics.

Subjects and methods: A cross sectional study, including 2501 patients, who visited the outpatient clinics at two private general hospitals in Jeddah during the years 2018 through to 2019. All patients were examined and diagnosed by specialists.

Data were collected using check list form to obtain personal characteristics and area of residence; vital signs, anthropometric measurements, clinical characteristics and outcome of the visits. Statistical analysis: SPSS version 23 (IBM), was used. Chi square, and logistic regression tests were used. OR, and 95% IC were used to describe the relationships. Level of significance was 0.05.

Results: Out of all the visits to the outpatient clinics, DM constituted 5.5%. Type 2 DM was common in those aged 40 years and above, while Type 1 DM was common in those aged 18 years and younger. Males were at 1.7 times more likely to develop DM compared to females (OR 1.715; 95% CI: 1.146, 2.257, p <0.009). The males with T2DM had significantly more frequent edema of the lower limbs compared to the females. Polyuria was the most common symptom, while HBA1C and FBS were the most common investigations ordered, and Biguanides and sulfonylurea and insulin were the common treatment prescribed. These were similar in both the males and females. Hypertension (22%), IHD (6%), and dyslipidemia (6%) were encountered among patients with T2DM; however, these CVDs were similar in the males and females.

Conclusion: DM is a common chronic disorder, which imposes burden on the primary health care in Saudi Arabia. It is more common in males than females, however, the pattern of cardiovascular complications and health care management were similar in both genders.

Key words: DM, Gender, outpatient clinics, Saudi Arabia,

Background

Diabetes Mellitus (DM) is a common metabolic disease; it is caused by defective insulin secretion by pancreatic β-cells and/or the inability of insulin-sensitive tissues to respond to insulin. It is classified as type 1 DM (T1DM), and type 2 DM (T2DM), and those with ketoacidosis (DKA) as a complication of uncontrolled DM (1 - 4). Diabetes affects a substantial proportion of hospitalized patients and is associated with considerable costs. Biologically males and females have similar diabetes prevalence. Gender differences in the social structure, gender differentials in diagnosis, access to care, access to medications and follow up, adherence to medications, life style modifications and all other self-care behaviors are likely to introduce a dramatic contrast in the experiences of women with diabetes. Prevalence of T2DM is higher in young women than young men (5 - 7). DM is associated with multi-system symptoms e.g. fatigue, urinary incontinence and polyuria, neuropathy, gastrointestinal manifestations, and headache (8 -16). DM is usually associated with comorbidities e.g. thyroid dysfunction, hypertension, dyslipidemia and cardiovascular disorders and neuroglycopenia (17 - 22). As DM is a systemic disorder which affects different systems of the body, routine investigations done on patients with DM may include a multitude of tests in addition to those to assess the blood sugar level (23-30). There are different types, or classes, of drugs that work in different ways to lower blood sugar levels: Alpha-glucosidase inhibitors, Biguanides, Bile Acid Sequestrants, Dopamine-2 Agonists, DPP-4 inhibitors, Meglitinides, SGLT2 Inhibitors, Sulfonylureas, TZDs , and Oral combination therapy (31-34). The aim of this study was to explore the impact of gender differences on the burden, clinical aspects and management of DM among outpatient visits.

Subjects and methods

It was a cross sectional study which was conducted in the outpatient clinics of two private general hospitals; one in a relatively high socioeconomic standard region, and the other in a relatively lower socioeconomic standard region of Jeddah city, Saudi Arabia. The sampling technique was a non-probability convenient one; the total number of patients examined was 2501 during a two yearsperiod (2018 – 2019). Data were collected on the patients by specialists in the outpatient clinics; it included clinical history, anthropometric and vital signs assessments, clinical assessment (which included physical examination, diagnosis, investigations and management), and outcome of the visits. Data were analyzed using the Statistical Package for Social Sciences (IBM SPSS, version 22, Armonk, NY: IBM Corp.). Chi Square and multinomial logistic regression tests of significance were employed. The Odds ratio (OR), and 95% confidence interval (95% CI) were calculated. The level of significance for the study was 0.05.

Ethical considerations

Ethical clearance was obtained from the institutional research review board (IRRB). Permission was obtained from the directors of the outpatient clinics for collecting data on the outpatient visits. In order to keep confidentiality of any information provided by study participants, the data collection procedure was anonymous.

Results

Table 1 shows the distribution of outpatient clinics (OPCs) visits according to type of diabetic disorders. Out of all the visits, those due to DM were 5.5%. T1DM was the most common in those aged 18 years or less (75%), while T2DM was most common in those aged 40 years old or older (95.5%). DKA was recorded only in those younger than 18 years old. These differences were statistically significant where p value was < 0,000. T2DM was higher in males compared to females (72.9% and 27.1% respectively); while T1DM and DKA were similar in both genders ($p < 0.005$). T2DM and DKA (62% and 100% respectively) were more common in the North of Jeddah region compared to the Southern region (37.6% and 0.0% respectively); this difference was statistically significant ($p <0.029$). The majority of patients with T2DM were discharged (96.2%) compared to patients with T1DM (75%); on the other hand all patients with DKA were admitted to the hospital. These differences were statistically significant where $p < 0.000$.

Table 2 reveals the distribution of outpatient visits due to T2DM according to presenting symptoms and signs. A large proportion of patients with T2DM visited the OPCs for follow up (46.6) and renewal of medicine. Polyuria was the most frequent complaint (11.3%) among the T2DM patients; fatigue, headache, and dyspepsia (9.0% each) were also common complaints among T2DM patients. Numbness in the hands and feet (6.8%), dizziness and polydipsia (5.3 each), and oedema of the lower limbs (3.8%) were reported complaints by the T2DM patients. Least frequent complaints were weight gain (1.5%) and weight loss, heartburn and hypotension (0.8% each). All these complaints were similar in males and females ($p >0.05$), except for oedema of the lower limbs which was significantly more common in males (11.0%) compared to females (1.0%), where $p < 0.007$. Among patients with T2DM, 22.0% had HTN, 8.3% had IHD, 6. 0% had dyslipidaemia, while DVT was encountered among 0.8% of the patients. No significant differences were found between males and females regarding these CVDs ($p > 0.05$).

Table 3 displays distribution of T2DM patients according to gender and type of investigation done. The majority of blood tests for assessment of DM were HBA1C (36.1%) and FBS (35.3%). RBS was done on 18.8% of the patients, while 2HPPG test was the least to be ordered (3.0%). No significant differences were found between males and females in ordering these investigations ($p > 0.05$). Next in frequency were tests for lipid profile (17.5%), Serum creatinine (16.5%), and urine analysis 15.0%).

Table 4 reveals the distribution of the T2DM patients according to gender and type of medication prescribed. About 13% of the patients with T2DM were prescribed insulin to control DM, mainly in the form of short acting insulin (SAI, 5.3%), and combination insulin (4.5%). Rapid acting insulin (RAI: 1.5%) and long acting insulin (LAI: 1.5%), were also prescribed to some T2DM patients. None of the patients with T2DM was prescribed intermediate acting insulin (IAI: 0.0%). No significant differences were found between males and females ($p > 0.05$). The groups of oral T2DM drugs included mainly biguanide antidiabetic medication 24.8%), Sulfonylureas medication (24.8%), Dipeptidyl peptidase drugs (6.0%) and to a lesser extent thiazolidinedione drugs (3.8%). The following antidiabetic drugs: Amylinomimetic, Alpha-glucosidase inhibitors, Dopamine agonist, GLP-1, Meglitinides, and SGLT were not prescribed to any patient with T2DM. This was similar in both males and females ($p > 0.05$). Vitamin B complex preparations (24.8%), and antihypertensive drugs (21.8%) and to some extent hypolipidemic drugs (6.8%) were, also, prescribed to patients with T2DM. Aspirin was prescribed to only, 3.8% of the patients. No significant differences were found between males and females ($p > 0.05$).

Table 5 reveals the Multi-nominal Logistic regression results between DM and age, gender, district and hospital admission. DM tends to occur among relatively younger age groups in patients who visit the outpatient clinics (B = - 0.065). Females were at 1.7 times more risk to develop DM compared to males (OR: 1.715; 95% CI: 1.146, 2.570, $p < 0.009$).

Table 1: Distribution of studied subjects according to having DM and personal and sociodemographic variables

Variables	Diabetes mellitus					X2 (p-value)
	No DM No %	T1DM N0 %	T2DM No %	DKA No %	Total No %	
Age (years)						
<18	1118 47.3%	3 75.0%	3 2.3%	2 100.0%	1126 45.0%	223.414 (.000)
18 - <40	481 20.4%	0 0.0%	3 2.3%	0 0.0%	484 19.4%	
40+	763 32.3%	1 25.0%	127 95.5%	0 0.0%	891 35.6%	
Gender						
Male	1353 57.3%	2 50.0%	97 72.9%	1 50.0%	1453 58.1%	12.830 (.005)
Female	1009 42.7%	2 50.0%	36 27.1%	1 50.0%	1048 41.9%	
District						
South	1050 44.5%	4 100.0%	50 37.6%	0 0.0%	1104 44.1%	9.048 (.029)
North	1312 55.5%	0 0.0%	83 62.4%	2 100.0%	1397 55.9%	
Outcome						24.225 (.000)
Discharged	2054 87.0%	3 75.0%	128 96.2%	0 0.0%	2185 87.4%	
Admitted	308 13.0%	1 25.0%	5 3.8%	2 100.0%	316 12.6%	

Table 2: Distribution of Type 2 DM patients according to gender and reason for visit outpatient clinics and clinical aspects

Variable	Categories	Doctor diagnosed DM				*Total*		*X2* (p- value)
		Male		Female				
		N	%	N	%	N	%	
Come for follow up	No	53	54.6%	18	50.0%	71	53.4%	.227[a] (.634)
	Yes	44	45.4%	18	50.0%	62	46.6%	
Fatigue	No	89	91.8%	32	88.9%	121	91.0%	.227[a] (.609)
	Yes	8	8.2%	4	11.1%	12	9.0%	
Polydipsia	No	92	94.8%	34	94.4%	126	94.7%	.008[a] .927
	Yes	5	5.2%	2	5.6%	7	5.3%	
Polyuria	No	86	88.7%	32	88.9%	118	88.7%	.001[a] .970
	Yes	11	11.3%	4	11.1%	15	11.3%	
Polyneuritis	No	89	91.8%	35	97.2%	124	93.2%	1.245[a] .265
	Yes	8	8.2%	1	2.8%	9	6.8%	
Dizziness	No	92	94.8%	34	94.4%	126	94.7%	.008[a] .927
	Yes	5	5.2%	2	5.6%	7	5.3%	
Hypotension	No	96	99.0%	36	100.0%	132	99.2%	.374[a] .541
	Yes	1	1.0%	0	0.0%	1	0.8%	
Edema of lower limbs	No	96	99.0%	32	88.9%	128	96.2%	7.374[a] .007
	Yes	1	1.0%	4	11.1%	5	3.8%	
Headache	No	87	89.7%	34	94.4%	121	91.0%	.723[a] .395
	Yes	10	10.3%	2	5.6%	12	9.0%	
Heartburn	No	96	99.0%	36	100.0%	132	99.2%	.374[a] .541
	Yes	1	1.0%	0	0.0%	1	0.8%	
Dyspepsia	No	87	89.7%	34	94.4%	121	91.0%	.723[a] .395
	Yes	10	10.3%	2	5.6%	12	9.0%	
Weight gain	No	95	97.9%	36	100.0%	131	98.5%	.754[a] .385
	Yes	2	2.1%	0	0.0%	2	1.5%	
Weight loss	No	96	99.0%	36	100.0%	132	99.2%	.374[a] .541
	Yes	1	1.0%	0	0.0%	1	0.8%	
History of Hypertension	No	78	80.4%	25	71.4%	103	78.0%	1.211[a] .271
	Yes	19	19.6%	10	28.6%	29	22.0%	
History of Ischemic heart disease	No	89	91.8%	33	91.7%	122	91.7%	0.000 .987
	Yes	8	8.2%	3	8.3%	11	8.3%	
Deep vein Thrombosis	No	96	99.0%	36	100.0%	132	99.2%	.374[a] .541
	Yes	1	1.0%	0	0.0%	1	0.8%	
Dyslipidemia	No	93	95.9%	32	88.9%	125	94.0%	2.268[a] .132
	Yes	4	4.1%	4	11.1%	8	6.0%	

Table 3: Distribution of Type 2 DM patients according to gender and type of investigation done on them

Variable	categories	Doctor diagnosed DM				Total		X2 (p- value)
		Male		Female				
		N	%	N	%	N	%	
1. FBS	No	62	63.9%	24	66.7%	86	64.7%	
	Yes	35	36.1%	12	33.3%	47	35.3%	
2 Hours Post Prandial Glucose test	No	94	96.9%	35	97.2%	129	97.0%	.009[a] (.925)
	Yes	3	3.1%	1	2.8%	4	3.0%	
Random Blood sugar	No	75	77.3%	33	91.7%	108	81.2%	3.541[a] (.060)
	Yes	22	22.7%	3	8.3%	25	18.8%	
Glycosylated hemoglobin	No	58	59.8%	27	75.0%	85	63.9%	2.632 (105)
	Yes	39	40.2%	9	25.0%	48	36.1%	
Lipid profile	No	78	80.4%	32	88.9%	110	82.7%	1.319[a] (.251)
	Yes	19	19.6%	4	11.1%	23	17.3%	
Urine analysis	No	84	86.6%	29	80.6%	113	85.0%	.750[a] (.386)
	Yes	13	13.4%	7	19.4%	20	15.0%	
Serum creatinine	No	82	84.5%	29	80.6%	111	83.5%	.301[a] (.583)
	Yes	15	15.5%	7	19.4%	22	16.5%	
Serum uric acid	No	93	95.9%	34	94.4%	127	95.5%	.125[a] (.724)
	Yes	4	4.1%	2	5.6%	6	4.5%	
Complete Blood Count	No	91	93.8%	33	91.7%	124	93.2%	.192[a] (.661)
	Yes	6	6.2%	3	8.3%	9	6.8%	
ALT & AST	No	95	97.9%	34	94.4%	129	97.0%	1.099[a] (.295)
	Yes	2	2.1%	2	5.6%	4	3.0%	
Sodium and potassiuminblood	No	95	97.9%	35	97.2%	130	97.7%	.061[a] (.805)
	Yes	2	2.1%	1	2.8%	3	2.3%	
T3 AND T4	No	97	100.0%	35	97.2%	13299.2%		2.715[a] (.099)
	Yes	0	0.0%	1	2.8%	1	0.8%	
H pylori	No	96	99.0%	34	94.4%	130	97.7%	2.438[a] (.118)
	Yes	1	1.0%	2	5.6%	3	2.3%	
I Troponin	No	93	95.9%	35	97.2%	128	96.2%	.131[a] (.717)
	Yes	4	4.1%	1	2.8%	5	3.8%	
Echocardiography	No	94	96.9%	35	97.2%	129	97.0%	.009[a] (.925)
	Yes	3	3.1%	1	2.8%	4	3.0%	
ECG	No	93	95.9%	33	91.7%	126	94.7%	.933[a] (.334)
	Yes	4	4.1%	3	8.3%	7	5.3%	

Table 4: Distribution of Type 2 DM patients according to gender and type of treatment given

Variable	categories	Doctor diagnosed DM				Total		X2 (p- value)
		Male		Female				
		N	%	N	%	N	%	
SAI	No	93	95.9%	33	91.7%	126	94.7%	.933[a] (.334)
	Yes	4	4.1%	3	8.3%	7	5.3%	
RAI	No	96	99%	35	97.2%	131	98.5%	.541[a] (.462)
	Yes	1	1%	1	2.8%	2	1.5%	
IAI	No	97	100.0%	36	100.0%	133	100.0%	
	Yes							
LAI	No	96	99.0%	35	97.2%	131	98.5%	.541[a] (.462)
	Yes	1	1.0%	1	2.8%	2	1.5%	
Combination Insulins	No	92	94.8%	35	97.2%	127	95.5%	.344[a] (.557)
	Yes	5	5.2%	1	2.8%	6	4.5%	
Amylinomimetic Drug	No	97	100.0%	36	100.0%	133	100.0%	
	Yes							
Alpha-glucosidase Inhibitors	No	97	100.0%	36	100.0%	133	100.0%	
	Yes							
Biguanides	No	71	73.2%	29	80.6%	100	75.2%	.762[a] (.383)
	Yes	26	26.8%	7	19.4%	33	24.8%	
Dopamine agonist	No	97	100.0%	36	100.0%	133	100.0%	
	Yes							
Dipeptidyl peptidase-4	No	90	92.8%	35	97.2%	125	94.0%	.915[a] (.339)
	Yes	7	7.2%	1	2.8%	8	6.0%	
GLP-1	No	97	100.0%	36	100.0%	133	100.0%	
	Yes							
Meglitinides	No	97	100.0%	36	100.0%	133	100.0%	
	Yes							
SGLT	No	97	100.0%	36	100.0%	133	100.0%	
	Yes							
Sulfonylureas	No	71	73.2%	28	77.8%	99	74.4%	3.342[a] (.188)
	Yes	26	26.8%	7	19.4%	33	24.8%	
Thiazolidinediones	No	95	97.9%	33	91.7%	128	96.2%	2.854[a] (.091)
	Yes	2	2.1%	3	8.3%	5	3.8%	
Asprin	No	92	94.8%	36	100.0%	128	96.2%	1.928[a] (.165)
	Yes	5	5.2%	0	0.0%	5	3.8%	
Hypolipidemic	No	92	94.8%	32	88.9%	124	93.2%	1.477[a] (.224)
	Yes	5	5.2%	4	11.1%	9	6.8%	
Vitamin B complex	No	71	73.2%	29	80.6%	100	75.2%	.762[a] (.383)
	Yes	26	26.8%	7	19.4%	33	24.8%	
Vitamin D	No	97	100.0%	35	97.2%	132	99.2%	2.715[a] (.099)
	Yes	0	0.0%	1	2.8%	1	0.8%	
Antihypertensive drugs	No	77	79.4%	27	75.0%	104	78.2%	.296[a] (.587)
	Yes	20	20.6%	9	25.0%	29	21.8%	

Table 5: Multi-nominal Logistic regression between DM and age, gender, district and hospital admission

Independent variables	B	Sig.	Exp (B)	95% Confidence Interval for Exp (B)	
				Lower Bound	Upper Bound
Intercept	5.453	.000	-	-	-
Age in years	-.065	.000	.937	.927	.947
Gender	0.540	.009	1.715	1.146	2.570
Hospital	-.304	.117	.738	.505	1.079
Hospital admission	.669	.095	1.953	.891	4.283

Discussion

This study, to our knowledge, is the first one to compare the gender differences in the clinical presentation, diagnosis, treatment and self-management practices of type 2 diabetes in Jeddah, KSA. Biologically there is no difference between men and women in the prevalence and characteristics of type 2 diabetes (1). The difference is likely to be much wider in developing countries where the position of women in the society is still poor. In this context the gender differences in the care of type 2 diabetes becomes very important. The present study looked at symptoms of diabetes, mode of diagnosis, blood sugar control levels and self- management behaviors among both males and females.

Changes in lifestyle and human behavior have increased the occurrence of DM, and an estimated 220 million people who are affected by DM was reported in 2010 (1).

In the present study, out of all the outpatient clinic visits, those due to DM were 5.5%. T1DM was most common in those aged 18 years or less (75.0%). This is in line with a previous study, which reported that 85.0% of T1DM was found in those younger than 20 years old (5). In the present study T2DM was more prevalent in those aged 40 years or older. This is consistent with previous studies (3, 7). DKA is caused by a decrease in effective circulating insulin associated with elevations in counter-regulatory hormones. This potentially life-threatening complication of T1DM is frequently mismanaged, leading to morbidity and increased length of hospital stay. DKA is not a rare presentation to hospital, despite being an entirely preventable condition (3).

In the present study DKA was recorded only in those younger than 18 years old.

Previous study revealed that prevalence of T2DM is higher in young women than young men due to more severe insulin resistance during puberty, whilst systemic insulin resistance is greater in middle-aged men than middle-aged women (8) We found that T2DM was higher in males compared to females, while T1DM and DKA were higher in females compared to males. In the present study, T2DM and DKA were more common in the higher social class region compared to the relatively lower one. The majority of patients with T2DM were discharged, compared to patients with T1DM; on the other hand all patients with DKA were admitted to the hospital. This is in agreement with previous studies (10, 11). A large proportion of patients with T2DM visited the OPCs for follow up (46.6%) and renewal of medicine; this was similar in both genders. On the contrary previous research reported that women utilized more medical care than men (34); this revealed that women have worse survival, higher risk of cardiac, renal complications and blindness compared to men (33). However, this was not the case in the present study.

In the present study it was found that polyuria, headache, fatigue, and dyspepsia, were common complaints among T2DM. However they were similar in both the males and females. This was contrary to other study which found that somatic and visceral pain syndromes such as fibromyalgia, migraine headache, pelvic pain, and interstitial cystitis were diagnosed more frequently in women (16). One likely reason for fatigue in diabetes (uncomplicated by severe comorbidities) is alterations in blood glucose levels. Altered blood glucose metabolism may result in acute and chronic hyperglycemic episodes, hypoglycemia, or blood glucose fluctuations (13). Diabetic neuropathies are common and rising in prevalence with the global burden of T2DM. Polyneuropathy is also emerging as a complication of impaired glucose tolerance, without frank diabetes (29). In the present study, numbness was encountered among about 7% of patients with T2DM. However, it was similar in both genders. Neuroglycopenia causes a rapid impairment of cerebral function through direct effects on neurons, and induces various symptoms, e.g. sense of warmth, weakness, difficulty thinking, confusion, tiredness and drowsiness occur (28). In the present study dizziness was encountered among 5.3% of the patients.

Patients with diabetes have a 2–5 times greater risk for developing peripheral arterial disease (PAD) as compared with the nondiabetic population (17). In the present study about 5% of patients with diabetes developed lower limb oedema and it was more common among females. Hypertension is common among patients with diabetes, with the prevalence depending on type and duration of diabetes, age, sex, race/ethnicity, BMI, history of glycaemic control, and the presence of kidney disease, among other factors (22). Hypertension was encountered among 22% of the patients in the present study. Despite advances made in the prevention and management of cardiovascular disease, people with diabetes mellitus continue to have

alarmingly high morbidity and mortality secondary to cardiovascular disease (25). In the present study T2DM patients had increased both CVD and dyslipidaemia.

The HbA1c is now recommended as a standard of care for testing and monitoring diabetes, specifically the type 2 diabetes (2). In the present study the majority of blood tests for assessment of DM were HBA1C, FBS and RBS; while 2HPPG test was the least to be ordered (3.0%). No significant differences were found between males and females in ordering these investigations. Prolonged hyperglycemia is associated with altered lipid metabolism, increased oxidative stress and alterations in the liver function test, which in turn result in different micro-vascular complications such as retinopathy, neuropathy, nephropathy and macro-vascular complications like cardiovascular diseases (25). In the present study lipid profile was done on 17.5% of the patients with DM. Annual screening for kidney function test is recommended by the American Diabetes Association (ADA), as a high proportion of patients with type 2 diabetes are found to have overt nephropathy shortly after diagnosis of their diabetes (9, 26). In the present study Serum creatinine (16.5%), and urine analysis 15.0%) were conducted on patients with DM to assess the kidney function; no significant differences between males and females were found.

The prevalence of high ALT levels may reach 20% in diabetics (12). Elevation of these enzymes is strongly related to obesity, diabetes and dyslipidemia (28). Insulin has been shown to decrease extracellular potassium concentration as well, likely through activation of Na-K-ATPase (29). At low insulin sensitivity, relatively minor changes in TSH levels are associated with marked changes in lipid risk factors and thus cardiovascular risk (6, 30). In the present study investigations for heart diseases e.g. ECG, Troponin I, and echocardiograph were also conducted on a small sector of patients with T2DM. No significant differences were found between males and females. Also tests such as CBC (6.8%), Serum uric acid (4.5%), ALT and AST (2.3%), Na+ and K+ (2.3%), and T3 and T4 (0.8%) were all ordered similarly in both males and females. Postprandial glycemic control plays a substantial role in reaching recommended HbA1c goals in diabetes (1). Compared with regular human insulin (RHI), rapid-acting insulin analogues (insulin aspart, insulin lispro and insulin glulisine) have provided better postprandial glucose control through an earlier and greater peak glucose-lowering effect (2, 3). Nevertheless, absorption of current rapid-acting insulins occurs too slowly to adequately replicate endogenous prandial insulin action (4, 5). Consequently, optimum postprandial glucose control remains a challenge in patients with diabetes (32). In the present study about 13% of the patents with T2DM were prescribed insulin to control DM, mainly in the form of short acting insulin (SAI, 5.3%), and combination insulin (4.5%). Rapid acting insulin (RAI: 1.5%) and long acting insulin (LAI: 1.5%), were also prescribed to some T2DM patients. None of the patients with T2DM was prescribed intermediate acting insulin. No significant differences were found between males and females. In the present study, the groups of oral T2DM drugs included mainly biguanide antidiabetic medication (24.8%), Sulfonylureas medication (24.8%), Dipeptidyl peptidase drugs (6.0%) and to a lesser extent thiazolidinedione drugs (3.8%). Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs) are useful tools for treating type 2 diabetes mellitus (T2DM). In their recent position statement, the American Diabetes Association and European Association for the Study of Diabetes recommend GLP1-RAs as add-on to metformin when therapeutic goals are not achieved with monotherapy, particularly for patients who wish to avoid weight gain or hypoglycemia (1, 31). In the present study Amylinomimetic, Alpha-glucosidase inhibitors, Dopamine agonist, GLP-1, Meglitinides, and SGLT were not prescribed to any patient with T2DM. This was similar in both males and females. Vitamin B complex preparations (24.8%), and antihypertensive drugs (21.8%) and to some extent hypolipedimic drugs (6.8%) were, also, prescribed to patients with T2DM. Aspirin was prescribed to, only 3.8% of the patients. This pattern of treatment was similar in both males and females.

HbA1c is now recommended as a standard of care (SOC) for testing and monitoring diabetes, specifically type 2 diabetes (2). In the present study the majority of blood tests for assessment of DM were HBA1C (36.1%) and FBS (35.3%).

Prolonged hyperglycemia is associated with altered lipid metabolism, increased oxidative stress (OS) and alterations in the liver function test (LFT), which in turn results in different micro-vascular complications such as retinopathy, neuropathy, nephropathy and macro-vascular complications like cardiovascular diseases (40). In the present study, lipid profile (17.5%) was ordered on about 18% of the T2DM patients. Annual screening for microalbuminuria is recommended by the American Diabetes Association (ADA) [9], as a high proportion of patients with type 2 diabetes are found to have MAU or overt nephropathy shortly after diagnosis of their diabetes. Screening by means of a semi-quantitative dipstick test is easy, immediate and accurate (35). In the present study Serum creatinine (16.5%), and urine analysis 15.0%) were ordered for patients with T2DM. No significant differences were found between males and females ($p > 0.05$). Postprandial glycaemic control plays a substantial role in reaching recommended glycated haemoglobin (HbA1c) goals in diabetes (1). Compared with regular human insulin (RHI), rapid-acting insulin analogues (insulin aspart, insulin lispro and insulin glulisine) have provided better postprandial glucose control through an earlier and greater peak glucose-lowering effect(2, 3). Nevertheless, absorption of current rapid-acting insulins occurs too slowly to adequately replicate endogenous prandial insulin action (4, 5). Consequently, optimum postprandial glucose control remains a challenge in patients with diabetes (44). In the present study, about 13% of the patients with T2DM were prescribed insulin to control DM, mainly in the form of short acting insulin (SAI, 5.3%), and combination insulin (4.5%). Rapid acting insulin (RAI: 1.5%) and long acting insulin (LAI: 1.5%), were also prescribed to some T2DM

patients. None of the patients with T2DM was prescribed intermediate acting insulin (IAI: 0.0%). No significant differences were found between males and females ($p > 0.05$).

Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs) are useful tools for treating type 2 diabetes mellitus (T2DM). In their recent position statement, the American Diabetes Association and European Association for the Study of Diabetes recommend GLP1-RAs as add-on to metformin when therapeutic goals are not achieved with monotherapy, particularly for patients who wish to avoid weight gain or hypoglycemia (1, 41). In the present study, Amylinomimetic, Alpha-glucosidase inhibitors, Dopamine agonist, GLP-1, Meglitinides, and SGLT were not prescribed to any patient with T2DM. The groups of oral T2DM drugs included mainly biguanide antidiabetic medication 24.8%), Sulfonylureas medication (24.8%), Dipeptidyl peptidase drugs (6.0%) and to a lesser extent thiazolidinedione drugs (3.8%). This is in line with other studies (1, 26, 27). Vitamin B complex preparations (24.8%), and antihypertensive drugs (21.8%) and to some extent hypolipidemic drugs (6.8%), were also prescribed to patients with T2DM. Aspirin was prescribed to only 3.8% of the patients. No significant differences were found between males and females ($p > 0.05$).

Conclusion

DM is a common chronic disorder, which imposes burden on the primary health care in Saudi Arabia. It is more common in males than females, however, the pattern of cardiovascular complications and health care management were similar in both genders.

Limitations of this study

This study was based on a non-probability convenient sample. As it is a nonprobability sample, so its findings cannot be generalized to the general population; however, it was an exploratory study, included sizable proportions of patients visiting the outpatient clinics, and reflected the burden imposed on the primary health care.

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Prevention of developmental delays among children at public healthcare facilities of Pakistan: protocol for a cluster Randomized Controlled Trial

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Abstract

Objectives: This cluster Randomized Controlled Trial (cRCT) aims to evaluate the effectiveness of an integrated ECD package in preventing developmental delays among children aged two years, in public health care centers, as compared to a control arm.
Methods: This is a parallel, two-arm, cluster randomized controlled trial. 768 mother-child pairs ('dyads') attending any of the 24-public health centers in two districts of Pakistan will be recruited, with an average of 32 participants per cluster. In the intervention arm, ECD based counselling sessions will be delivered to mother–child dyads by trained staff at public health care centers. Our primary outcome is reduction in prevalence of two or more developmental delays among children, from 38% to 23% in the intervention arm. Unit of randomization will be public health care center. 24 eligible clusters recruited will be randomized into intervention and control arms, using 1:1 allocation.

Discussion: The integrated model of child care into primary health care has the potential to provide a feasible and sustainable model for improving child developmental scale.

Key words: Early Child Development; Prevention; Developmental Delays; Public healthcare facilities

Introduction

In low-and-middle-income countries, 200 million young children are at risk of childhood developmental delays (1). In Pakistan, like most developing countries, early child development is a grossly neglected area of public health importance, with around 15% of children, suffering from a developmental delay (2). Exposure to risk factors or stressors such as malnutrition and lack of stimulation during first 2 years of life can place children at a higher risk of developmental delays (3) accounting for the higher 30% prevalence of developmental delays among children who are from disadvantaged families in Pakistan (4).

Evidence based programs in low resource settings have proven to be successful in improving childhood developmental by directly targeting the risk factors such as malnutrition and lack of stimulation for children under 2 years of age (5,6). Recognizing the established effectiveness of ECD care interventions, 'Advancing ECD series by the Lancet, 2017' highlights the need to integrate early childhood development programs into the existing public health services to enhance the reach and effectiveness of ECD packages in improving child development at a national level (7).

In Pakistan, public health facilities remain the most accessible and affordable source of health care especially for the less-advantaged, including the majority of the population who belongs to rural areas. The public health care doctors and health staff currently do not offer ECD care due, in part, to a lack of evidence-based contextualized care package and staff training for delivering integrated child development care. Therefore, we aim to address this need by developing an integrated ECD care package and evaluating its effectiveness in improving child development by embedding it within the already existing public health care centers.

Objectives of the study are:

1. To assess the effectiveness of integrated ECD care package in reducing prevalence of two or more developmental delays among children aged two years, from 38% to 23% in public health care centers and improving childhood stunting compared to usual care.
2. To explore acceptability and feasibility of ECD care package for both the providers and participants by conducting a mix-method process evaluation.

Materials and Methods

1. Study design, settings and participants

A parallel, two arm, cluster-randomized controlled trial will be conducted in public healthcare settings of Pakistan to evaluate the effectiveness of an integrated early child care package in reducing developmental delays among children as compared to treatment as usual. Each public health rural center or public hospital will serve as the cluster unit of randomization to avoid risk of contamination of intervention across arms. 24 clusters of public health centers will be randomized to intervention and control arm, using 1:1 allocation ratio.

Ethical approval for the study has been obtained from National Bioethics Committee (NBC) Pakistan (Ref No NBC255). The study will be conducted in public rural health care centers (RHCs) and sub-district hospitals of two districts i.e., Rawalpindi and Lahore, of Pakistan. In these two selected districts about one-third of the population live in rural and peri-urban areas (i.e., 4.5 million out of 14 million). People seeking medical care from public healthcare centers in Pakistan mostly belong to low socio-economic status. The average household size is around 6.5 persons with two out of five individuals being less than 12 years old. Four out of ten women in these two districts is illiterate. Women are mostly housewives; whereas the majority of men work on small sized farm lands, and supplement their earning by working for daily wages (when possible) (8,9). The rural and peri-urban population in these two districts is served by 24 public health facilities i.e., 16 rural health ECD care centers and 8 sub-district hospitals. Each rural health center and sub-district hospital has three or more doctors and lady health visitors (LHV, a nurse-midwife). The facility-based care is also supplemented by community-based health promotion care by community ('lady') health workers. The public health facilities are the main accessible and affordable source of healthcare for a majority of the target population.

The research participants will be 768 mother-child dyads recruited from 24 public health clusters from Rawalpindi and Lahore Districts. Mother-child dyads where the child is aged 12 to 13 months and the mother does not intend to move out of the area during study period will be considered eligible for participation in the study.

2. Package of Care in intervention and control arm

In the control arm, the designated LHVs at the selected public health facilities will be given a basic training on measurement of anthropometric measures and recording and reporting tools. This basic strengthening of the control facilities will be done to ensure standardized measurements and records across both arms and avoid any possible bias. Mother-child dyads will receive the usual treatment in control arm clusters.

In addition to the procedures listed above, in the intervention arm, a contextualized care package will be developed for the early child development. The care package will include a counselling tool (i.e. flipbook) and training module for LHVs. LHV will be given an additional 2-days training (along with the basic training given in the control arm for measurement and recording & reporting) by the research supervisors delivering standardized counselling sessions to mothers for early child development using the flipbook.

The ECD counselling sessions to mothers will be delivered by LHVs in public health centers on a quarterly basis to promote the early child development. Intervention components of ECD will include: a) infant nurturing and child brain development; b) weaning food and continued

breast feeding; and c) infection control e.g., food hygiene, sanitation, hand washing. Content of the materials used in counselling sessions has been developed in consultation with local and international ECD health experts. The LHVs will have quarterly sessions with the mothers and the ECD counselling will be divided into three sessions (i.e., at child age of 12, 16, and 20 months). Each counselling session to mothers will use 4-5 pages of the pictorial flipbook to deliver the core messages and will take at least 10-15 minutes.

3. Data collection and outcomes

Our primary outcome is reduction in prevalence of two or more childhood developmental delays of children aged 24 months, compared to treatment as usual using the adapted version of the Ages and Stages Questionnaire (10). ASQ is a brief, valid and reliable measure of childhood development that is widely used to assess childhood developmental difficulties ((11).

ASQ has 30 items, with 5 sub-scales measuring communication skills, fine motor, gross motor, problem solving and personal-social skills. Items are rated on a three-point Likert scale (0=No, 5= sometimes, 10=Yes). Total score is calculated by summing the responses of all items.

Secondary outcomes include anthropometric measures of child. Child's height (cm) and weight (kg) will be measured at baseline and endpoint by the research team to measure stunting.

4. Randomization and masking

All 24 health centers and sub-district hospitals in two selected districts will be invited to participate in the study. To minimize the risk of contamination, the unit of randomization will be a health center cluster. Clusters will be randomized before recruitment of research participants from each cluster. The clusters taking part in the study will be randomized to the intervention or control arm by an independent statistician, on a 1:1 allocation ratio. Statistical Package for the Social Sciences will be used to generate the randomization sequence code. Once a public health facility is allocated to a group, then all eligible clients attending the facility and agreeing to participate will receive the same child development care package (either the intervention or the usual care control), regardless of client social circumstances and/or preferences. The assessment team, Principal Investigators and the trial statistician will be blind to the allocation status of clusters.

5. Sample Size Calculations

A sample size of 11 clusters and 385 children per arm (i.e., a total of 22 clusters and 770 mother-child pairs) is required. The assumptions are as follows; decrease from 38% to 16% delays in child development domains; (12) at 80% power, 5% level of significance, average cluster size of 35 and an intra-class correlation coefficient of 0.04 (13) and assuming 10% loss to follow-up.

6. Data Management

Data management team will ensure data quality by running quality control checks to ensure there are not any outliers or missing fields in data. All data files will be encrypted and password protected while hard copy data will be kept under lock and key. Participant safety and confidentiality will be ensured by following Good Clinical Practices (GCP) guidelines (14) for data management.

7. Statistical analysis

Study results will be reported using CONSORT guidelines for cluster RCTs. (15). The data will be single entered and analyzed in SPSS version 21. To minimize data errors, data quality assurance procedures will be used, including training of data entry operators and checking data entry quality at regular intervals (16). The baseline characteristics will be compared across arms to assess baseline comparability of participant characteristics. The individual and cluster level analysis will be done following intention to treat principle. The binary and continuous outcomes will be analyzed by doing crude analysis which will calculate cluster level proportions and means respectively followed by an independent t-test to estimate the treatment effect (i.e., absolute difference in outcome proportions) between the two arms at endpoint using a 95% CI and significance value. Confounding variables will be adjusted by using logistic regression model for individual level data outcomes and covariate adjusted differences for cluster level outcomes. Z-scores for anthropometric measures will be calculated using the WHO child growth standards (17). No interim analysis is planned.

8. Process evaluation

A mix-method process evaluation will be conducted for the study following the guidelines of MRC (18). Quantitative data from study records and qualitative data from in-depth interviews with participants and providers will help inform the main factors associated with implementation of the intervention in public health care settings. Qualitative data will be analyzed using framework analyses to compare information from different participants.

9. Economic evaluation

An exploratory economic evaluation will be conducted to assess the cost-effectiveness of the integrated ECD program in public health care centers. Project budgets and expenditure reports will be used to estimate the costs of intervention. Incremental cost-effectiveness ratio will be calculated using the intervention costs.

10. Ethical considerations

All members of the research team will comply with Good Clinical Practices (14) to ensure safety and rights of participants. Voluntary participation will be ensured for all participants. Written informed consent will be obtained from the participants who are willing to participate in the study using the informed consent forms in local language. Participants' confidentiality will be ensured throughout the project. All reports and publications arising from the study will use anonymised and de-identified data to protect participants' privacy and confidentiality.

Discussion

Despite the established effectiveness of Early Childhood Development (ECD) care packages in improving child development, the majority of the population do not have access to these packages (19). To address poor child development outcomes in low and middle income countries, integration of early child development packages within private or public health care centers has the potential to improve child development at scale (20).

In Pakistan, there is a recognized gap in provision of child development care at public healthcare facilities (21). This study aims to address this gap by establishing the effectiveness of delivering an integrated child development care package in public health centers of two districts of Pakistan. This study will generate evidence for the effectiveness of delivering ECD care package in reducing childhood developmental delays by embedding it within public health care settings.

The intervention and relevant materials will be adapted for delivery in the context of public health centers in consultation with relevant stakeholders and international ECD experts. However, some potential challenges in intervention implementation may include; a) Low-attendance rate of mothers in follow-up sessions; in primary health care settings, patients are less likely to adhere to the follow-up schedule and tend to miss appointments with their healthcare providers which might lead to a lower effectiveness outcome due to less number of sessions attended by the mothers and b) Mothers in treatment arm might be more familiar with the development milestones of their child, leading to recall bias during the endpoint assessment. A process evaluation study will help explore these challenges in detail after completion of trial.

The study aims to create a public health impact by embedding the contextualized integrated package of early child care within the public health care system of the country. The findings from this study will be disseminated to relevant stakeholders including policymakers, researchers, program managers and national and international agencies using different platforms.

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Trial registration
The trial has been registered with the Current Controlled Trials ISRCTN14396904.

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A retrospective study of thyroid hormone in Pediatrics: relationships with growth hormone correlation with effects of diabetes in Riyadh, Saudi Arabia

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Abstract

Background: Inadequate Thyroid Hormone at birth in newborns is known as Congenital Hypothyroidism (CH) and it has a critical role in their growth and brain development. As a result, untreated CH and abnormal GH/IGF1 levels can lead to failure to thrive, osteoporosis, and Diabetic Retinopathies, among other problems. This retrospective study examines the chances of developing growthhormone disruption and Diabetes Mellitus in patients diagnosed with Congenital Hypothyroidism at the Security Forces Hospital in Riyadh, Saudi Arabia.

Methodology: A retrospective chart review of growth hormone deficient (GHD) patients was done at the security force hospital in Riyadh, Saudi Arabia. The data was collected from the medical records of the patients. The study included all patients with growth hormone deficiency (GHD) who had complete clinical, diagnostic and treatment data.

Result: At the beginning of the research, 287 growth hormone-deficient (GHD) children ranging in age from 1 to 15 years old were evaluated for diabetes. A total of 151 (52.6%) of the 287 patients gotlevothyroxine therapy, while the remaining 136 (47.4%) did not (control group). Because the p-value <0.05 ($t(149) = 1.165$, $p = 0.246$), the mean difference in blood sugar level changes is not statistically significant ($t(149) = 1.165$, $p = 0.246$).

Conclusion: We found that levothyroxine therapy has no discernible effect on blood sugar level fluctuations in males and females.

Key words: Growth hormone deficiency, Kingdom of Saudi Arabia, Diabetes.

Introduction

Thyroid Hormone has a crucial role in an infant's growth and neurological development, hence its essentiality in the Myelin Sheath formation process (1) (2). Especially in the early years of an infant's life, the Disturbance of Thyroid Hormone function results in irremediable neurocognitive impairment (2). Inadequacy of Thyroid Hormone at birth in newborns is known as Congenital Hypothyroidism(CH), and worldwide it is one of the most common endocrinal disorders in this age group (1) (3). In Saudi Arabia, literature presents higher CH incidence rates in comparison to the world population (4) (3) (5). In addition to thyroid hormone physiology, it stimulates the secretion of Growth hormone(GH), insulin-like growth factor 1(IGF1) production, and bone maturation (2). Thereby, untreated CH and disturbed GH/IGF1 levels can lead to other complications of failure to thrive, osteoporosis, and Diabetic Retinopathies (2) (6). Diabetes Mellitus (DM) is one of the most common endocrine disorders in children (7). Although the exact cause of type 1 DM is idiopathic, Type 2 DM is related to Obesity (8). Hyper-secretion of growth hormone in relation to Diabetes was related to insulin resistance development, impaired metabolic control, and growth deterioration in insulin-dependent DM (9) (10). In the pediatric age group worldwide, a dramatic increase of DM Type 2 is reported with higher mortality of DM type 2 in relation to DM Type 1 (8). The World Health Organization ranks Saudi Arabia as second highest in the middle east and as 7th worldwide in the prevalence of Diabetes (11). Both endocrine disorders of Hypothyroidism and Diabetes are common and can be easily misdiagnosed clinically, which increases the risk of complications if not properly diagnosed and treated early (7). Since November 1989, the Saudi national newborn screening program for Congenital Hypothyroidism has been conducted (4). Since early diagnosis and intervention has a better outcome on patient health, this study is looking retrospectively for risks of developing growth hormone disturbance and Diabetes Mellitus inpatients diagnosed with Congenital Hypothyroidism at Security Forces Hospital in Riyadh, Saudi Arabia.

Methodology

(GHD) patients was done at the Security Forces Hospital in Riyadh, Saudi Arabia. In the Security Forces Hospital, children aged from 1 to 15 years were diagnosed with growth hormone deficiency (GHD). At the beginning of the study, 273 growth hormone deficient (GHD) children ranging in age from 1 to 15 years old had their blood sugar levels checked. Patients with missing or partial data were not included in the study.

The information was gathered from the medical records of the patients. All patients with growth hormone deficiency (GHD) who had complete clinical, diagnostic, and therapy data were included in the study. Patients' demographics, clinical features, investigations, and therapy parameters were among the variables. The method for determining was whether there were any links that exist between developing growth hormone disturbance and Diabetes Mellitus in patients diagnosed with Congenital Hypothyroidism. The Institutional Review Board (IRB) of the Security Forces Hospital in Riyadh city authorized this study under the IRB code H-01-R-069 (11, 4, 2021).

The JMP statistical program was used to conduct the statistical analysis. To characterize and present the research variables, descriptive statistics analysis was used. For continuous variables, mean and standard deviation were calculated.

Results

A total of 287 growth hormone-deficient (GHD) children with the age range of 1 to 15 years old were investigated for Diabetes. On average, the children were enrolled in the study at eight years old (SD = 2.53) and completed at 14 years old (SD = 2.34). This shows that, on average, each child's Diabetes was measured at 3.44 years of age (SD = 2.26). At the beginning of the study, the mean blood sugar level was 135.0 mg/dL (SD = 15.48) and recorded to increase to 140.7 (SD = 16.39) at the end of the study.

A total of 151 (52.6%) of the 287 patients were given levothyroxine medication, whereas the remaining 136 (47.3%) were not (control group).

We wanted to see if there was a substantial difference in blood sugar level changes between the treatment and control groups in this study.

The null and alternative hypotheses for this study hypothesis are as follows:
H0: The variations in blood sugar levels in the treatment and control groups are not significantly different.
H1: The differences in blood sugar levels between the treatment and control groups are significantly different.
To test this hypothesis, an independent sample t-test is used, assuming that the variances of the treatment and control groups are equal.

This is supported by Levene's test for equality of variance testing.

Because the p-value is not less than 0.05 ($F = 0.001$, $p = 0.991$), the changes in blood sugar levels for the treatment and control groups had equal variances.

Table 2 shows that the changes in blood sugar level were higher among patients who received the treatment ($M = 6.169$, $SD = 20.83$) than those who did not receive the treatment ($M = 5.271$, $SD = 21.36$). However, because the p-value is more than 0.05, the t-test reveals that the mean difference between the two groups was not statistically significant ($t(285) = 0.360$, $p = 0.719$).

This demonstrates that there is no substantial difference in blood sugar fluctuations between patients who received growth hormone treatment and those who did not (Table 2).

Table 1. Summary statistics

Variable		N	Mean	Std. Deviation	Minimum	Maximum
Age (years)	Study start	273	8.21	2.53	1	15
	Study end	273	14.11	2.34	3	18
	Study Duration	273	3.44	2.26	1	12
Blood Sugar Level (mg/dL)	Study start	273	135.0	15.48	110.3	162.6
	Study end	273	140.7	16.39	112.1	169.0
	Changes	273	4.937	22.79	-48.89	55.15

Table 2. Results for independent t-test on blood sugar level changes between treatment and control group

Group	N	Mean	Std. Deviation	Mean Difference	t-test		
					t-value	df	p-value
Control	151	6.169	20.83	0.897	0.360	285	0.719
Treatment	136	5.271	21.36				

An independent t-test is further carried out to see whether there is a significant difference in the changes in blood sugar level among treatment groups based on gender. Among the treatment group, 79 (52%) patients were identified as males, and 72 (48%) were females. Figure 3 shows that the males have just slightly lower changes in sugar blood levels as compared to females. A formal test with the independent t-test can be confirmed whether this difference between males and females is significant or not.Because the p-value is greater than 0.05 ($F = 2.483$, $p = 0.117$), Levene's test implies that the independent t-test for comparing variations in blood sugar levels between males and females should be conducted under the premise of equal variances. Because the p-value is more than 0.05 ($t(149) = 1.165$, $p = 0.246$), the independent t-test shows that the mean difference in blood sugar level changes is not statistically significant ($t(149) = 1.165$, $p = 0.246$). As a result, we may infer that levothyroxine medication has no discernible effect on blood sugar level variations in males and females.

Table 3. Results for independent t-test on changes in blood sugar level between males and female

Gender	N	Mean	Std. Deviation	Mean Difference	t-test		
					t-value	df	p-value
Male	79	4.285	18.61	3.950	1.165	149	0.246
Female	72	8.235	22.97				

Discussion

The study purpose was to determine whether there are any links that exist between developing growth hormone disturbance and Diabetes Mellitus in patients diagnosed with Congenital Hypothyroidism at Security Forces Hospital in Riyadh, Saudi Arabia, and it was done retrospectively, the findings of our study revealed that out of 287 patients, 151 (52.6%) received levothyroxine treatment and the rest 136 (47.4%) did not receive the treatment (control group) and that the changes in blood sugar level were higher among patients who received the treatment (M = 6.169, SD = 20.83) than those who did not receive the treatment (M = 5.271, SD = 21.36). And this can be supported by another study that found similar results. This might be explained by how levothyroxine affects insulin resistance (15). We also conclude that levothyroxine treatment does not make any significant difference in blood sugar level changes between males and females. There is a link between Thyroid gland and Diabetes; it has been displayed that they both affect each other and there is an association between the conditions. Thyroid hormones also have a role in the regulation of carbohydrate metabolism and pancreatic function (13). However, we found that there was no significant difference in the changes of blood sugar level between patients who were treated with growth hormone and those who were not. Even though GH is well known to have effects on glucose metabolism, GH increases glucose production through gluconeogenesis and glycogenolysis from the liver and kidney (14). Males who are Growth deficient have a slow growth velocity, as compared to females who displayed an acceleratory trend (15). Pediatric Diabetes is increasing internationally; the World Health Organization rank Saudi Arabia at 7th in prevalence and 5th in incidence of type 1 diabetes (16).A study conducted in King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia, concluded that because of the increasing endocrine disorders, more pediatricians need to be trained to meet the requirement (17). Diabetes patients should be screened for thyroid abnormality when are clinically stable or once getting glycemic control; also every 1-2 years unless the patient develops thyroid disorder symptoms such as thyromegaly, an abnormal growth rate, or glycemic changes (16). Type 1 diabetes and hypothyroidism are common but they can be missed on initial presentation (18). Screening of the neonatal helps with early diagnosis and management of asymptomatic infants (19). When treating patients that are type 1 diabetic and growth hormone-deficient there are some challenges, but growth hormone treatment is considered safe and effective (20).

Conclusion

In our research, we found that patients who received levothyroxine therapy have increased their blood sugar level compared to patients who did not receive the treatment and we also found that levothyroxine treatment does not make any significant difference in blood sugar level changes between males and females.

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Impact of COVID-19 on patients receiving chemotherapy for gynecological cancer

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Abstract

Background: Cancer patients' increased susceptibility to serious COVID-19 complications can be attributed to the immunosuppressed state caused by the disease and anticancer treatments such as chemotherapy or surgery.

Objectives: To assess the effect of COVID-19 pandemic on gynecological cancer patients receiving chemotherapy.

Methods: A cross-sectional study was conducted on patients receiving chemotherapy for gynecological cancer between (March 2020 to February 2021) at King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia. Clinical data collected from medical records included patients' ages, medical history data, cycles of chemotherapy, COVID-19 infection, complications and death.

Results: Total of 84 patients were identified. The mean age of studied patients was 53.81 ± 13.76 years, and the most common chronic diseases were HTN (35.7%) and DM (23.8%). The majority of diagnoses were ovarian cancer (41.7%) followed by uterine cancer (33.3%). Of studied patients, 17.9%, 19.1%, 27.4 and 33.3% had I, II , III and IV cancer stages respectively. The mean number of cycles of chemotherapy was 7.14 ± 5.55. 52.4% had first line chemotherapy. 57 percent of patients had delays due to various causes, including COVID-19 infection, and 9 percent of patients had COVID-19 while on therapy. 15 percent of the delays were caused by patients who were affected by Covid-19 while receiving chemotherapy and 2% of the patients died as a result of COVID-19 . Patients with recurrent disease had a significantly higher percentage of patients detected with COVID-19, and all cases detected with COVID-19 died with respiratory failure. Patients who had their chemotherapy delayed had a significantly higher mean number of cycles.

Conclusion: Improved communication and management programs are required to keep cancer patients and their healthcare providers connected, as well as to allow cancer patients to survive a pandemic.

Key words: Impact, COVID-19, patients, chemotherapy, Jeddah, Saudi Arabia.

Introduction

anything from a simple cold to life-threatening illnesses. A fairly new coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) produced an outbreak called “COVID-19” in December 2019 in Wuhan, China [1].

Fever, cough, shortness of breath, and diarrhea are all common COVID-19 symptoms. COVID-19 has been linked to severe consequences including acute respiratory distress syndrome, acute renal failure, acute respiratory injury, septic shock, and severe pneumonia. PCR testing via nasal or mouth swabs is the preferred screening and diagnostic method [2].

To date, there have been 483,221 thousand confirmed cases of COVID-19 in Saudi Arabia, and unfortunately 7,775 deaths have occurred [3]. Despite the initial increase in the number of newly confirmed daily cases of COVID-19 in Saudi Arabia, the number of reported daily active cases started to stabilize after 2 months from the start of the pandemic in the country and the overall recovery rate was 71.4%. Furthermore, COVID-19 was more common among adults and males compared to other demographic groups [4].

The induced immunosuppression of cancer patients (whether induced by the disease or by treatment) increases their risk of infection as compared to the general population. Immunosuppression can also put cancer patients at risk of major infection-related consequences, which can lead to treatment delays and unneeded hospitalizations, all of which can have a detrimental impact on the disease’s prognosis [5,6].

The increased susceptibility of cancer patients to serious COVID-19 complications can be related to the immunosuppressed state caused by the cancer and anticancer treatments such as chemotherapy or surgery (7,8). Patients who had received chemotherapy or surgery within the 30 days before presenting with COVID-19 had a greater risk of serious events than those who had not received chemotherapy or surgery [9].

In this study our aim iwas to provide a descriptive study that reports how COVID-19 has impacted cancer patients who were receiving chemotherapy (for example did it lead to increased chemo doses, decreased time spent in hospital or decreased day care visits, etc.). The setting is in Jeddah, KAUH, day care wards.

Methods

Study design, setting and time frame: a cross-sectional study was done in King Abdulaziz University Hospital (KAUH) Jeddah, Saudi Arabia from March 2020 to February 2021.

Study participants: the inclusion criteria were all patients receiving chemotherapy for gynecological cancer.
Data collection: a checklist was prepared to collect data about patients age, clinical data, complications, COVID-19 infection and type of cancer and stage, number of cycles and line of chemotherapy and delay of chemotherapy and death

Ethical consideration: ethical approval for the study was obtained from the research ethics committee of King Abdulaziz University. Data were stored at the principle investigator’s office and could only be accessed by the authors. Data analysis: data were analyzed by the SPSS program version 26. Qualitative data was presented in numbers and percentages, and Chi- squared test ($\chi 2$) was used to test the relationship between variables. Quantitative data was expressed as mean and standard deviation (Mean ± SD) and Mann-Whitney and Kruskal Wallis tests were applied for non-parametric variables. A p-value of <0.05 was considered as statistically significant.

Results

Table 1 shows that the mean age of studied patients was 53.81 ± 13.76 years, and the most common chronic diseases were HTN (35.7%) and DM (23.8%). The highest diagnosis was ovarian cancer (41.7%) followed by uterine cancer (33.3%). Of studied patients, 17.9%, 19.1%, 27.4 and 33.3% had I, II , III and IV cancer stages respectively. The mean number of cycles of chemotherapy was 7.14 ± 5.55. 52.4% had first line chemotherapy. Table 2 showed that 56% had a delay in chemotherapy with a mean duration of delay of 5.67 ± 5.38 weeks. The most common cause of chemotherapy delay was bed unavailability (42%), and 7.1% were diagnosed to be COVID-19 positive during treatment. Of studied patients, 13.1% died and the most common cause among them was metastasis and 1(9%) died because of COVID-19 respiratory failure. Table 3 shows that patients who had recurrent disease had a significantly higher percentage of patients who had been detected with COVID-19 (p=< 0.05). On the other hand, a non-significant relationship was found between COVID-19 infection and cycles or delay of chemotherapy or death (p=> 0.05).

(Figure 1) shows that all cases detected with COVID-19 significantly died with a respiratory failure (p=< 0.05). While a non-significant relationship was found between COVID-19 infection and chemotherapy delay as a complication (p=> 0.05) (Figure 2).

Table 4 shows that patients who had delayed chemotherapy had a significantly higher mean number of cycles (p=< 0.05). On the other hand, a non-significant relationship was found between chemotherapy delay and patients’ age, clinical data, first line of chemotherapy or death (p=≠ 0.05).

Table 1: Demographic characteristics (number of patients= 84)

Variable	No. (%)
Age	53.81 ±13.76
Medical Diseases	
Chronic hypertension	30 (35.7)
Diabetes mellitus	20 (23.8)
Hepatitis C	1 (1.2)
Hyperthyroidism	9 (10.7)
Dyslipidemia	7 (8.3)
Ischemic heart disease	5 (6)
Renal disease	1 (1.2)
Rheumatoid Arthritis	1 (1.2)
Asthma	1 (1.2)
Diagnosis	
Cervical Cancer	17 (20.2)
Gestational Trophoblastic Disease	3 (3.6)
Ovarian Cancer	35 (41.7)
Uterine Cancer	28 (33.3)
Vaginal Cancer	1 (1.2)
Stage of Cancer	
Undocumented	2 (2.4)
I	15 (17.9)
II	16 (19.1)
III	23 (27.4)
IV	28 (33.3)
Number of the cycles of Chemotherapy per patient	7.14 ±5.55
Line of chemotherapy	
Undocumented	5 (6)
First line	44 (52.4)
Recurrent disease	35 (41.7)

Table 2: Effect of COVID - 19 on chemotherapy treatment

Complications (Delay or Not)	
Delay No	47 (56)
Delay	34 (40.5)
Unknown	3 (3.5)
Duration of Delay (weeks)	5.67 ±5.38
Reason for the delay	
Anxiety/Grief	2 (4.2)
Bed availability	20 (42)
COVID-19 confirmed	6 (13)
Patient not able to come on her schedule	10 (21.3)
Contact for COVID 19 patient (Suspect COVID19)	4 (8.5)
Waiting for surgery	5 (11)
Patient had COVID-19 during treatment	
Detected	6 (7.1)
Not Detected	21 (25)
Not Done	57 (67.9)
Death	
Alive	73 (86.9)
Deceased	11 (13.1)
Reason for death (No. II)	
Cardiac arrest	4 (36)
COVID-19 respiratory failure	1 (9)
Metastasis	5 (46)
Sepsis	1 (9)

Table 3. Relationship between COVID-19 infection and cycles of first line and delay of chemotherapy and death

Variable	Patient had COVID-19 during treatment		Test	P-value
	Detected	Not Detected		
Number of the cycle of Chemotherapy	7 ±2.94	7.15 ±5.67	0.51*	0.604
First line chemo or recurrent disease				
Undocumented	2 (100)	0 (0.0)	11.78	0.008
First line	0 (0.0)	44 (100)		
Recurrent disease	4 (11.4)	31 (88.6)		
Duration of Delay (weeks)	3.67 ±1.52	5.81 ±5.53	0.35*	0.737
Death				
Alive	3 (4.1)	70 (95.9)	3.38	0.066
Deceased	2 (18.2)	9 (81.8)		

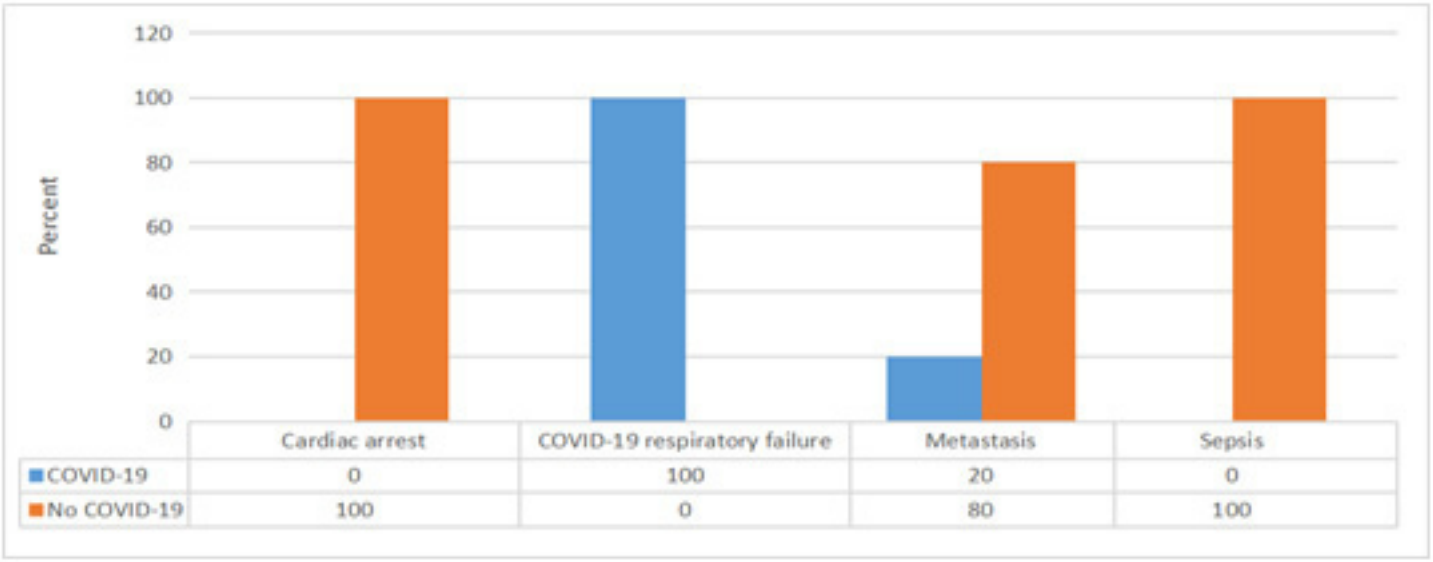
N.B.: *= Mann Whitney test

Table 4: Relationship between chemotherapy delay and patients' age, clinical data, first line and cycles of chemotherapy and death

Variable	Complications			Test	P-value
	Delay	No delay	Unknown		
Age	55.66 ±13.73	50.73 ±13.72	59.66 ±11.06	2*	0.2
Medical Diseases					
Chronic hypertension	16 (53.3)	12 (40)	2 (6.7)	1.31	0.519
Diabetes mellitus	12 (60)	7 (35)	1 (5)	0.42	0.81
Hepatitis C	1 (100)	0 (0.0)	0 (0.0)	0.79	0.671
Hyperthyroidism	7 (77.9)	2 (22.2)	0 (0.0)	2.04	0.359
Dyslipidemia	3 (50)	3 (50)	0 (0.0)	0.41	0.812
Ischemic heart disease	2 (50)	2 (50)	0 (0.0)	0.27	0.873
Renal disease	1 (100)	0 (0.0)	0 (0.0)	0.79	0.671
Rheumatoid Arthritis	1 (100)	0 (0.0)	0 (0.0)	0.79	0.671
Asthma	0 (0.0)	1 (100)	0 (0.0)	1.53	0.464
Diagnosis					
Cervical Cancer	5 (35.3)	11 (64.7)	0 (0.0)		
Gestational Trophoblastic Disease	2 (66.7)	1 (33.3)	0 (0.0)	7.7	0.463
Ovarian Cancer	23 (65.7)	10 (28.6)	2 (5.7)		
Uterine Cancer	15 (53.6)	12 (42.9)	1 (3.6)		
Vaginal Cancer	1 (100)	0 (0.0)	0 (0.0)		
Number of the cycle of chemotherapy per patient	8.37 ±6.34	5.42 ±3.79	5.5 ±0.7	2*	0.004
First line chemotherapy or recurrent disease					
Undocumented	4	1 (33.3)	3 (6.8)	4.79	0.571
First line	22 (50)	19 (43.2)	0 (0.0)		
Recurrent disease	21 (60)	14 (40)	0 (0.0)		
Death					
Alive	42 (57.5)	29 (39.7)	2 (2.7)	1.4	0.495
Deceased	5 (45.5)	5 (45.5)	1 (9.1)		
Reason for death (No.11)					
Cardiac arrest	3 (75)	1 (25)	0 (0.0)	7.77	0.456
Coronavirus respiratory failure	0 (0.0)	1 (100)	0 (0.0)		
MET	2 (40)	2 (40)	1 (20)		
Sepsis	0 (0.0)	1 (100)	0 (0.0)		

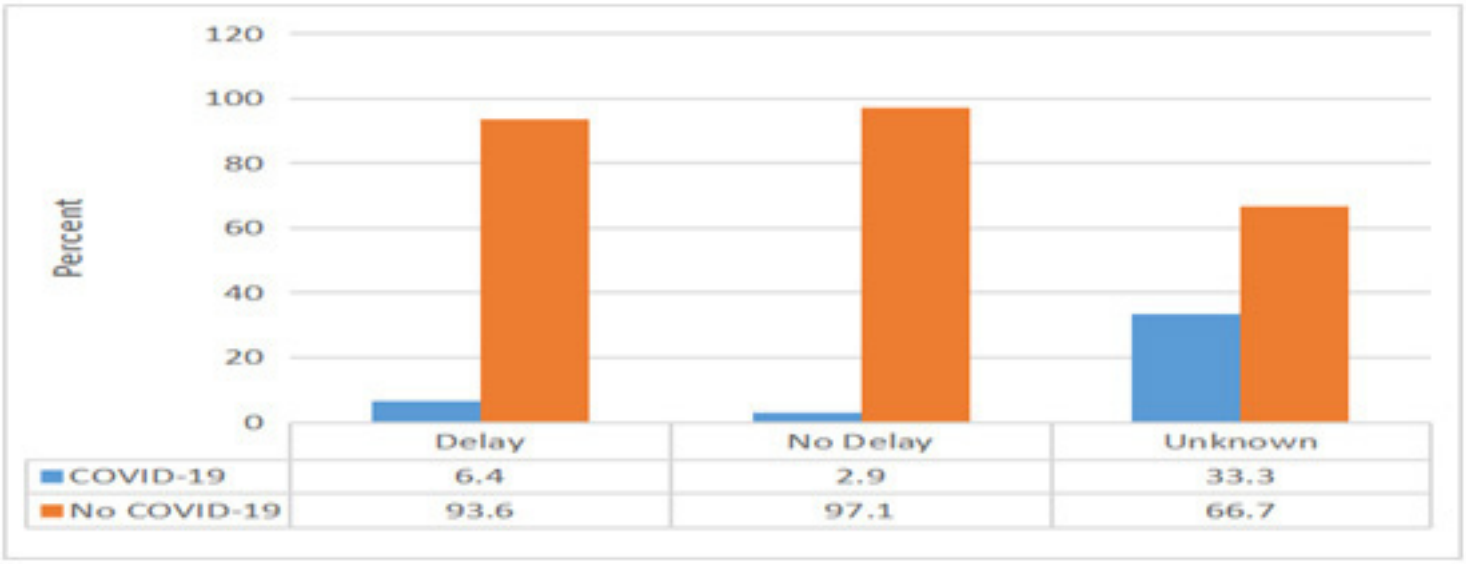
N.B.: * =Kruskal Wallis test

Figure 1: Relationship between COVID-19 infection and cause of death



N.B.: ($\chi 2$= 18.32, p-value= 0.0011)

Figure 2: Relationship between COVID-19 infection and chemotherapy delay as a complication



N.B.: ($\chi 2$= 4.58, p-value= 0.101)

Discussion

This study was a descriptive study that reported how COVID-19 has impacted cancer patients who were receiving chemotherapy during the pandemic in Jeddah, KAUH, Saudi Arabia. The demographic of these patients reflects a gynecological cancer patient

.

Results of the present study revealed that age distribution of the participants ranged from 21 years old to 78 years old. All patients were females. 45% of the patients were diagnosed with ovarian cancer, 31% with uterine cancer, 19% with cervical cancer, 2% gestational trophoblastic, 1% valvular and 1% choriocarcinoma. Six out of the 84 patients receiving chemotherapy were COVID-19 positive and 1 patient ended up dying. In the UK a study showed a link between COVID-19 and patients with urological cancer receiving treatment. This was a retrospective case series done on predominantly male patients and median age was 71. It is prudent to ensure that all possible precautionary measures be implemented to protect oncology patients from being exposed to COVID-19; developing additional protective measures, such as a vaccine, is important to prevent infection in this vulnerable population. Developing effective antiviral treatment will help in saving the lives of affected patients [15].

Patients did not feel safe visiting the hospital during the pandemic due to fear of contracting the virus in a high risk setting; however, when visiting the hospital they were satisfied with the hospital precautionary measures implemented. The majority of patients reported a preference for telemedicine, a precautionary measure adopted by most hospitals worldwide. Of the 204 responses, 65.1% reported a preference for telemedicine and virtual clinic visits of which 80% reported a fear of contracting the virus as the main reason for this preference. The majority of patients gave positive responses for a continuation of telemedicine post-pandemic [16].

To the best of our knowledge, only a trial study evaluating the effect of the COVID-19 pandemic on cancer patients in Najran, Saudi Arabia has been conducted. The study revealed a comparable mortality for patients with cancer patients before and during the COVID-19 pandemic. There was a doubling of the death risk in the year 2020 among patients younger than 65 (42% vs 21%). This can be explained by the death of two young lymphoma cases with chest infection of unknown etiology [17]. This is in line with two studies assessing sources of and exposure to media information regarding COVID-19 [18,19].

A current study in Saudi Arabia found a substantial relationship between sources of COVID-19 knowledge and fear of COVID-19. This study revealed that immunocompromised and chronic disease patients are vulnerable to fear and anxiety during epidemic infectious diseases such as COVID-19 [20]. For COVID-19 information, we discovered that the official website of the Saudi Ministry of Health, a credible source of information, was accessed more than social media and other sources. Based on this finding, reporters, policymakers, and healthcare professionals can use their official platforms to promote mental health (e.g., provide awareness messages, preventive guidelines, and measures targeting various groups) and provide mental health services to patients with chronic diseases and the general population [20].

During the COVID-19 outbreak, providing information and mental health services could help people with chronic conditions feel less afraid of COVID-19 during infectious disease epidemics [21].

In our study, 56% of patients had a delay in being provided with chemotherapy. The same result was revealed from other studies [22,23] and from a systemic review [24], where a delay in cancer health care was observed as a result of the COVID-19 pandemic. The conclusion of the study was that the administration of steroid didn't result in higher rates of infection or severe disease in that the rate of chemotherapy and immunotherapy associated complications during COVID-19 were no higher than in pre-COVID-19 times [10].

Despite the fact that delays in cancer patient identification and treatment were widely recognized during the COVID19 pandemic, [11] there is a scarcity of data measuring actual delays suffered by cancer patients [12]. Several researchers have reported on quality-based cancer care planning during the COVID19 epidemic. There is a scarcity of evidence on the impact of actual disruptions in cancer care services [13,14].

Limitations

The main limitation of the present study was the use of a cross-sectional study design, where the association between variables could be revealed but without the causal relationships.

Conclusion

Results of the present study revealed that COVID-19 has moderately affected the patients during their therapy as 56% of the patients had delays due to different causes including COVID-19 infection; 9% of the patients had COVID-19 during therapy which means 15% of the delays were because of the patients who got affected by COVID-19 during their chemotherapy and 2% of the patients died because of COVID-19. Patients who had recurrent disease had a significantly higher percentage of patients who had been detected with COVID-19 and all cases detected with COVID-19 significantly died due to respiratory failure. Patients who had delayed chemotherapy had a significantly higher mean number of cycles. Despite the fact that a significant number of patients received delayed chemotherapy during the COVID-19 pandemic, no significant relationship was found between delay and complications or death. Improved communication and management programs are required to keep patients and their healthcare providers connected and safe, as well as to allow cancer patients to emerge successfully during a pandemic.

Acknowledgement

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Immune system response to the Covid 19 virus and 3rd boosters

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Abstract

A recent finding that the two-dose vaccination for the Covid-19 virus leads to a rapid loss of protection in many patients within 6 months. Thus the need for a 3rd injection has been found to be mandatory for continuing protection, as well as to highlight the need to monitor immune compromised patients and those with comorbidities particularly in indigenous populations where co-morbidities may be present preventing an adequate response to the initial vaccination. This has also highlighted the problem of lack of vaccines in the less developed parts of the world that requires urgent attention, as this is where new variants arise. The virus must be contained in these countries before we run out of letters in the Greek alphabet.

Key words: Covid 19, virus, vaccines, 3rd injection, immunity, mutations, WHO

Summary

The immune system is unique to each individual depending on the stimuli received during a person's life. It is well accepted that the immune system responses does diminish in the elderly but at a variable rate. It is known that Covid19 antibody levels after infection and/or vaccination will vary according to age and gender (1). Israel as the first country to mass vaccinate its population for Covid-19, in an arrangement with Pfizer Inc, where it agreed to share all details of the result with Pfizer and hence the general community. Thus, its early papers and subsequent results should be regarded seriously as they would be a forewarning of things to come in countries that are only now reaching high levels of vaccination.
Recently the Israeli press reported that Covid-19 cases in Israel have been rising sharply since July despite the high vaccination rate achieved by February 2021. New daily cases there reached an all-time high of 12,113 on August 24 2021, surpassing the January peak of 11,934.
What is now known to be a 4th wave of infection sparked by the Delta mutation Covid-19 cases in Israel were reported as rising sharply since July despite the high vaccination rate achieved by February 2021. The Israel Center for Disease Control – ICDC noted that the number of new confirmed patients of COVID-19 in Israel between 2/5/21 and 3/8/21 went from low double figures to almost 4000 (2)

New daily cases in the country reached an all-time high of 12,113 on August 31st, surpassing the January peak of 11,934 (3).

It had been noted in a study conducted at 17-hospital study, that many older patients with other pathologies and immunosuppression are more prone to severe Corona-19 virus infection and even after being fully vaccinated (4).
Importantly as reported in a paper in the New England Journal of Medicine (5)'number of patients vaccinated against the virus can have a much lower level of antibodies than other inoculated individuals and are therefore more at risk to get infected, They report that 39 breakthrough cases of Covid-19 were detected through RT-PCR testing of 1,497 of their vaccinated workers between January 20 and April 28. In 37 of these cases, the suspected source was an unvaccinated person. None of the infected workers required hospitalization. However, at six weeks after their diagnosis, 19% reported having long Covid symptoms including a prolonged loss of smell, persistent cough, fatigue, weakness, dyspnea, or myalgia.

As a result of these studies and a reported rising infection in fully vaccinated patients, The Israeli Department of Health recommended a 3rd booster vaccine to all its eligible citizens. This was based on the information in the medical records of tens of thousands of members of Israeli HMO Leumit Health Funds, that suggested that people vaccinated before late February 2021 were currently twice as likely to experience a breakthrough SARS-CoV-2 infection than are people vaccinated since late February. It is uncertain whether this is because most early vaccinators were elderly and/have waned waning over time.

Initial reports in Israel following the 3rd booster suggested that antibody titers in the patients receiving a third booster rose by a factor of 10-20 times(6). Subsequently it has been reported in the press that this was successful with cases and hospitalisation were falling dramatically.

Following this, much of Europe, the UK and the USA confirmed that they intend to commence a 3rd booster vaccination project.

A trial of 4868 vaccinated hospital workers in a 6-month longitudinal prospective study who were tested monthly for the presence of anti-spike IgG and neutralizing antibodies after vaccination. This showed how the fall in IgG antibodies decreased and varied as depending on age, immunosuppression and gender they noted obesity as being a further important factor(7). Even in a group that had participants who were still working and thus did not include the very sick elderly who would be most susceptible to a fall in the level of antibodies and thus most likely require a booster earlier the age related fall in immunity levels was significant. Further transplant patients appear to have developed enhanced immunity following a 3rd injection (8)

On the 4th August 2021 the Director of the World Health Organization noted after the announcement of the 3rd dose of vaccine being recommended." And yet even while hundreds of millions of people are still waiting for their first dose, some rich countries are moving towards booster doses." Noting that in the poorer countries' vaccines were very hard to obtain as the richer countries had pre bought a majority of the vaccine production (9). He asked the "rich world" not to pursue COVID-19 vaccine boosters, citing lack of evidence of need and asking such nations to wait until the poorer nations had been able to vaccinate their citizens. He asserted that the rich countries appear to have bought the vast majority of vaccines for their populations, leaving poorer countries unable to effectively vaccinate their citizens.

These so-called rich countries are in the main democratic with an elected parliament and an active opposition. This intervention shows a complete lack of understanding by the Director-General of how democracies function. No leader of a democratic country with a proper opposition would survive the voter's wrath by stating in these current pandemic vaccines that would protect the citizens from illness and death should be sent to a third world country.
Yet this is exactly what must happen as the more the virus that is allowed to circulate the more variants will spring up. We are in the midst of the Delta (Indian) variant that is causing havoc in the vaccinated rich countries and prompted the need for the 3rd injection. Other variants have come to notice recently including the Lambda variant in South America and as this paper was being written the most mutated variant yet is reported by the National Institute for Communicable Diseases in South Africa issued an alert about the "C.1.2 lineage"(10) . We have yet to learn how infectious and deadly these and future variants are going to be.

The continuing rise of variants may well undo the efforts of rich countries to protect their citizens. It is in the rich world's interest to make sure enough vaccines are produced to ensure a worldwide coverage as quickly as possible. What is urgently required is increased vaccine production; the rich world should create a fund to fund new vaccine production facilities as a matter of urgency and purchase the vaccines thus produced for free distribution to the poorer countries. This may require a multibillion dollar investment, yet it will be a cheap investment, failure to do so will not only allow variants to develop some even more deadly then those now present that will cause great health and economic disruption in countries ravaged by the rampant virus. Otherwise already precarious health systems are liable to collapse, requiring significant financial assistance and waves of refugees fleeing from countries where the health system has collapsed and the economy has failed, potential resulting in significant civil unrest and the need for significant UN support and call upon the rich world to finance any rescue. It will be in the rich worlds interest to make sure enough vaccines to ensure a rapid worldwide coverage.

Conclusion

1. Being aware of the variable response to vaccination among the immunocompromised, elderly and those with co-mobilities that may prevent a full response to vaccination, the response to vaccination should be checked say 8-12 weeks after the second dose to make sure there has been an effective and in some cases a 3rd dose may need be given much earlier than the 6 months currently being considered in other countries.
2. Rather than have a blanket population 3rd vaccination drive before giving a 3rd injection the response to the initial vaccination should be checked to make certain a third injection is required.
3. Similarly in the case of the indigenous populations in view of the fact that in many cases they have health conditions and comorbidities that may prevent the immune system from responding fully to the Covid immunization, we should check their response shortly say 8 weeks after the second injection to check if the immune response is below acceptable levels.
4. The WHO fund if it is well funded will be able to order from commercial companies the billions of vaccines required and the companies with an assured sale will I believe ramp up production quite rapidly. The vaccine thus ordered but be ones that fit the health systems and economies of the underdeveloped countries. Whilst the two dose vaccines such as Pfizer and Astra -Zeneca can be used in larger centers with good medical facilities. In poorer and distant areas they may be difficult to administer. In reality the WHO should concentrate on one dose vaccines such as the Johnson & Johnson vaccine as use of this will require less use of scarce medical resources and lead to for quicker "herd Immunity" in those countries.
5. Similarly, an oral vaccine reported as now in trials in Israel should be looked at and encouraged, as this would be the best vaccine in poorer countries with stained medical facilities.

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Impact of Covid-19 on asthmatic patients in Western region in Saudi Arabia

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Abstract

Background: Respiratory symptoms are a characteristic feature present in covid-19 patients, and they usually range from mild to severe. Asthma is a chronic disease involving the airways that carry air in and out of the lungs. However, there is limited resources that discuss the relation between asthma and prevalence of COVID-19.

Aims: Identify the impact of covid19 on asthmatic patients.

Methodology: This is a descriptive cross-sectional study that was conducted to study the impact of COVID-19 on asthmatic patients, which was conducted using a prepared questionnaire which was distributed online among 300 patients with asthma. After collecting the data, MS Excel was used for data entry while SPSS version 24 was used for data analysis.

Results: In this study, we were able to collect data from 311 asthmatic patients in response to our questionnaire. Most of the asthmatic patients were females (67.2%) with a ratio of females: males of 2:1. Moreover, most patients thought that they control their asthma well and only 13.5 % indicated that they had frequent emergency visits because of asthma. The prevalence of COVID-19 in asthmatic patients was 64.3 % where a third of patients needed to go to hospital because of their bad condition, 12.6 % needed to be hospitalized in ICU and 56.4 % needed oxygen. Moreover, severity of COVID-19 symptoms and outcomes are related to the control of asthma where better control of asthma was associated with better outcomes including lower need for ICU admission and oxygen need.

Conclusion: Prevalence of COVID-19 in asthmatic patients was much higher than the general population especially in female patients aged between 31-40 years old. Moreover, COVID-19 had more severe outcomes in asthmatic patients including higher prevalence of ICU admission and oxygen need. Poorer outcomes of COVID-19 were associated with poor control of asthma.

Key words: Asthma, Covid-19, Western Region, Saudi Arabia

Introduction

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A new coronavirus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) infection started to spread in Wuhan city in China in early December 2019 and has spread around the world. This disease related with coronavirus was called corona¬virus disease 2019 (COVID-19), and this outbreak was announced as a pandemic on March 11, 2020, by the World Health Organization (WHO) [1]. On May 15, 2020, the spread had reached 4,580,498 confirmed cases and 305,618 deaths, and only 1,735,657 patients had recovered around the world [2]. SARS-CoV-2 protein spikes attach to a protein on the surface of cells, called angiotensin converting enzyme 2 (ACE2) receptors in host cells which are present in the lungs, heart, and intestine and, after all of the research, there are no specific treatments or vaccines for coronavirus [2–5].

Respiratory symptoms are a characteristic feature present in covid-19 patients, and they usually range from mild to severe. A considerable number of patients may present with acute respiratory distress syndrome (ARDS); these serious manifestations are usually coming in combination with some cytokine, specifically IL-6 [6]. Studies showed that co-morbidities such as cardiovascular patients (especially hypertension) and patients with disease that affects the metabolism (obesity and diabetes), and old age were considered as a risk factor for developing morbidity and mortality in COVID-19 affected individuals [7–9]. On the other hand, asthma and COPD are still not considered as a risk factor [10].

The Global Initiative for Asthma (GINA) Global Strategy for Asthma Treatment and Prevention of 2015 described asthma as a heterogeneous condition characterized by chronic inflammation of the airway and variable remodeling that results in a range of clinical presentations, treatment responses and natural history across the life course of the patient [11].

Asthma is a chronic disease involving the airways that carry air in and out of the lungs. These airways are inflamed in people with asthma. This chronic disease involves a history of respiratory symptoms including wheeze, shortness of breath, chest tightness and cough where these symptoms are varying over time and also vary in intensity. The expiratory airway limitation and hyper-responsiveness is due to exposure to a range of stimuli, such as exercise and inhaled irritants. At the population level, a group of individuals with asthma exhibit an accelerated decline in lung function over their lifetime [9,11]. Our goal is to identify the impact of covid19 on asthmatic patients.

Methodology

This is a descriptive cross-sectional study that was conducted to study the impact of COVID-19 on asthmatic patients. The study was conducted among asthmatic patients who live or who are residents in the western region of Saudi Arabia. The study included all male and female asthmatic patients who lived in any city of the western region. Non-asthmatic population, pediatric population and population with no access to internet connection were excluded from the study. The study sample size was calculated using electronic software Raosoft ® with confidence level of 95% and a confidence interval (margin of error) of 5.0 leading to a sample size of 300 patients. The study depended on a prepared questionnaire which was distributed online using the available social media. The questionnaire was designed to collect data about demographic factors of participants such as age, gender, residence, education level and type of work. Moreover, the questionnaire assessed the severity of asthma in patients including frequency of asthmatic symptoms, interference of symptoms with daily activity, the degree of asthma control and frequency for the need for emergency treatment. Finally, the questionnaire assessed the severity of COVID-19 in patients with positive COVID-19 including need for hospitalization, ICU and oxygen.

Moreover, the study was conducted after obtaining approval from each participant and all participants had the right to withdraw from the study at any time. Completed questionnaires were calculated. After collecting the data, MS Excel was used for data entry while SPSS version 24 was used for data analysis. Moreover, frequency and percentage were used for describing categorical variables such as age, gender and education of participants while mean, and standard deviation, were calculated for description of ongoing variables. Chi-test and t-test were used for describing the relation between different variables where p-value under or equal to 0.05 indicated significance.

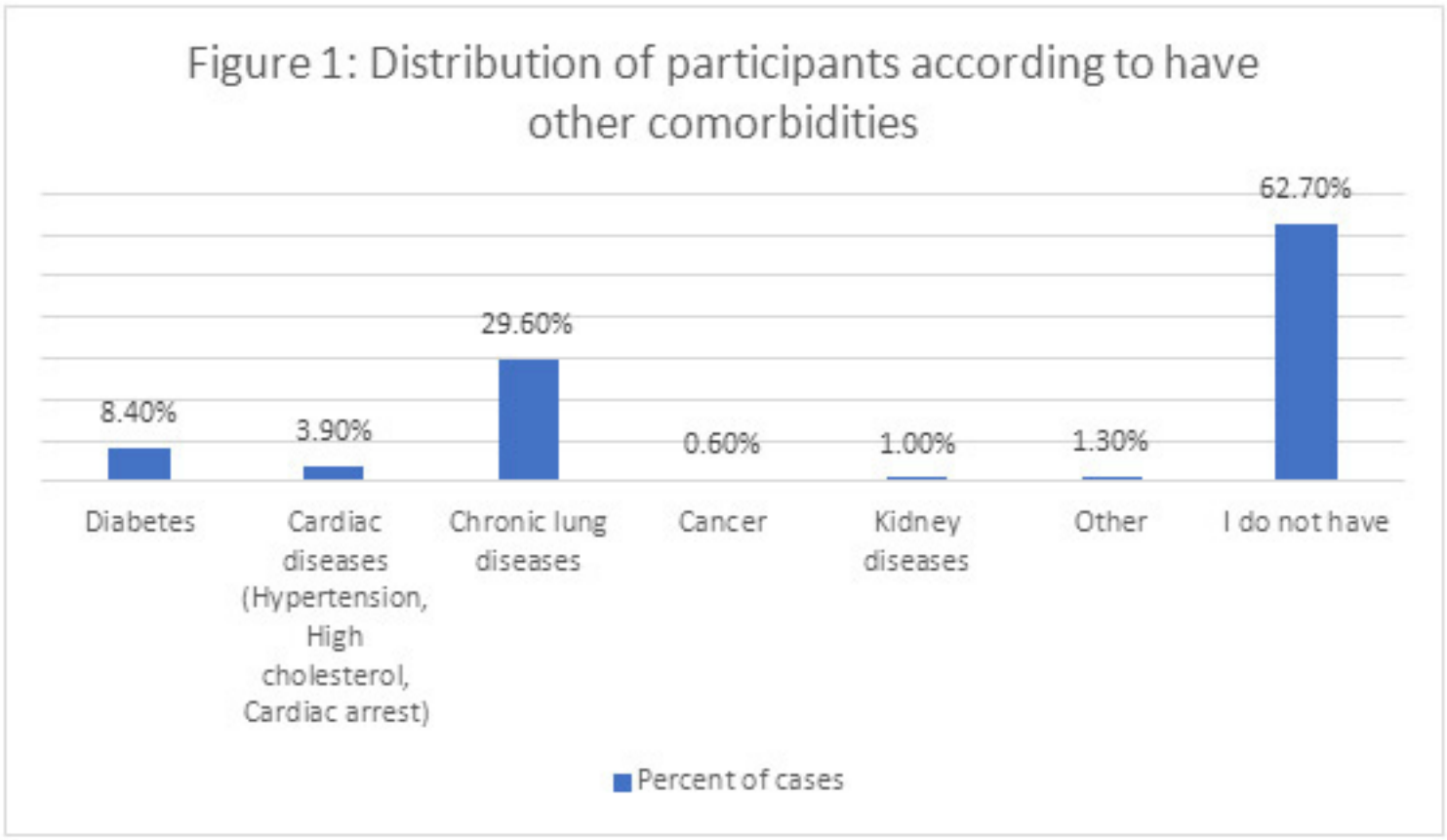
Results

Table 1: Demographic factors of participants (N=311)

		Count	Column N %
Gender	Male	102	32.8%
	Female	209	67.2%
Age	Less than 20 years	45	14.5%
	20-30 years	167	53.7%
	31-40 years	58	18.6%
	41-50 years	31	10.0%
	More than 50 years	10	3.2%
Nationality	Saudi	294	94.5%
	Non - Saudi	17	5.5%
Place of residence	Taif	84	27.0%
	Makkah	52	16.7%
	Jeddah	81	26.0%
	Yanbu	12	3.9%
	Medina	82	26.4%
Marital status	Single	214	68.8%
	Married	97	31.2%
Educational level	Primary school	6	1.9%
	Secondary school	20	6.4%
	High school	49	15.8%
	Bachelor	202	65.0%
	Postgraduate	34	10.9%
Job	Indoor work	63	20.3%
	Outdoor work	26	8.4%
	In and outdoor work	47	15.1%
	Unemployed	175	56.3%

In this study, we were able to collect data from 311 asthmatic patients in response to our questionnaire. Most asthmatic patients were females (67.2%) with ratio of females: males of 2:1. Moreover, most of participants were aged between 20-30 years old (53.7 %) and almost all participants were Saudi Arabian (94.5 %). Considering the residency, almost three quarters of the sample lived in Taif (27 %), Jeddah (26 %) and Medina (26.4 %) while 16.7 % lived in Makkah. Moreover, most participants were single (68.8 %) and had bachelor degree (65 %). Considering their work, we found that most participants were unemployed while 20.3 % of them had indoor jobs, and 8.4 % had outdoor jobs (Table 1).

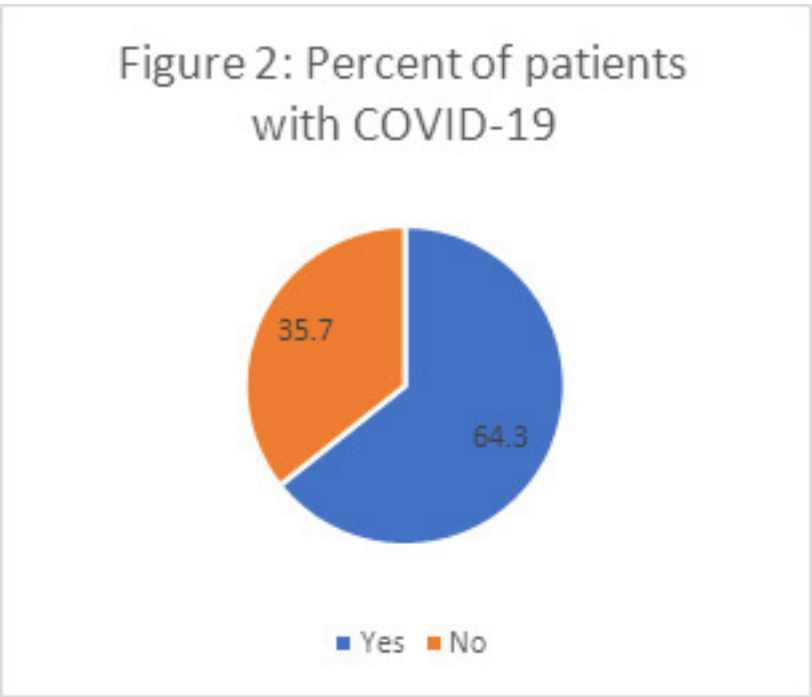
Moreover, we found, as shown in Figure 1, that most participants did not have other comorbidities (62.7 %) while chronic lung diseases other than asthma was the main comorbidities (29.6 %) followed by diabetes (8.4 %).

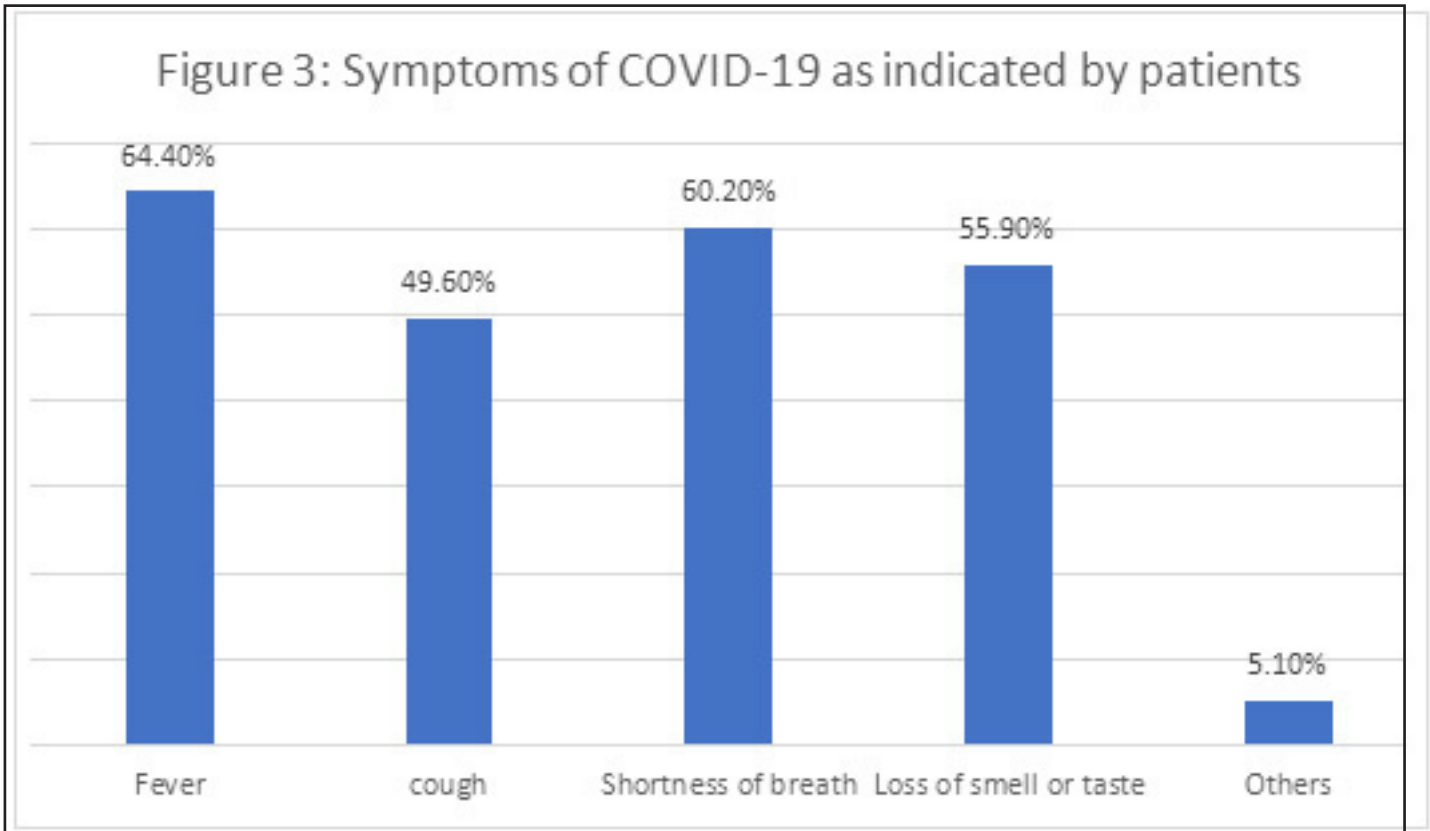


Furthermore, we found that 84.2 % of our patients need one asthma inhaler that is used when needed and 72.3 % of them had symptoms of asthma in less than two days per week while 4.8 % had a daily symptom of asthma. Moreover, 66.6 % of participants indicated that asthma symptoms waked them less than twice per month while 20.6 % 3-4 times per month. Furthermore, 41.8 % of patients reported that asthma symptoms had little interference on their daily activity and 26 % indicated moderate interference. In addition, 70.1 % of participants indicated needing to use inhaler to control symptoms in two days or even less weekly and 10.9 % needed them daily. Finally, most patients thought that they control their asthma well and only 13.5 % indicated that they had frequent emergency visits because of asthma (Table 2).

Table 2: Severity of Asthma and its symptoms among our sample			
		N	N%
Are you using	One asthma inhaler as needed	262	84.2%
	Two asthma inhalers continuously	46	14.8%
	Others	3	1.0%
Symptoms of asthma appear	Less than two days a week	225	72.3%
	More than two days a week	62	19.9%
	Daily	15	4.8%
	More than once a day	9	2.9%
Waking up due to asthma symptoms	Less than twice a month	207	66.6%
	3-4 times a month	64	20.6%
	More than once a week, but not daily	31	10.0%
	Daily	9	2.9%
Asthma symptoms interfere with daily activities:	NEVER	94	30.2%
	Little resistance	130	41.8%
	Moderate resistance	81	26.0%
	Severe resistance	5	1.6%
Need to use an asthma inhaler to control symptoms	Two days or less a week	218	70.1%
	More than two days a week, but not daily	52	16.7%
	Daily	34	10.9%
	More than once a day	7	2.3%
Asthma control	Good	282	90.7%
	Not Good	29	9.3%
Emergency visits because of asthma:	Sometimes	269	86.5%
	Frequent	42	13.5%

Considering infection with COVID-19 virus, we found that 64.3 % of asthmatic patients reported that they had previous infection with COVID-19 (Figure 2). Among patients with COVID 19, the main symptoms included fever (64.4 %), shortness of breath (60.2 %) and loss of smell or taste (55.9 %) (Figure 3).





In our sample, most participants had both symptoms and positive lab results of having COVID 19 (64.2 %) while 20.2 % had symptoms with negative results. Moreover, 70.9 % of patients had symptoms of COVID-19 for 2-4 days before diagnosed while 7.3 % needed more than 2 weeks of having symptoms until having diagnosis with COVID-19. Moreover, 76.8 % of patients with COVID-19 visited hospitals for 1-3 times per month and 8.8 % need to have visits for more than 6 months after infection. Moreover, a third of patients needed to go to hospital because of their bad condition, 12.6 % needed to be hospitalized in ICU and 56.4 % needed oxygen (Table 3).

Table 3: Severity of COVID-19 infection on patients

		N	N %
What applies to you from the following?	The presence of symptoms and the result is positive	156	64.2%
	The presence of symptoms and the result is negative	49	20.2%
	No symptoms, positive result	38	15.6%
How long did your symptoms last before you were diagnosed with COVID-19	2-4 days	156	70.9%
	A week	48	21.8%
	2 weeks or more	16	7.3%
How many visits did you have to the emergency department after confirming that you had covid19:	1-3 times /month	149	76.8%
	3-6 times/month	28	14.4%
	More than 6 months	17	8.8%
Did you go to hospital because your condition was bad:	Yes	82	33.1%
	No	166	66.9%
Have you been admitted to the intensive care unit?	Yes	31	12.6%
	No	216	87.4%
Did you need oxygen?	Yes	137	56.4%
	No	106	43.6%

In Table 4, we discussed the relation between incidence of COVID-19 and severity of its symptoms and demographic factors of patients. Considering the gender, we found a significant difference between genders considering the prevalence of COVID-19 where the prevalence of COVID-19 was higher in males than in females (p=0.011) however there was no significant difference between genders considering severity of COVID-19. Moreover, we found that prevalence of COVID-19 was highest in the population with age between 31-40 years old which was significantly higher in the need for ICU and oxygen (P=0.001, 0.012 and 0.00). Furthermore, we did not find significant difference between participants according to their job, however severity of COVID-19 was higher in patients with comorbidities.

Table 4: The relation between severity of COVID-19 and demographic factors of Asthmatic patients

		Did you have COVID19		Did you go to hospital because your condition was bad:		Have you been admitted to the intensive care unit?		Did you need oxygen?	
		Yes	No	Yes	No	Yes	No	Yes	No
Gender	Male	67.6%	32.4%	34.1%	65.9%	13.1%	86.9%	58.3%	41.7%
	Female	62.7%	37.3%	32.5%	67.5%	12.3%	87.7%	55.3%	44.7%
	P- value	0.011*		0.799		0.054		0.199	
Age	Less than 20 years	68.9%	31.1%	37.5%	62.5%	7.5%	92.5%	87.5%	12.5%
	20-30 years	58.7%	41.3%	31.3%	68.7%	8.7%	91.3%	48.2%	51.8%
	31-40 years	86.2%	13.8%	38.2%	61.8%	25.9%	74.1%	57.4%	42.6%
	41-50 years	48.4%	51.6%	24.1%	75.9%	6.9%	93.1%	46.2%	53.8%
	More than 50 years	60.0%	40.0%	33.3%	66.7%	22.2%	77.8%	44.4%	55.6%
	P- value	0.001*		0.697		0.012*		0.00*	
Job	Indoor work	74.6%	25.4%	46.3%	53.7%	22.2%	77.8%	58.5%	41.5%
	Outdoor work	76.9%	23.1%	36.4%	63.6%	14.3%	85.7%	45.5%	54.5%
	In and outdoor work	66.0%	34.0%	29.3%	70.7%	12.2%	87.8%	37.5%	62.5%
	Unemployed	58.3%	41.7%	28.2%	71.8%	8.4%	91.6%	63.3%	36.7%
	P- value	0.057		0.111		0.081		0.024*	
Comorbidities	Yes	60.3%	39.7%	43.5%	56.5%	26.1%	73.9%	60.2%	39.8%
	No	66.7%	33.3%	26.9%	73.1%	4.5%	95.5%	54.2%	45.8%
	P- value	0.26		0.007*		0.00*		0.362	

Moreover, in Table 5, we discussed the relation between incidence of COVID-19 and severity of its symptoms and severity of asthma and its impaction on patients. We found that patients indicated that severity of COVID-19 symptoms was significantly higher in patients who reported that they did not control their asthma symptoms where they needed ICU and more visits to hospital, than those who indicated good asthma control (P=0.017, 0.003) however, no difference was found considering prevalence of COVID -19.

Table 5: The relation between severity of COVID-19 and severity of asthma symptoms

		Did you have COVID19		Did you go to hospital because your condition was bad:		Have you been admitted to the intensive care unit?		Did you need oxygen?	
		Yes	No	Yes	No	Yes	No	Yes	No
Asthma symptoms interfere with daily activities:	NEVER	64.9%	35.1%	22.9%	77.1%	10.0%	90.0%	49.3%	50.7%
	Little resistance	60.8%	39.2%	34.0%	66.0%	6.1%	93.9%	52.5%	47.5%
	Moderate resistance	67.9%	32.1%	41.1%	58.9%	21.9%	78.1%	66.2%	33.8%
	Severe resistance	80.0%	20.0%	25.0%	75.0%	25.0%	75.0%	100.0%	0.0%
	P- value	0.586		0.107		0.001*		0.096	
Asthma control	Good	64.5%	35.5%	30.6%	69.4%	10.4%	89.6%	54.4%	45.6%
	Not Good	62.1%	37.9%	53.8%	46.2%	30.8%	69.2%	73.1%	26.9%
	P- value	0.791		0.017*		0.003*		0.069	
Emergency visits becaus e of asthma:	Sometimes	65.8%	34.2%	30.3%	69.7%	11.0%	89.0%	53.9%	46.1%
	Frequent	54.8%	45.2%	48.6%	51.4%	21.6%	78.4%	70.3%	29.7%
	P- value	0.165		0.029*		0.071		0.064	

Discussion

On March 11, 2020, the World Health Organization declared COVID-19 a global pandemic. Since then clinicians around the world have been particularly concerned about the impact of patients 'pre-existing chronic diseases (particularly lung and cardiovascular diseases) on the course of this new disease. While hypertension and diabetes are closely related to the frequency and severity of COVID-19 cases, care-related data suggest that COVID-19 did not affect asthmatic patients to nearly the same extent [12–14]. In order to understand the impact of COVID-19 on patients with asthma, we conducted a cross-sectional study that collected data from asthmatic patients in the western region, Saudi Arabia.

In our study, we collected data from 311 asthmatic patients in the western region, Saudi Arabia. In this population, we found that females represented two thirds of asthmatic patients. The prevalence of asthma in females was reported in other studies including the study of Izquierdo et.al., who collected data from 71,182 asthmatic patients finding that 59 % of them were females [15], the study of P. Pignatti, which found that 65.7 % of the asthmatic patients were females [16] and the study of Uchmanowicz who reported that 71% of asthmatic patients were females [17]. Moreover, chronic lung diseases other than asthma were the main comorbidities (29.6 %) followed by diabetes (8.4 %). In contrast, the study of Uchmanowicz reported that Arterial hypertension and diabetes were the most common comorbidities found among asthmatic patients [17]. Considering the severity of asthma among our patients, we found that symptoms of asthma ranged between mild to moderate where most patients thought that they control their asthma well and only 13.5 % indicated that they had frequent emergency visits because of asthma.

Considering infection with COVID-19 virus, we found that 64.3 % of asthmatic patients reported that they had previous infection with COVID-19. This prevalence was much higher than reported in other studies including the study of Izquierdo et.al. who reported a prevalence of 1.41 % of asthmatic patients [15]. However, many other studies had reported that the prevalence of COVID-19 was significantly higher in asthmatic patients rather than non-asthmatic patients [18–20] which suggests the possibility that individuals with asthma may be more likely than individuals without asthma to be diagnosed with COVID-19 in Saudi Arabia. Among patients with COVID 19, the main symptoms include fever (64.4 %), shortness of breath (60.2 %) and loss of smell or taste (55.9 %). The study of Johnston SL, indicated that the most frequent presentation signs of COVID19, dry cough and shortness of breath also were common [21]. Moreover, a third of patients needed to go to hospital because of their bad conditions; 12.6 % needed to be hospitalized in ICU and 56.4 % needed oxygen.

Considering the impact of demographic factors that increase the prevalence of COVID-19 and lead to poor outcomes including ICU admission and oxygen need, we found that female gender, and age between 31-40 years old were associated with increased prevalence of COVID-19 while age between 31 and 40 years and comorbidities increase the risk for poor outcomes including need for ICU admission and oxygen need. These results were opposite to the results of Elhadi M, in the general population who needed ICU because of COVID-19 findings that most patients who need ICU were males and older patients over 60 years old [22]. However, the study conducted by Izquierdo J, showed that females represented 66 % of asthmatic patients who had COVID-19 and COVID-19 prevalence was higher in older age and asthmatic patients who had other comorbidities [15].

Considering the relation between incidence of COVID-19 and severity of its symptoms and severity of asthma and its impact on patients, we found that patients who reported that they did not control their asthma symptoms needed ICU, and more visits to hospital than those who indicated good asthma control. These results indicate that prevalence of COVID-19 was higher in asthmatic patients over the prevalence of other comorbidities. Moreover, this indicates that severity of COVID-19 symptoms and outcomes are related to the control of asthma where better control of asthma was associated with better outcomes including lower need for ICU admission and oxygen.

Our study had some limitations which could not be avoided which include depending on self-reported questionnaire which could lead to some personal bias where there was not a method to ensure the truth of the participants about the provided data. Moreover, the depending on online method for distribution of the questionnaire may lead to some sampling bias toward younger participants and those who are more likely to use social media applications. On the other hand, this study was, to our knowledge, the first study to assess the impact of COVID-19 on asthmatic patients in the western region, Saudi Arabia.

In conclusion, prevalence of COVID-19 in asthmatic patients was much higher than the general population especially in female patients who were aged between 31-40 years old. Moreover, COVID-19 had more severe outcomes in asthmatic patients including higher prevalence of ICU admission and oxygen need. Poorer outcomes of COVID-19 were associated with poor control of asthma.

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Knowledge, Attitude and Awareness towards Corneal Donation in Aseer Region, Saudi Arabia

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Abstract

Background: Corneal transplantation is the mainstay procedure performed for sight restoration in patients with corneal blindness, which can be caused by infection, corneal dystrophy, degenerative disorders such as keratoconus or traumatic causes. Most corneal transplants in Saudi Arabia are performed using imported corneas.

Aims: To determine the level of knowledge and awareness and the factors affecting corneal donation in Aseer region, Saudi Arabia.

Subjects and Methods: A descriptive cross-sectional approach was used targeting the population of Aseer region aged 18 years and above. The data were collected using electronic self-administered questionnaire. The tool covered the participants' biodemographic data, knowledge related questions and willingness of corneal donation and factors affecting such attitudes.

Results: Of the 641 participants, 66.1% were males, 47.6% were in the age group 20 – 30 years and 19.2% claimed to have enough knowledge about corneal donation. The mean knowledge score (SD) was 2.13 (1.757) out of 8. Regarding participants' attitude, 26.7% were willing to donate their own cornea. The willingness was significantly associated with good level of knowledge ($p = 0.008$). Females were more inclined to donate their corneas than males (30.9% vs 24.5%, $p = 0.025$).

Conclusion: The study revealed a low level of knowledge of corneal donation in Aseer region, Saudi Arabia. Approximately one quarter of the participants reported willingness of corneal donation. Lack of knowledge was the main barrier, as it was reported by almost two thirds.

Key words: Cornea, Donation, Awareness, Penetrating Keratoplasty, Saudi Arabia

Background

The cornea is the transparent layer that covers the iris and the pupil, and it is the main refractive surface that focuses light into the retina. Permanent loss of corneal transparency caused by traumatic or pathological conditions will lead to corneal blindness. Globally, 4.9 million and 23 million individuals have bilateral or unilateral corneal blindness, respectively (1). Fortunately, corneal blindness is fully reversible with a corneal transplant. The pathological conditions that lead to loss of corneal function include infection, corneal dystrophy or degenerative disorders such as keratoconus (2).

The burden of corneal diseases in Saudi Arabia is a major concern as it contributes to 3.5% – 9.5% of cases of visual impairment (3). In Aseer region the estimated incidence of keratoconus is 20 new cases per 100,000 population (4). Furthermore, keratoconus is ranked as the first diagnosis requiring corneal transplantation at King Khalid Eye Specialist Hospital (KKESH) (5,6).

Corneal transplantation is the mainstay procedure performed for sight restoration in patients with corneal blindness. The optimal time for harvesting the donor's cornea is within 6 hours after death (7). The procedure is done by excising the cornea with a rim of the sclera (8). The donor-recipient blood group matching is not mandatory for the donation and the contagious conditions such as viral hepatitis or Human Immunodeficiency virus (HIV) being the only contraindication (7).

One of the main challenges that encounter the eye banks is the increasing demand for corneal transplantation. A worldwide survey of eye banking and corneal transplantation done by Gain et al. found a shortage of transplantable corneal tissues indicated by a ratio of approximately 1:70 of people benefiting from, and those waiting for, corneal transplantation (9). Locally, the majority of corneal transplants in Saudi Arabia are performed using imported corneas (5,10). KKESH alone imported 16,800 corneas with a rough estimated cost 179.76 million Saudi Riyals (10). According to the Saudi Center of Organ Transplantation, the cornea is the least donated organ (11).

Several studies have been conducted in Saudi Arabia to assess the level of awareness of corneal donation. Some of them targeted medical students (7,12,13). Others targeted the general population and they showed low level of awareness (10,14,15).

The main purpose of this study was to determine the level of knowledge and awareness and the factors affecting corneal donation including motives and barriers among the population in Aseer region, Saudi Arabia.

Subjects and Methods

This descriptive cross-sectional study targeted the population of Aseer region aged 18 years and above. Those who cannot read or understand Arabic were excluded. The data were collected using electronic self-administered questionnaire distributed via social media platforms during August 2021.

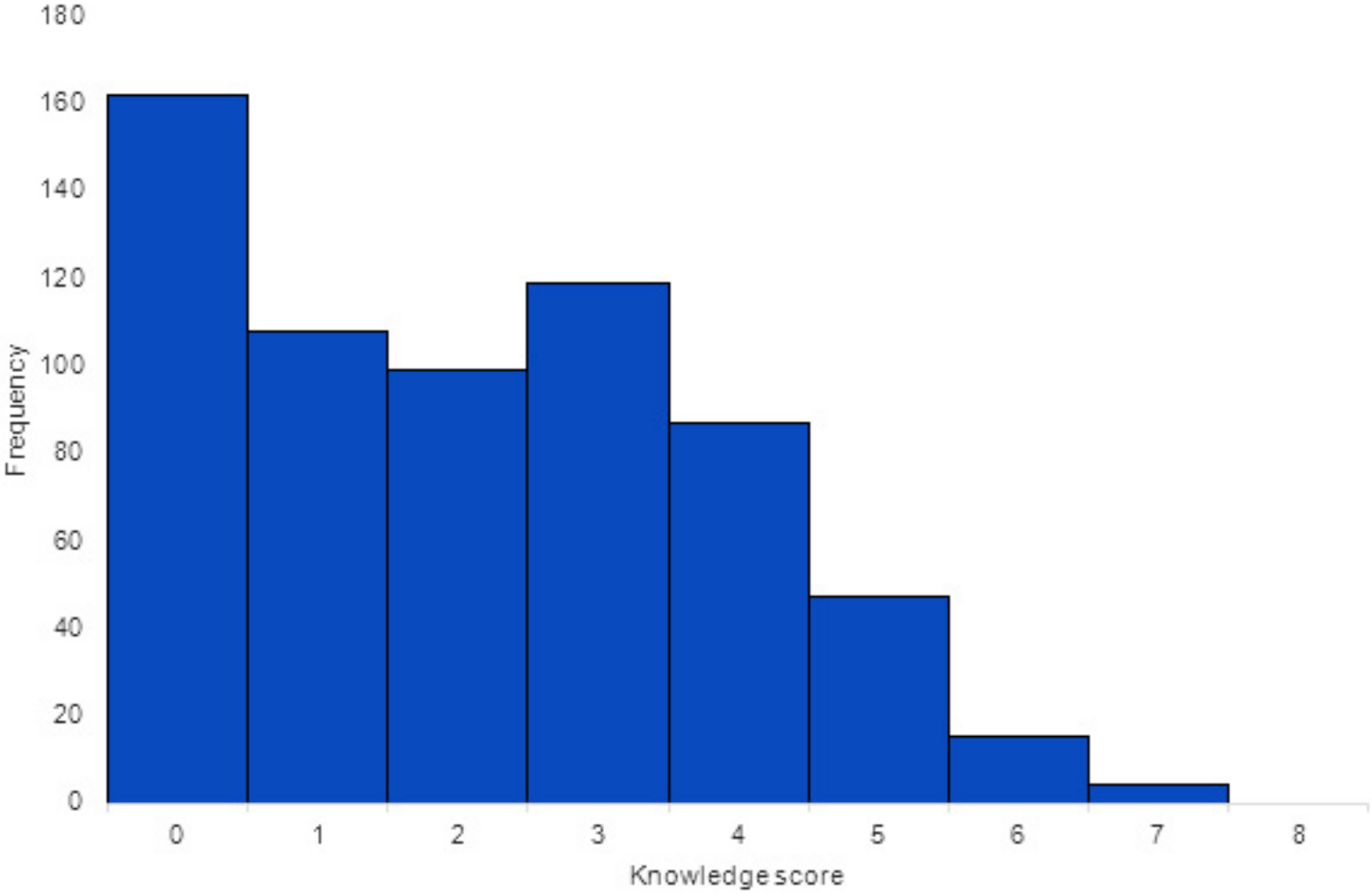
The questionnaire was developed after revision of the past literature. The tool covered the following three parts: (1) biodemographic data; (2) knowledge related questions consisting of self-assessed level of knowledge followed by a question about the source of the knowledge and a subscale of knowledge containing eight questions assessing different domains of knowledge about corneal donation; and (3) willingness of corneal donation and factors affecting such attitudes.

For knowledge questions, each correct answer was scored one point. Thus, a total knowledge score (0 – 8) was calculated. A participant with a score between (5 – 8) was considered to have good knowledge. On the other hand, poor knowledge was considered if the participant had a score of (0 – 4).

The data were analyzed using IBM SPSS Statistics, descriptive statistics (mean, SD, frequencies and percentages) were obtained. The primary outcome variable, knowledge score, was not normally distributed (Figure 1), tested by Kolmogorov-Smirnov test ($p < 0.001$) and Shapiro-Wilk test ($p < 0.001$). Thus, non-parametric tests including Mann-Whitney U test and Kruskal-Wallis test were used to estimate the association between continuous and categorical variables and Chi-Square test was used for the categorical variables. P-value ≤ 0.05 is considered significant.

Informed consent was obtained from all participants. Collected data were kept confidential and used only for research purposes. Furthermore, the questionnaire was anonymous. The ethical approval was obtained from the Research Ethics Committee at King Khalid University, Abha, Saudi Arabia,

Figure 1: A histogram showing right skewness of the distribution of the knowledge score



Conclusions

A total of 641 participants were enrolled in the present study. Almost two thirds of them were males (66.1%), and 47.6% were in the age group 20 – 30 years. The majority of the participants were Saudi (98.1%). Most of the participants had a high educational status, as 75% had a bachelor's degree or higher. Only 187 (29.2%) were involved in the medical field. Exactly 123 (19.2%) claimed to have enough knowledge about corneal donation

(Table 1), with doctors and health care workers being the most frequently reported source of information (58.5%) (Figure 2).

The question asking about the eye part concerned with corneal donation was the most correctly answered question (cornea, 47.7%), followed by whether corneal donation treats all eye diseases (no, 43.8%). The least correctly answered question was the appropriate age for corneal donation (more than 1 year, 2.2%). 30.9% of the participants knew that blood group mismatch is not a contra-indication for corneal donation. Only 134 (20.9%) claimed to know where and how to apply for corneal donation. 44.1% to 59% of the participants declared having no knowledge about the question being asked (Table 2).

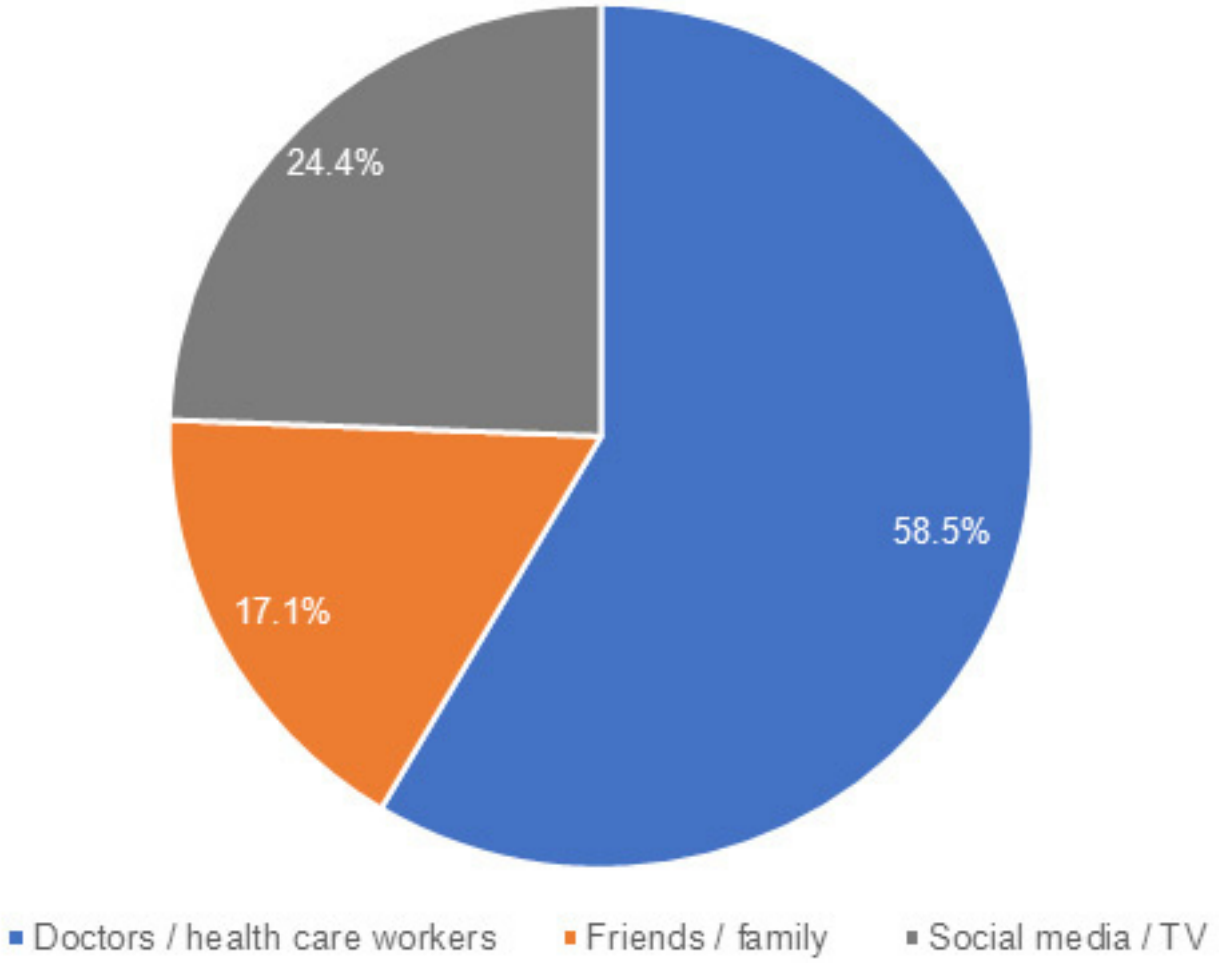
The mean knowledge score (SD) was 2.13 (1.757). It was higher among medical versus non-medical (2.93 vs 1.80, $p < 0.001$). Those who claimed to have enough knowledge had statistically significant higher knowledge score (3.37 vs 1.83, $p < 0.001$). However, no association of knowledge score was found with age ($p = 0.139$), gender ($p = 0.207$) or educational level ($p = 0.541$) (Table 3).

Regarding participants' attitude, 26.7% were willing to donate their own cornea, and 14.4% were willing to donate their first-degree relative's cornea (Table 2). The association between willingness of corneal donation and different factors is shown in Table 3. The willingness was reported by 30.9% of females compared to 24.5% of males ($p = 0.025$), and by 39.4% of participants classified to have good knowledge versus 25.2% of participants with poor knowledge ($p = 0.008$). The most frequently reported barrier against corneal donation was the lack of knowledge (Figure 3). On the other hand, the religious belief of doing good was the main motive, as it was reported by 543 (84.71%) (Figure 4).

Table 1: Bio-demographic characteristics of the participants

	Factor	Frequency	Percentage
Age (years)	Less than 20	53	8.3
	20 – 30	305	47.6
	31 – 40	111	17.3
	More than 40	172	26.8
Gender	Male	424	66.1
	Female	217	33.9
Nationality	Saudi	629	98.1
	Non-Saudi	12	1.9
Educational level	Up to middle school	21	3.3
	High school	139	21.7
	Bachelor	434	67.7
	Post-graduate study	47	7.3
Career / study field	Medical	187	29.2
	Non-medical	454	70.8

Figure 2: Source of previous knowledge



Note. The percentages are calculated based on the number of participants who claimed to have enough knowledge

Table 2: Participants' knowledge and attitudes towards corneal donation

The question		Frequency	Percentage
Eye part to be donated	All eye parts	45	7.0
	Cornea	306	47.7
	Retina	4	0.6
	Lens	3	0.5
	Don't know	283	44.1
Ideal time to harvest the cornea	As fast as possible	152	23.7
	Within6 hours	107	16.7
	24 hours – 1 week	31	4.8
	Don't know	351	54.8
Appropriate age for corneal donation	Birth – 75 years	103	16.1
	More than 1 year	14	2.2
	More than 10 years	146	22.8
	Don't know	378	59.0
Contra-indication of corneal donation	Optic nerve affection	119	18.6
	Retinal affection	81	12.6
	Viral hepatitis / HIV	104	16.2
	Don't know	337	52.6
Corneal donations treat all eye diseases	Yes	50	7.8
	No	281	43.8
	Don't know	310	48.4
Blood group mismatch is a contra-indication	Yes	112	17.5
	No	198	30.9
	Don't know	331	51.6
Living person can donate his cornea	Yes	138	21.5
	No	220	34.3
	Don't know	283	44.1
Do you know where and how to apply for corneal donation?	Yes	134	20.9
	No	507	79.1
Are you willing to donate your cornea?	Yes	171	26.7
	No	154	24.0
	Uncertain	316	49.3
Are you willing to donate your relative's cornea?	Yes	92	14.4
	No	268	41.8
	Uncertain	281	43.8

Table 3. Knowledge score and corneal donation willingness and their association with the biodemographics

Factor		Knowledge score			Corneal donation willingness		
		Mean	SD	p	Frequency	Percentage	p
Age (years)	Less than 20	2.17	1.661	0.139	20	37.7	0.057
	20 – 30	2.27	1.791		89	29.2	
	31 – 40	1.83	1.583		31	27.9	
	More than 40	2.06	1.817		31	18.0	
Gender	Male	2.08	1.838	0.207	104	24.5	0.025
	Female	2.21	1.587		67	30.9	
Nationality	Saudi	2.12	1.765	0.442	167	26.6	0.838
	Non-Saudi	2.42	1.311		4	33.3	
Educational level	Up to middle school	1.90	1.895	0.541	7	33.3	0.323
	High school	2.24	1.736		45	32.4	
	Bachelor	2.08	1.754		104	24.0	
	Post-graduate study	2.32	1.807		15	31.9	
Career / study field	Medical	2.93	1.836	< 0.001	58	31.0	0.166
	Non-medical	1.80	1.614		113	24.9	
Do you have enough knowledge?	Yes	3.37	1.651	< 0.001	40	32.5	0.093
	No	1.83	1.651		131	25.3	
Level of knowledge	Good				26	39.4	0.008
	Poor				145	25.2	

Figure 3. The barriers against corneal donation

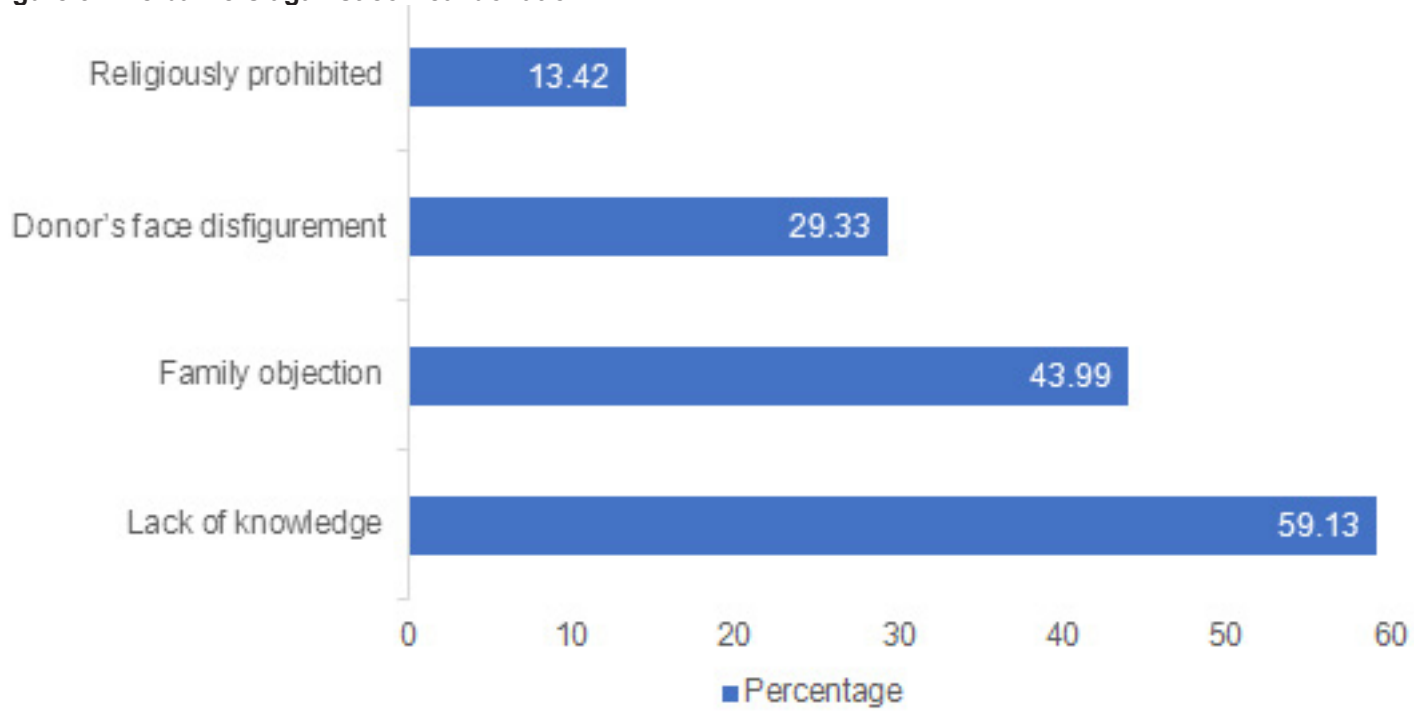
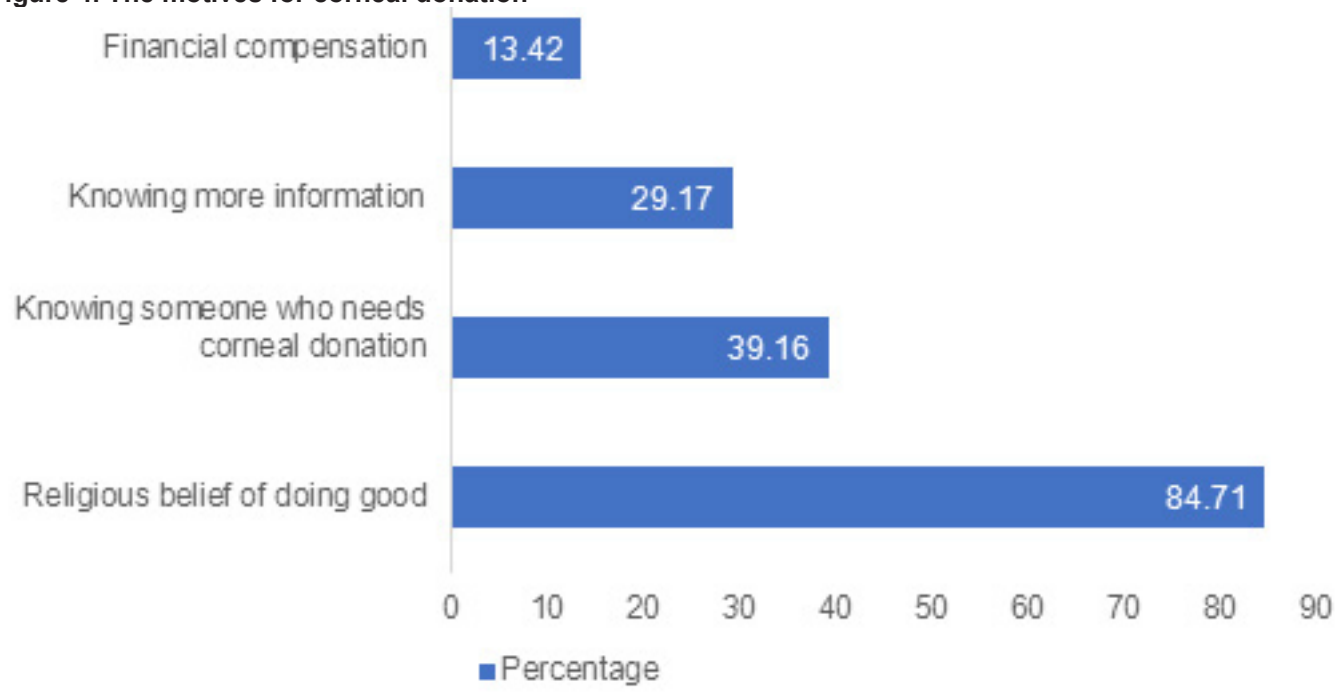


Figure 4. The motives for corneal donation



Discussion

In this study, the knowledge and awareness levels among the population were assessed and showed a low-level of knowledge, with only 10.3% of the participants having good knowledge based on our corneal donation knowledge scoring system, and 19.2% claimed to have enough knowledge. Religious belief of doing good and lack of knowledge were the most frequently reported motive and barrier to corneal donation, respectively.

The level of knowledge and awareness regarding corneal donation in our study is in agreement with those reported by other studies in the kingdom (10,14,15). The findings of this study showed that being involved in a medical field has a positive impact on the level of knowledge indicated by the mean knowledge score (2.93 vs 1.80, $p < 0.001$). Higher levels of knowledge and awareness were reported in studies targeting the medical students (7,12,13). The age was not a significant factor for the level of knowledge. However, Alibrahim and Al Jindan, (14) revealed that older participants are more knowledgeable.

The overall percentage of participants who declared to be willing to donate their own corneas was 26.7%. A similar percentage (28.5%) was reported by Alibrahim and Al Jindan, (14), and a higher percentage (61.5%) was reported by Bugis et al., (15). The females were significantly more inclined to donate their corneas than the males (30.9% vs 24.5%, $p = 0.025$). On the contrary, Alanazi et al., (10) reported that females are 35.3% less likely to declare willingness of corneal donation than males.

Lack of knowledge was the most frequently reported barrier, as it was reported by 59.13%, followed by family objection (43.99%). On the other hand, the most frequently reported motive was religious belief of doing good (84.71%). The factors affecting the corneal donation reported by this study are consistent with those reported by Alanazi et al., (10).

The limitation of this study includes not structurally recruiting a random sample from the entire population of Aseer region. Another limitation was using self-reporting questionnaire, and subsequently some questions might be misinterpreted.

Conclusion

In conclusion, the study revealed a low level of knowledge of corneal donation in Aseer region, Saudi Arabia. Approximately one quarter of the participants reported willingness of corneal donation. Lack of knowledge was the main barrier, as it was reported by almost two thirds. These results highlight the necessity for campaigns and other modalities to improve the level of awareness of corneal donation.

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Comparison of Body Image Perception and Depression in Polycystic Ovarian Syndrome (PCOS) and Non-PCOS Women

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Abstract

Objectives: The aim of the current study was to appraise the relationship between women's body image perception and depression in case and controls.

Methods: In this case-control study 60 polycystic ovarian syndrome patients established agreeing to the Rotterdam criteria and 60 healthy controls of reproductive age group were enrolled.

The PCOS patients and healthy controls were evaluated on questionnaire for physical appearance and depression. Body image perception was accessed using the validated Body Esteem Scale. The symptoms of Depression were evaluated with the Quick Inventory of Depressive Symptomatology-Self Report.

Results: 55% of PCOS patients had depression while 36.7% were found with depression in the control group. In the PCOS group 65% of patients were found with positive body image while 98.3% of patients were found with positive body image. Significant association of study cases group was found with BMI group (p=0.049), diet habit (p=0.013), depression (p=0.044) and body image (p=0.000). Patients with depression are also more likely to have PCOS in comparison with those who haven't (OR=2.111).

Conclusion: There was a significant association of study group with body image perception and depression. Therefore, health of the patients with this set of symptoms is essential to be acknowledged more fully, predominantly in relation to the despair and poor body image. The outcomes of this study foster implications for clinical practice and propose that a multidisciplinary team should be involved in treatment of PCOS.

Key words: Polycystic Ovary Syndrome (PCOS), Quick Inventory of Depressive Symptomatology (QIDS), Depression.

Introduction

Polycystic ovarian disorder is very recurrent endocrine condition in child bearing age with occurrence of around 6–8% in the reproductive years (1). Worldwide the total prevalence and phenotypic highlights of polycystic ovary syndrome (PCOS) is the utmost widely renowned endocrine disorder among reproductive age women (2). This alteration in occurrence of PCOS around the world is generally due to diverse diagnostic criteria and because of racial antithetic groups. And so, to overcome these major investigative dissimilarities it is essential to consider for racial and cultural specific approaches for PCOS (3). PCOS is a set of symptoms characterized and labelled by irregular menstrual cycle, barrenness, androgen superfluous and insulin resistance(4). Polycystic ovarian syndrome has long-term risks such as cardiovascular illnesses, Type-2 Diabetes Mellitus, dyslipidemia and endometrial carcinoma (5).

Body image is perception of one's appearance, and disappointment with one's bodily outlook. It is the psychosomatic involvement of the look and function of her body which influences on PCOS females very badly and may lead to miserable, stressed and low quality of life (6). PCOS patients also experience higher rates of depression and disquiet than normal healthy females in the concurrence on ladies' health features of polycystic ovary syndrome (PCOS). Emotional aspects must also be considered in all women with PCOS so they must be evaluated for psychological disorder (7) Many studies have shown negative body image perception in PCOS compared to non PCOS even with no difference in body mass index (BMI) (8). It is seen that one's personality perception is the psychological depiction of one's body image appearance, state of well-being, and completeness of life (9). PCOS is also linked by psychological complications, comprising chronic stress, dejection, anxiety and low self-confidence that may affect an individual's personality consciousness (10). It is shown from past research that PCOS patients are more prone to have depression as compared to healthy women (11).

Obesity and negative self-esteem have shown association with depression in PCOS compared to normal persons. Also, PCOS with Hyperandrogenism symptoms including excessive body hairs and acne have more chances of negative personality perceptions than non PCOS (12). Displeased physical appearance perceptions of PCOS include disappointment with general body look, loss of femininity and sense of less sexually appeal (13). Feelings of self-confidence may help in managing new and chronic illness, whereas lack of confidence is associated with anxiety, depression and general psychiatric symptoms (14).

The World Health Organization (WHO) has assessed that by the end of year 2020, depressive disorders will be recognized as the leading mental disability in women (15). In some published data prevalence of depression globally is about 40% in women with PCOS (16). The PCOS patients are at high risk of negative body image perception and low self-esteem as compared to the general population which may cause serious damage to social, professional and intimate affiliations (17). PCOS women were associated with possibility for higher body discontent at age 31 and 46 (Odds ratio, OR 2.39,) was found by one study (18).

Rationale:
Body image perception is a key factor which may predict the development of depressed mood. Also, body image in PCOS patients may upset the worth of life of a sufferer. Low self-confidence due to body image and associated depression may lead to a negative impact on her emotional attitude and psychiatric illness. So, in order to avoid major psychological and social upset of PCOS patient these factors should be considered and treated well as a top priority along with other comorbidities of PCOS.

Aim
In the present study we intended to determine association of body image perception, and depressive symptomatology in women with polycystic ovary syndrome (PCOS) in association with healthy controls.

Objectives
1. To assess and compare the body image perception between PCO positive and PCO negative study subjects.
2. To evaluate and compare frequency of depression between PCO positive and PCO negative study subjects.

Material and Methods

This case control study was conducted at Jinnah postgraduate medical center in alliance with Aga Khan University, Karachi. Ethical clearance was taken from the institutional review committee (NO.F.2-81-IRB/2017-GENL/418/JPMC). The study period was one year after ethical clearance from 2017 to 2018. A minimum sample size of 80 women was mandatory to achieve a power of 90 and an alpha of 5%, with a prevalence of PCOS as 15% in local population. We included 120 patients (60 in each group). 120 subjects gave permission and participated in this study. The inclusion criteria for cases were females of reproductive age group established as PCO per Rotterdam criteria. Rotterdam criteria for PCOS diagnosis states that a woman may present with any 2 out of 3 conditions: Anovulation, hirsutism or less commonly male pattern alopecia or raised free testosterone, or polycystic ovaries on ultrasound (when 10 small antral follicles are seen in each ovary) (4). Absence of the aforementioned states was deliberated to be inclusion for the normal control subjects.

Study partakers were divided into two groups:
i) Group A: PCO group included individuals with diagnosed polycystic phenotypes n=60
ii) Group B: Control group included individuals without any PCO phenotypes n=60.

The PCOS patients and healthy controls were evaluated on questionnaire for body image perception and depression. Body dissatisfaction was measured using the validated Body Esteem Scale (19). Depression symptoms

were measured with the Quick Inventory of Depressive Symptomatology-Self Report 16 (20)

Subjects with any systemic diseases like atherosclerosis, diabetes mellitus, hypertension, and any other reproductive disorders such as congenital adrenal hyperplasia, androgen secreting tumors, Cushing syndrome, thyroid dysfunction and hyper prolactinaemia were excluded from this study. After obtaining written and informed consent from the subjects, their biophysical parameters were measured.

Data were analyzed by using SPSS version 26. Mean and standard deviation were computed for quantitative variable. Frequency and percentage was calculated for qualitative variables. Stratification was done with regards to qualitative variables to see the effect of these modifiers on study group by using chi square and Fisher exact test as appropriate. Odds ratios were calculated by univariate and multivariate binary logistic regression. P-value ≤0.05 was considered as significant.

Results

A total 120 patients (60 in PCOS and 60 in Control group) were included in the study. Overall mean age was 27.86±6.62 years while mean age in PCOS and Control group was 26.61±6.68 years and 29.11±6.37 respectively. Mean disease duration in PCOS group was 18.81±10.27 months while mean Body mass index in PCOS and Control group was 28.56±5.54 kg/m2 and 28.41±4.11 kg/m2 respectively as presented in Table 1.

Among 60 patients in the PCOS group, 21(35%) have regular and 39(65%) have irregular menstrual cycle while in the control group all patients have regular menstrual cycle as presented in Figure 1. 40% of patients in the PCOS group have past medical history of diabetes; 23.3% have drug history while only 3.3% do exercise. Ultrasound was done for the PCOS group in which 19 (31.7%) were found with right ovary cyst, 20 (33.3%) with left ovary cyst and 21 (35%) with both ovary cyst. We found 55% of PCOS patients with depression while 36.7% were found with depression in the general group. In the PCOS group 65% of patients were found with positive body image while 98.3% of patients were found with positive body image in the control group as presented to Table 2.

We found significant mean difference of age (p=0.038) and number of children (p=0.000) according to study groups as presented in Table 1. We found significant association of study group with BMI group (p=0.049), diet habit (p=0.013), depression (p=0.044) and body image (p=0.000) as presented in Table 2.

By univariate logistic regression we found that married patients were more likely to have PCOS in comparison to unmarried patients (OR=2.471). Patients with Normal BMI (OR=1.328) and Overweight (OR=3.701) are more likely to have PCOS in comparison with obese patients. Those who have family history of hypertension are also more likely to have PCOS in comparison with those who haven't (OR=1.429). Patients with depression are also more likely to have PCOS in comparison with those who haven't (OR=2.111). Detailed results of odds ratios are presented in Table 3.

Table-1: Mean Comparison of study group with quantitative variables

	Mean±SD			P-Value
	Overall	PCOS	Control	
Age(years)	27.86±6.62	26.61±6.68	29.11±6.37	0.038
No of Children (n=107)	2.07±1.97	1.08±1.51	3.15±1.85	0.000
Height(m)	1.54±0.05	1.54±0.05	1.54±0.06	0.828
Weight(kg)	63.13±11.14	63.56±13.12	62.70±8.82	0.672
Body Mass Index	28.49±4.86	28.56±5.54	28.41±4.11	0.872
BGL(mg/dl)	108.90±28.31	113.63±34.45	104.16±19.59	0.067

Independent t-test was applied.
P-Value ≤0.05 considered as significant

Figure 1: Frequency distribution of menstrual cycle among study groups

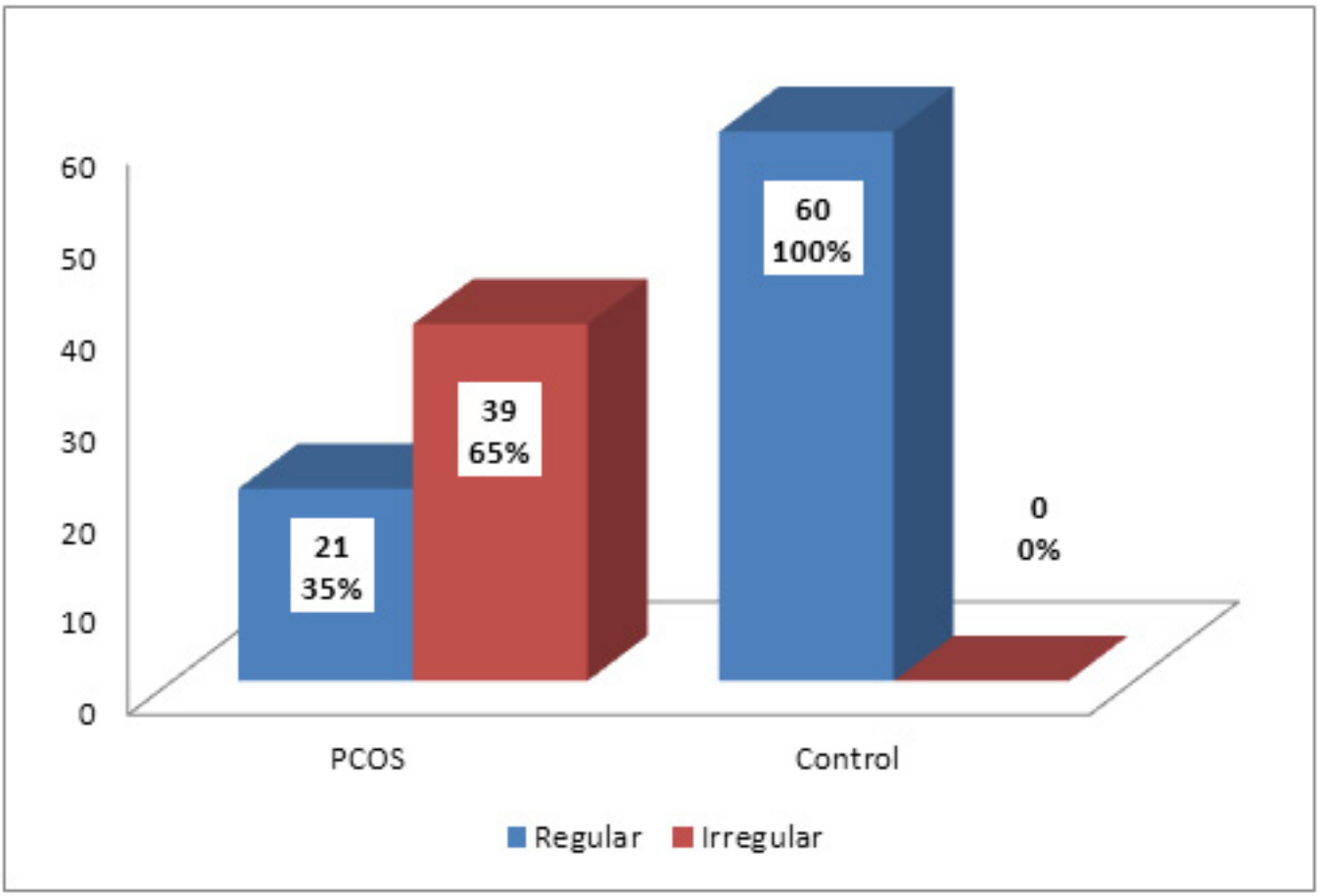

Table 2: Comparison and association of study group with qualitative variables

	N (%)			P-Value
	PCOS (n=60)	Control (n=60)	Total (n=120)	
Marital Status				0.142
Married	56(93.3)	51(85)	107(89.2)	
Unmarried	4(6.7)	9(15)	13(10.8)	
BMI Group				0.049
Normal	21(35)	22(36.7)	43(35.8)	
Overweight	16(26.7)	6(10)	22(18.3)	
Obese	23(38.3)	32(53.3)	55(45.8)	
Diabetes Family History				0.066
Yes	12(20)	21(35)	33(27.5)	
No	48(80)	39(65)	87(72.5)	
Hypertension Family History				0.346
Yes	25(41.7)	20(33.3)	45(37.5)	
No	35(58.3)	40(66.7)	75(62.5)	
CAD Family History				1.000
Yes	2(3.3)	3(5)	5(4.2)	
No	58(96.7)	57(95)	115(95.8)	
Surgical History				1.000*
Yes	4(6.7)	3(5)	7(5.8)	
No	56(93.3)	57(95)	113(94.2)	
Diet Habit				0.013
Healthy	42(70)	53(88.3)	95(79.2)	
Unhealthy	18(30)	7(11.7)	18(30)	
Depression				0.044
Yes	33(55)	22(36.7)	55(45.8)	
No	27(45)	38(63.3)	65(54.2)	
Body Image				0.000
Positive	39(65)	59(98.3)	98(81.7)	
Negative	21(35)	1(1.7)	22(18.3)	

Chi-square test was applied.
*Fisher Exact test was applied.
P-Value ≤0.05 considered as significant.

Table 3: Odds ratio for PCOS cases

	Un-Adjusted*		Adjusted**	
	P-Value	Odds Ratio(95% CI)	P-Value	Odds Ratio(95% CI)
Marital Status				
Married	0.152	2.471(0.717-8.515)	--	--
Unmarried®		1		
BMI Group				
Normal	0.489	1.328(0.595-2.964)	--	- -
Overweight	0.017	3.710(1.259-10.930)	--	--
Obese®		1		
Diabetes Family History				
Yes	0.069	0.464(0.203-1.060)	--	- -
No®		1		
Hypertension Family History				
Yes	0.347	1.429(0.680-3.002)	--	- -
No®		1		
CAD Family History				
Yes	0.650	0.655(0.106-4.069)	--	- -
No®		1		
Surgical History				
Yes	0.698	1.357(0.290-6.341)	--	- -
No®		1		
Diet Habit				
Healthy	0.017	0.308(0.118-0.807)	0.05	0.350(0.123-0.999)
Unhealthy®		1		
Depression				
Yes	0.045	2.111(1.016-4.385)	0.260	1.606(0.704-3.664)
No®		1		
Body Image				
Positive	0.001	0.031(0.004-0.244)	0.001	0.035(0.005-0.278)
Negative®		1		

*Univariate binary logistic regression was applied.
**Multivariate logistic regression was applied.
®Reference group
P-Value≤0.05 considered as significant

Discussion

Body image is a very important aspect among PCOS patients. In the current study, 98.3% of patients in the control group were showing positive body image while 65% of patients showed positive body image in the PCOS group which reflects a healthy state of mind. There is a significant association found between the study group with body image perception. Also more than over half of PCOS (55%), females had depression due to Body image perception. However, there is a significant association found between depression and study group. Various literary studies show antithetic findings regarding body image perception. Along with these PCOS (cases) have 2.11 times more odds to develop depression as compared to those without PCOS.

One of the studies showed the same results as the current study of increased risk of Body-image perception in women with polycystic ovary syndrome, which is the cause of lifetime distress (21). Similar to our results, one of the published research showed that there was a difference of body perception between PCOS and non-PCOS. PCOS women had a lower score of body image as compared to healthy females (22). Another finding from one study is in accordance with our results showing bad impact exerted by self-pride, increased risk of body image perception, unhealthy and unhappy sexual life of PCOS, in contrast to healthy subjects (23).

Another study found that body excess weight is the primary cause of low self-esteem, unhealthy mind state and depression. Further these patients are more willing to go for a weight loss plan of action (24). Similar to this study result published data showed body image dissatisfaction odds ratio higher (OR 2.39) than non PCOS subjects (25).

One of the studies showed high prevalence of depression among young PCOS patients, which is considered a very important health, issue commonly seen in PCOS. It may be because of some underline pathophysiology of PCOS like metabolic dysfunctions and different reproductive pathologies (26). One of the researchers published data found increased odds of depression and poor body image perception in PCOS females same as seen in this study (27).

Similar to our result one of the research studies showed the increased incidence of depressive symptoms in PCOS females in comparison to healthy individual (28). A systematic review on depression in PCOS females found increased odds of depression as OR 3.78; to OR 4.18; in different studies which are similar to this study (29).

Like this current study some other research found an insignificant relationship between depression and PCOS (30). Besides these promising findings, some of the limitations of this study were its sample size and inability to perform invasive investigations. Another limitation of this study is that the newly diagnosed subject could not show that long-lasting hormonal imbalance effect in PCOS women.

Conclusion

There is a profound significant difference of body image found between cases and controls with significant association regarding depression in cases and controls. Likelihood of negative body image perception and depressive symptomatology was shown higher in cases as compared to controls. However, some PCOS subjects also experienced depression due to body image so this may be a sign for psychiatric illness in PCOS, which needs to be treated as a high priority to improve quality of life of PCOS patients.

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Factors Associated with Not Continuing Initiated Breastfeeding among Saudi Females in Abha

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Abstract

Background: Despite the health, social and economic benefits of breastfeeding (BF) for both mother and child are well established and accepted throughout the world, the prevalence of breast feeding worldwide has not met the optimal target of WHO recommendation.

Objectives: To assess the prevalence of breastfeeding and determinants of not continuing initiated breast feeding among Saudi females.

Methods: A descriptive cross-sectional study was conducted in the primary healthcare centers` clinics and outpatient pediatric clinics of Abha maternity and children hospital, Saudi Arabia. It included a random sample of Saudi mothers with children aged up to two years of life. A validated questionnaire was utilized for data collection. It included three main parts: socio demographic data, the medical and health condition for the mother and current child and the attitudes of mother toward BF, BF pattern for the last child, and reasons for discontinuity of BF.

Results: The study included 276 mothers. The majority of them (88.1%) were aged between 20 and 39 years and were Saudi nationals (90.2%). History of receiving any health education about breast feeding was observed among the majority of the participants (91.7%). The most frequently reported source of health education was self-education through reading (39.1%), followed by doctors (30.4%), nurses (29.6%) and relatives/friends (27.7%). Overall, slightly more than half of them (51.1%) expressed a positive attitude towards breast feeding; particularly non-Saudi mothers (adjusted odds ratio "aOR":0.44, and those whose main source of information was nurses or self-education (aOR: 0.27 and 0.12, respectively). The majority of the participating women (86.2%) initiated breastfeeding for their newborns. Among them, 80.7% discontinued BF; particularly Saudi mothers (aOR: 0.08), mothers with higher education (aOR: 5.05-10.21), governmental employees (aOR: 3.51), those living in a separate house (aOR: 2.21), delivered by cesarean section (aOR: 11.14), reported NICU admission of their newborns (aOR: 9.13) and those who expressed a negative attitude towards BF (aOR: 0.25). The commonest reported causes of discontinuation of BF among the participants were thinking that breast milk is not enough (39.9%), going back to work (38.5%) and thinking that baby will be demanding on breastfeeding (13.3%).

Conclusion: Initiation of breastfeeding was very highly practiced by mothers in Abha city, Saudi Arabia. However, its discontinuation before the recommended time is also a highly reported practice.

Key words: Breastfeeding, initiation, discontinuation, Saudi Arabia.

Introduction

Breastfeeding (BF) is the process in which the mother can feed her newborn or infant, either directly or using pumping methods, naturally with the milk produced from her breast. Breastfeeding is essential and it is one of the most effective ways to ensure child health and survival. The health, social and economic benefits of breastfeeding, for both mother and child, are well established and accepted throughout the world.

On the base of this evidence, the World Health Organization (WHO) and United Nations International Children`s Emergency Fund (UNICEF) recommend initiating breastfeeding within the first hour of birth and infants be exclusively breastfed for the first 6 months of life, meaning no other foods or liquids are provided, including water (5).

Yet, the prevalence of breast feeding worldwide has not met the optimal target of WHO recommendations. Globally about 38% of babies are exclusively breastfed during their first year of life (9). The prevalence of Middle Eastern newborns received breastfeeding initiated within an hour of birth is 34.3%. In Saudi Arabia the percentage of breastfeeding initiation on the first day of delivery is 94.4% (11).

Despite the high rate of breastfeeding initiation, the rate of exclusive breastfeeding for the first six months of the infants' life was found to be only 13.7%, which is very low based on the World Health Organization (WHO) recommendation for infants to be exclusively breastfed for six months, followed by the introduction of complementary food (12).

In the WHO country profile for Saudi Arabia there is no data about BF types and durations or their determinants because no recent or sufficient data are locally available, (13) although many studies from different cities in Saudi Arabia are done about multiple aspects of breastfeeding. Among those studies none of them were held to study the determinants of discontinuing initiated BF. There was a study done in Riyadh city to assess the determinants of the early initiation of BF in KSA (14). In contrast, another study was done in Mecca region to assess the factors associated with not breastfeeding and delaying the early initiation of BF, (15) whereas there were two studies done in Abha city to assess breastfeeding knowledge, attitude and practice and identify factors that may affect breastfeeding practice in the study population (12, 16). Therefore, the objective of our study is to provide updates about the possible risk factors related to not continuing initiated BF for the complete 2 years among Saudi females in Abha city.

Methodology

A descriptive cross-sectional study was used targeting all mothers with children aged up to two years of life in Abha city, Saudi Arabia. All those mothers were invited to participate in this survey using a validated questionnaire. The questionnaire form was developed and constructed after intensive literature review and expert's consultation. The study questionnaire was reviewed using a panel of five experts (3 family medicine consultants and 2 pediatric consultants) for content validity. The study questionnaire was translated to Arabic language then tested on 10 Saudi mothers from the target population using a pilot study. After obtaining permission from the Institutional ethics committee, data collection started. A total of 300 questionnaire papers were distributed to the target population mothers in different PHCC and pediatric outpatient clinics then collected during the period from November 2020 to July 2021. Exactly 276 respondents completed the study questionnaire with a response rate of 92%. The study questionnaire included three main parts: socio-demographic data, the medical and health condition of the mother and current child and the attitudes of the mother toward BF, BF pattern for the last child, and reasons for discontinuity of BF. The response of the mothers to attitude statements towards BF were scored in the way that the higher the score, the more positive the attitude towards BF. Thus, the score of some statements was reversed. Total score and its percentage were computed for each participant and the median value was estimated (it was 67.27%). Those who scored below the median value were treated as having a "negative attitude" whereas those who scored at median value or above were treated as having a "positive attitude".

Data analysis

The data were collected, reviewed and edited, and checked for completeness before feeding into Statistical Package for Social Science (SPSS) version 26. All statistical analyses were done using two tailed tests and alpha error of 0.05. The graphs were constructed using Microsoft Excel software. Descriptive statistics were used by using means, standard deviations and ranges for scale variables while frequency distributions were used for qualitative variables. Univariate analysis using chi-square test was done to identify the relation between attitude towards BF and breast-feeding status (continuing or not) with different factors. Multivariate logistic regression analysis was performed to control for the confounding effect and results were expressed as adjusted odds ratio (AOR) and 95% confidence interval (CI).

Results

The study included 276 mothers of children aged up to 2 years of life. Their sociodemographic characteristics are presented in Table 1. The majority of them (88.1%) were aged between 20 and 39 years and were Saudi nationals (90.2%). Approximately half of them (50.7%) were Bachelor holders and 51.4% were housewives. Regarding the father`s information, 53.7% were Bachelor holders and 50.5% were governmental employees. The family income ranged between 5000 and 10000 SR/month among 47.9% of the women whereas it exceeded 10000 SR/month among 42% of them. Most of them (71.4%) live in separate houses with their husbands and 48.2% have 2-3 children. Age of the youngest child ranged between >6 months and 2 years in 64.5% of women. Most of the women (73.9%) delivered the last child through spontaneous vaginal delivery.

Table 1: Sociodemographic characteristics of the participants (n=276)

	Frequency	Percentage
Age (years)		
<20	12	4.3
20-29	123	44.6
30-39	120	43.5
≥40	21	7.6
Nationality		
Saudi	249	90.2
Non-Saudi	27	9.8
Mother`s education		
Primary	19	6.9
Secondary/Diploma	107	38.8
Bachelor degree	140	50.7
Higher education	10	3.6
Mother`s occupation		
House wife	142	51.4
Governmental	113	41.0
Private/business	21	7.6
Father`s education		
Primary	10	3.6
Secondary/Military institute	105	38.0
Bachelor degree	148	53.7
Higher education	13	4.7
Father`s occupation		
Governmental	142	51.5
Private	62	22.5
Military	68	24.6
Retired	4	1.4
Monthly income (Saudi Riyals)		
<5000	28	10.1
5000-10000	132	47.9
>10000	116	42.0
Residence		
With own or husband`s family	79	28.6
Separate house	197	71.4
Number of children		
One	82	29.7
2-3	133	48.2
>3	61	22.1
Age of youngest child		
≤ 6 months	98	35.5
> 6 months – 2 years	178	64.5
Mode of delivery of last child		
Spontaneous vaginal delivery	204	73.9
Cesarean section	72	26.1

Health education: History of receiving any health education about breast feeding was observed among the majority of the participants (91.7%) as displayed in Figure 1. The most frequently reported source of health education was self-education through reading (39.1%), followed by doctors (30.4%), nurses (29.6%) and relatives/friends (27.7%) as shown in Figure 2.

Figure 1: History of receiving any health education about breast feeding among the participants

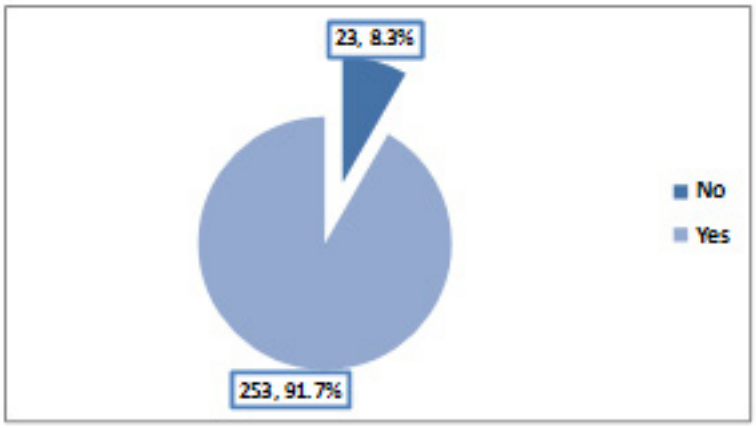
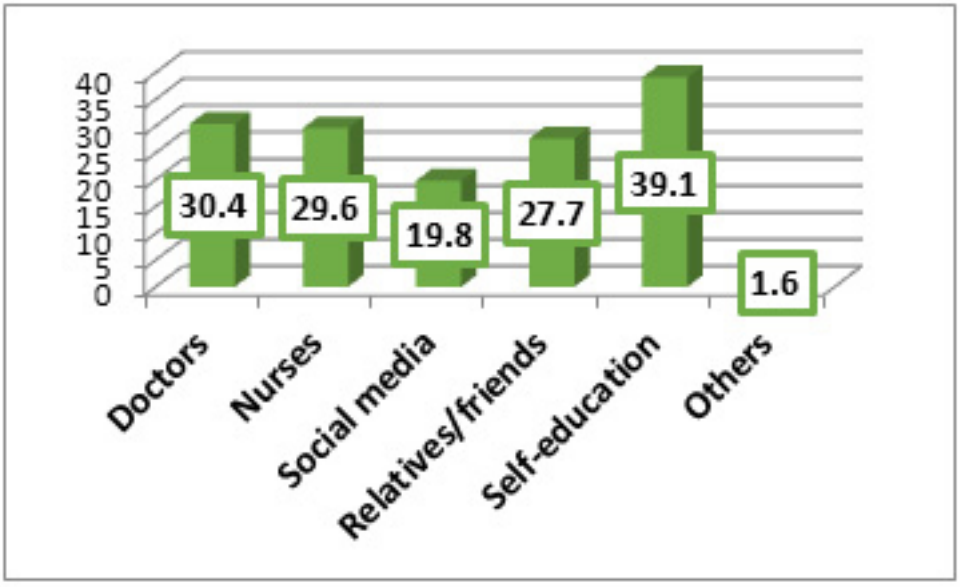


Figure 2: Source of health education about breast feeding among the participants (n=253)



Medical History: history of chronic diseases that did not contraindicate BF was reported among 7.2% of mothers. None of the participants reported history of psychiatric illness. History of taking any medications (including oral contraceptives) was mentioned by 26.8% of the participants. History of prematurity of the last child was reported by 6.9% of the participants. History of neonatal intensive care unit admission of the last child was reported by 8.3% of the participants. History of health problems of the last child was reported among four mothers (1.4%).

Smoking history: Only one mother reported history of smoking, representing 0.4% of the participants.

Attitudes of mothers towards breastfeeding: From Table 3, it is obvious that 72.1% of the participants either agreed or strongly agreed that healthcare workers encourage breastfeeding; 71.9% of them either agreed or strongly agreed that breastfeeding helps in weight loss and 69.9% either agreed or strongly agreed that breastfeeding is easier than artificial feeding. On the other hand, 61.9% of them either disagreed or strongly disagreed that breastfeeding has a negative effect on marital relationship and 60.4% either disagreed or strongly disagreed that work places offer suitable private places for breastfeeding.

Overall, slightly more than half of them (51.1%) expressed a positive attitude towards breast feeding as shown in Figure 3.
Non-Saudi mothers expressed a more positive attitude towards BF compared to Saudis (70.4% vs. 49%), p=0.035. Mothers delivered by spontaneous vaginal delivery had a more positive attitude towards BF compared to those delivered by cesarean section (56.4% vs. 36.1%), p=0.003. Source of information about BF significantly affected the attitude of mothers towards BS; the highest rate of positive attitude was observed among mothers who got their information about BF through self-education (76.4%) while the lowest rate was observed among those who got their information from social media (22.7%), p<0.001 (Table 3).

Multivariate logistic regression analysis revealed that compared to Saudi mothers, non-Saudis were less likely to have a negative attitude towards BF (adjusted odds ratio “aOR”:0.44, 95% confidence interval “CI”: 0.17-0.93, p=0.048). Considering doctors as the main source of information about BF as a reference category, mothers whose main source of information was nurses or self-education were less likely to have a negative attitude towards BF (aOR: 0.27, 95% CI: 0.10-0.74, p=0.011 and aOR: 0.12, 95% CI: 0.06-0.37, p<0.001; respectively). Mode of delivery of the last child was not significantly associated with mothers` attitude towards BF.

Figure 3: Overall attitude of the participants towards breastfeeding

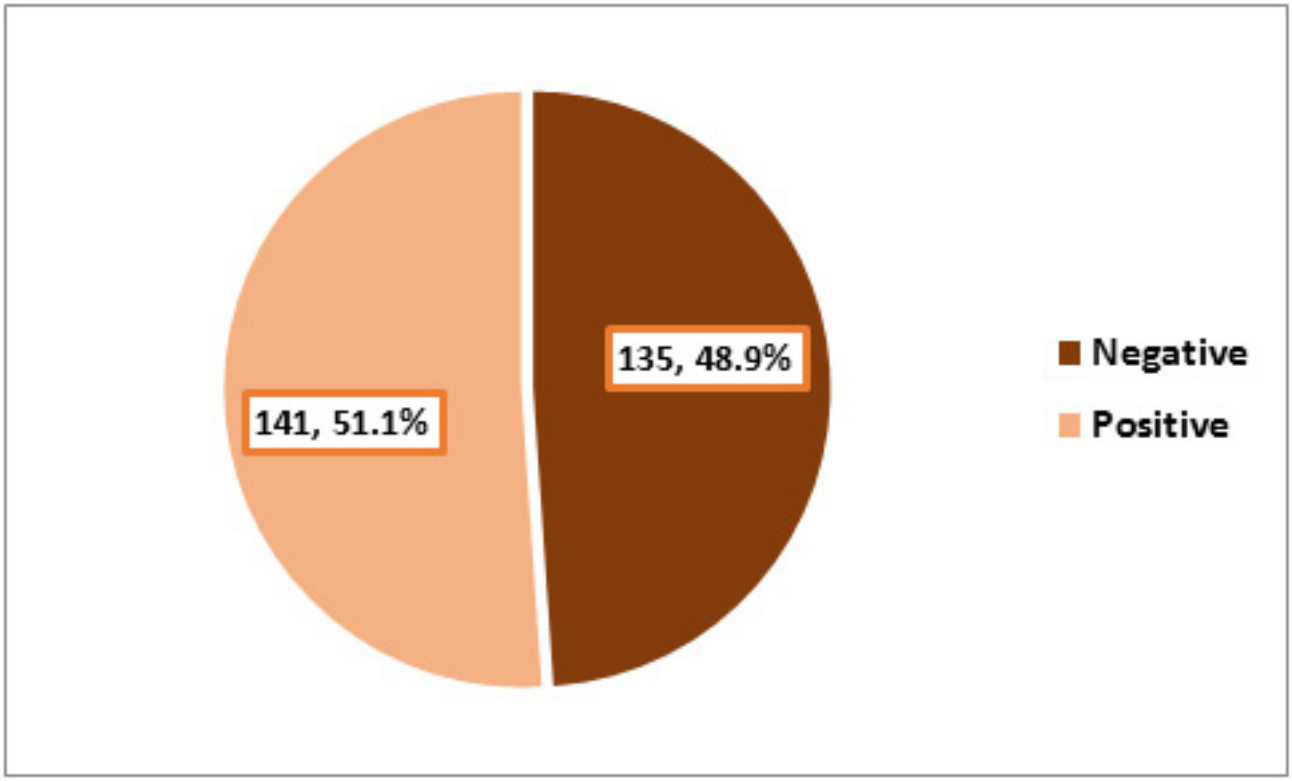


Table 2: Attitude of the participants towards breastfeeding

	1 N (%)	2 N (%)	3 N (%)	4 N (%)	5 N (%)
Breastfeeding is easier than artificial feeding	8 (2.9)	28 (10.1)	50 (18.1)	83 (30.1)	107 (38.8)
It is difficult for breast feeder to take care of her family	64 (23.2)	79 (28.6)	66 (23.9)	53 (19.2)	14 (5.1)
Breastfeeding has negative effect on marital relationship	116 (42.0)	55 (19.9)	61 (22.1)	35 (12.7)	9 (3.3)
Breastfeeding reduces family expenses	28 (10.1)	37 (13.4)	71 (25.8)	89 (32.2)	51 (18.5)
Artificial feeding preserves woman's breast shape	64 (23.2)	32 (11.6)	94 (34.1)	50 (18.1)	36 (13.0)
Breastfeeding helps in weight loss of the mother.	20 (7.2)	18 (6.5)	39 (14.1)	100 (36.3)	99 (35.9)
The community prefers breastfeeding over artificial feeding	7 (2.5)	32 (11.6)	105 (38.1)	58 (21.0)	74 (26.8)
Healthcare workers encourage breastfeeding	8 (2.9)	28 (10.1)	41 (14.9)	78 (28.3)	121 (43.8)
A vacation for 3 months is enough for successful breastfeeding	72 (26.1)	40 (14.5)	73 (26.5)	46 (16.7)	45 (16.3)
Work places offer suitable private places for breastfeeding	129 (46.6)	38 (13.8)	27 (20.7)	25 (9.1)	27 (9.8)
Breast milk is insufficient for the child	42 (15.2)	29 (10.5)	80 (29.0)	77 (27.9)	48 (17.4)

1= strongly disagree, 2= disagree, 3= neutral, 4= agree, 5= strongly agree.

Table 3: Factors associated with attitude of the participants towards breastfeeding

	Attitude towards breastfeeding		p-value*
	Negative N=135 N (%)	Positive N=(%)141 N	
Age (years)			
<20 (n=12)	7 (58.3)	5(41.7)	
20-29 (n=123)	64 (52.0)	59 (48.0)	
30-39 (n=120)	57 (47.5)	63 (52.5)	
≥40 (n=21)	7 (33.3)	14 (66.7)	0.385
Nationality			
Saudi (n=249)	127 (51.0)	122 (49.0)	
Non-Saudi (n=27)	8 (29.6)	19 (70.4)	0.035
Mother`s education			
Primary (n=19)	9 (47.4)	10 (52.6)	
Secondary/Diploma (n=107)	51 (47.7)	56 (52.3)	
Bachelor degree (n=140)	68 (48.6)	72 (51.4)	
Higher education (n=10)	7 (70.0)	3 (30.0)	0.600
Mother`s occupation			
House wife (n=142)	70 (49.3)	72 ((50.7)	
Governmental (n=113)	52 (46.0)	61 (54.0)	
Private/business (n=21)	13 (61.9)	8 (38.1)	0.405
Father`s education			
Primary (n=10)	6 (60.0)	4 (40.0)	
Secondary/Military institute (n=105)	57 (54.3)	48 (45.7)	
Bachelor degree (n=148)	64 (43.2)	84 (56.8)	
Higher education (n=13)	8 (61.5)	5(38.5)	0.218
Father`s occupation			
Governmental (n=142)	68 (47.9)	74 (52.1)	
Private (n=62)	31 (50.0)	31 (50.0)	
Military (n=68)	32 (47.1)	36 (52.9)	
Retired (n=4)	4 (100)	0 (0.0)	0.225
Monthly income (Saudi Riyals)			
<5000 (n=28)	15 (53.6)	13 (46.4)	
5000-10000 (n=132)	67 (50.8)	65 (49.2)	
>10000 (n=116)	53 (45.7)	63 (54.3)	0.636
Residence			
With own or husband`sfamily (n=79)	32 (40.5)	47 (59.5)	
Separate house (n=197)	103 (52.3)	94 (47.7)	0.077
Number of children			
One (n=82)	39 (47.6)	43 (52.4)	
2-3 (n=133)	63 (47.4)	70 (52.6)	
>3 (n=61)	33 (54.1)	28 (45.9)	0.656
Age of youngest child			
≤ 6 months (n=98)	42 (42.9)	56 (57.1)	
> 6 months – 2 years (n=178)	93 (52.2)	85 (47.8)	0.135
Mode of delivery of last child			
Spontaneous vaginal delivery (n=204)	89 (43.6)	115 (56.4)	
Cesarean section (n=72)	46 (63.9)	26 (36.1)	0.003
Having health education about BF			
No (n=23)	11 (47.8)	12 (52.2)	
Yes (n=253)	124 (49.0)	129 (51.0)	0.913

Table 3: Factors associated with attitude of the participants towards breastfeeding (continued)

If yes, source of information about BF (n=253)			
Doctor (n=35)	25 (71.4)	10 (28.6)	
Nurse (n=34)	14 (41.2)	20 (58.8)	
Social media (n=22)	17 (77.3)	5 (22.7)	
Relatives/friends (n=18)	9 (50.0)	9 (50.0)	
Self-education (n=55)	13 (23.6)	42 (76.4)	
Two sources (n=61)	33 (54.1)	28 (45.9)	
>two sources (n=28)	14 (50.0)	14 (50.0)	<0.001
Chronic diseases			
No (n=256)	129 (50.4)	127 (49.6)	
Yes (n=20)	6 (30.0)	14 (70.0)	0.079
Taking any medications			
No (n=202)	103 (51.0)	99 (49.0)	
Yes (n=74)	32 (43.2)	42 (56.8)	0.254
Prematurity of the last child			
No (n=257)	128 (49.8)	129 (50.2)	
Yes (n=19)	7 (36.8)	12 (63.2)	0.275
NICU admission of the last child			
No (n=253)	123 (48.6)	130 (51.4)	
Yes (n=23)	12 (52.2)	11 (47.8)	0.744
Health problems of the last child			
No (n=272)	135 (49.6)	137 (50.4)	
Yes (n=4)	0 (0.0)	4 (100)	0.067=

*Chi-square test [] Fischer Exact test

Table 4: Predictors of negative attitude towards BF" Multivariate logistic regression analysis

	Adjusted odds ratio	95% confidence interval	P-value
Nationality			
Saudi[a]	1.0		
Non-Saudi	0.44	0.17-0.93	0.048
Source of information about BF			
Doctor[a]	1.0		
Nurse	0.27	0.10-0.74	0.011
Social media	1.19	0.34-4.18	0.784
Relatives/friends	0.35	0.11-1.16	0.086
Self-education	0.12	0.06-0.37	<0.001
Two sources	0.43	0.17-1.06	0.067
> two sources	0.39	0.13-1.13	0.082

a: Reference category

Mode of delivery of the last child was not significant (removed from the final model)

Practice of breastfeeding: It is evident that the majority of the participating women (86.2%) initiated breastfeeding for their newborns.

- Use of a pacifier by the current child was reported by 38.4% of mothers.
- More than half (52.5%) of the mothers started BF after 24 hours of delivery. Regarding the type of feeding of the current child; exclusive breast feeding was mentioned by 16.7% of the participants, whereas artificial feeding was mentioned by 42% of them. Among mothers who initiated breastfeeding (n=238), 192 (80.7%) discontinued BF (Table 5).

Table 5: Details of history of breast feeding of the last child among the participants who initiated breastfeeding (n=238)

	Frequency	Percentage
When did you start BF?		
Within 24 hours of delivery	113	47.5
After 24 hours of delivery	125	52.5
What type of feeding is your current child on?		
Exclusive BF	46	16.7
Artificial formula	116	42.0
Mixed	113	40.9
Other	1	0.4
Discontinuation of breast feeding (n=238)		
Yes	192	80.7
No	46	19.3

Factors associated with discontinuation of breastfeeding

Table 6 demonstrates that Saudi mothers were more likely to discontinue BF compared to non-Saudis (85.3% vs. 44.4%), p<0.001. All higher educated mothers compared to only 37.5% of primary school educated reported discontinuation of BF, p<0.001. The majority of governmental employees (93.5%) compared to 66.7% of private employees/business women reported discontinuation of BF, p<0.001. The majority of mothers whose husbands are governmental employees or in the military (84.7%) compared to 66.7% of those whose husbands work in the private sector discontinued BF, p=0.030. The majority of mothers (86%) whose income exceeded 10000 SR/month compared to 45% of those whose income was <5000 SR/month discontinued BF, p<0.001. Women living in separate house were more likely to discontinue BF compared to those living with their own or husbands` family (86.5% vs. 65.7%), p<0.001. The majority of women who have 2-3 children (87.5%) compared to 67.3% of those who have >3 children reported discontinuation of BF, p=0.009. All women delivered by cesarean section compared to 74.3% of those delivered by spontaneous vaginal delivery had discontinued BF, p<0.001. All mothers who reported admission of their last child to NICU compared to 79.3% of those without such history had discontinued BF, p=0.028. Mothers who reported using pacifier by their last child were more likely to discontinue BF compared to their peers (88.1% vs. 76.6%), p=0.032. Mothers who expressed a negative attitude towards BF were more likely to report discontinuation of BF compared to those with a positive attitude (91.7% vs. 71.3%), p<0.001.

Multivariate logistic regression analysis revealed that compared to Saudi mothers, non-Saudis were less likely to discontinue BF (aOR: 0.08, 95% CI: 0.02-0.32, p<0.001). Considering primary school educated mothers as a reference category, mothers with higher education (secondary/Diploma, Bachelor and higher education) were at higher significant risk for discontinuing BF (aOR: 5.05, 95% CI: 1.29-19.73, p=0.020' aOR: 7.72, 95% CI: 1.94-30.66, p=0.004 and aOR 10.21, 95% CI: 4.16-100.04, p<0.001; respectively). As opposed to house wives, governmental employees were at almost 3-folds significant risk to discontinue BF (aOR: 3.51, 95% CI: 1.16-10.60, p=0.026) while private/business employees were at lower risk (aOR: 0.12, 95% CI: 0.02-0.79, p=0.028). Mothers living in separate house were at almost double the risk to discontinue BF compared to those living with her own or husband`s family (aOR: 2.21, 95% CI: 1.07-5.65, p=0.046). Mothers delivered by cesarean section were at higher risk to discontinue BF compared to those delivered by SVD (aOR: 11.14, 95% CI: 3.72-81.30, p<0.001). Mothers who reported NICU admission of their newborns were at higher risk to discontinue BF compared to others (aOR: 9.13, 95% CI: 2.17-76.11, p<0.001). Mothers who expressed a positive attitude towards BF were a lower significant risk to discontinue BF compared to those who expressed a negative attitude (aOR: 0.25, 95% CI: 0.090.67, p=0.006). Father`s occupation, income, number of children and use of pacifier were not significantly associated with discontinuation of BF (Table 7).

Table 6: Factors associated with discontinuation of breastfeeding among mothers who initiated it

	Discontinued initiated breast feeding		p-value*
	No N=46 N (%)	Yes N=192 N (%)	
Age (years)			
<20 (n=9)	3 (33.3)	6 (66.7)	
20-29 (n=106)	18 (17.0)	88 (83.0)	
30-39 (n=102)	22 (21.6)	80 (78.4)	
≥40 (n=21)	3 (14.3)	18 (85.7)	0.536
Nationality			
Saudi (n=211)	31 (14.7)	180 (85.3)	
Non-Saudi (n=27)	15 (55.6)	12 (44.4)	<0.001
Mother`s education			
Primary (n=16)	10 (62.5)	6 (37.5)	
Secondary/Diploma (n=96)	21 (21.9)	75 (78.1)	
Bachelor degree (n=120)	15 (12.5)	105 (87.5)	
Higher education (n=6)	0 (0.0)	6 (100)	<0.001
Mother`s occupation			
House wife (n=128)	34 (26.6)	94 (73.4)	
Governmental (n=92)	6 (6.5)	86 (93.5)	
Private/business (n=18)	6 (33.3)	12 (66.7)	<0.001
Father`s education			
Primary (n=7)	3 (42.9)	4 (57.1)	
Secondary/Military institute (n=85)	16 (18.8)	69 (81.2)	
Bachelor degree (n=136)	23 (16.9)	113 (83.1)	
Higher education (n=10)	4 (40.0)	6 (60.0)	0.124
Father`s occupation			
Governmental (n=124)	19 (15.3)	105 (84.7)	
Private (n=54)	18 (33.3)	36 (66.7)	
Military (n=59)	9 (15.3)	50 (84.7)	
Retired (n=1)	0 (0.0)	1 (100)	0.030
Monthly income (Saudi Riyals)			
<5000 (n=20)	11 (55.0)	9 (45.0)	
5000-10000 (n=118)	21 (17.8)	97 (82.2)	
>10000 (n=100)	14 (14.0)	86 (86.0)	<0.001
Residence			
With own or husband`s family (n=67)	23 (34.3)	44 (65.7)	
Separate house (n=171)	23 (13.5)	148 (86.5)	<0.001
Number of children			
One (n=67)	13 (19.4)	54 (80.6)	
2-3 (n=116)	15 (12.9)	101 (87.1)	
>3 (n=55)	18 (32.7)	37 (67.3)	0.009
Age of youngest child			
≤ 6 months (n=87)	18 (20.7)	69 (79.3)	
> 6 months – 2 years (n=51)	28 (18.5)	123 (81.5)	0.686
Mode of delivery of last child			
Spontaneous vaginal delivery (n=179)	46 (25.7)	133 (74.3)	
Cesarean section (n=59)	0 (0.0)	59 (100)	<0.001**

Table 6: Factors associated with discontinuation of breastfeeding among mothers who initiated it (continued)

Having health education about BF			
No (n=20)	6 (30.0)	14 (70.0)	
Yes (n=218)	40 (18.3)	178 (81.7)	0.207
If yes, source of information about BF (n=218)			
Doctor (n=25)	0 (0.0)	25 (100)	
Nurse (n=33)	4 (12.1)	29 (87.9)	
Social media (n=19)	4 (21.1)	15 (78.9)	
Relatives/friends (n=16)	1 (6.3)	15 (93.8)	
Self-education (n=54)	14 (25.9)	40 (74.1)	
Two sources (n=43)	10 (23.3)	33 (76.7)	
> two sources (n=28)	7 (22.2)	21 (77.8)	0.096
Chronic diseases			
No (n=226)	45 (19.9)	181 (80.1)	
Yes (n=12)	1 (8.3)	11 (91.7)	0.287**
Taking any medications			
No (n=183)	38 (20.8)	145 (79.2)	
Yes (n=55)	8 (14.5)	47 (85.5)	0.306
Prematurity of the last child			
No (n=223)	45 (20.2)	178 (79.8)	
Yes (n=15)	1 (6.7)	14 (93.3)	0.174**
NICU admission of the last child			
No (n=222)	46 (20.7)	176 (79.3)	
Yes (n=16)	0 (0.0)	16 (100)	0.028**
Health problems of the last child			
No (n=236)	46 (19.5)	190 (80.5)	
Yes (n=2)	0 (0.0)	2 (100)	0.650**
Using a pacifier by the current child			
No (n=154)	36 (23.4)	118 (76.6)	
Yes (n=84)	10 (11.9)	74 (88.1)	0.032
Attitude towards BF			
Negative (n=109)	9 (8.3)	100 (91.7)	
Positive (n=129)	37 (28.7)	92 (71.3)	<0.001

*Chi-square test **Fischer Exact test

Table 7: Predictors of discontinuation of breast feeding: Multivariate logistic regression analysis

	Adjusted odds ratio	95% confidence interval	P-value
Nationality			
Saudi[a]	1.0		
Non-Saudi	0.08	0.02-0.32	<0.001
Mother`s education			
Primary[a]	1.0		
Secondary/Diploma	5.05	1.29-19.73	0.020
Bachelor degree	7.72	1.94-30.66	0.004
Higher education	10.21	4.16-100.04	<0.001
Mother`s occupation			
House wife[a]	1.0		
Governmental	3.51	1.16-10.60	0.026
Private/business	0.12	0.02-0.79	0.028
Residence			
With own or husband`s family[a]	1.0		
Separate house	2.21	1.07-5.65	0.046
Mode of delivery of last child			
Spontaneous vaginal delivery[a]	1.0		
Cesarean section	11.14	3.72-81.30	<0.001
NICU admission of the last child			
No[a]	1.0		
Yes	9.13	2.17-76.11	<0.001
Attitude towards BF			
Negative[a]	1.0		
Positive	0.25	0.09-0.67	0.006

a Reference category

Terms of father`s occupation, income, number of children and using of pacifier were not significant (removed from the final model).

Causes of discontinuation of breastfeeding

Table 8 demonstrates that the commonest reported causes of discontinuation of BF among the participants were thinking that breast milk is not enough (39.9%), going back to work (38.5%) and thinking that baby will be demanding on breastfeeding (13.3%).

Table 8: Causes of discontinuation of breastfeeding among mothers (n=218)

	Frequency	Percentage
Health condition of the mother	23	10.5
Health condition of the child	6	2.8
Social issues	12	5.5
Economic issues	4	1.8
Complications from breastfeeding	4	1.8
Dissatisfaction	7	3.2
Going back to work	84	38.5
Thinking that breast milk is not enough	87	39.9
Thinking that baby will be demanding on breastfeeding	29	13.3
Others	19	8.7

Discussion

Despite the documented high initiation rate of breastfeeding in the Kingdom of Saudi Arabia,(22-24) there is reluctance in continuing exclusive breastfeeding, (22) as it has been reported to be between 12-14% (22, 23). The present study was carried out mainly to assess the prevalence of breastfeeding initiation and discontinuation as well as the determinants of discontinued initiated breast feeding among females in Abha city.

In the present study, the majority of mothers have initiated breast feeding (86.2%) with 47.5% of them having initiated it within 24 hours of delivery. However, only 19.3% of them continued BF while the remaining majority discontinued it. This practice is not in line with recommendations of the WHO and UNICEF which stated that mothers should initiate breastfeeding within the first hour of birth and babies be exclusively breastfed for the first 6 months of life (5).

In the Kingdom Saudi Arabia, the rate of breastfeeding initiation on the first day of delivery was 92% in an old study, (25) and reaching 94.4% in a relatively recent study (26). Also in another Saudi study, 37% of mothers reported exclusive breastfeeding in the first 6 months after birth, and 31.9% of them continued to breastfeed their infants for 24 months (27) and in a study carried out in Abha (2012), 90.9% of mothers have initiated breastfeeding, however only 13.7% exclusively breastfed their infants for the first six months of life (12). This drop in the percentage of breastfeeding since birth up to 6 months of age, gives us a clue that there is a defect leading mothers not to maintain breastfeeding exclusively in the first 6 months of their infants' lives. Close rates of initiation of breast feeding were also reported internationally. Uganda (85.7%),(28) Italy (91•6 %)(29) and Australia (93•3 %) (30).

This practice of discontinuing BF, despite the high initiation rate is not unique in the Kingdom of Saudi Arabia as it has been reported on a global level as approximately 38% of babies are exclusively breastfed during their first year of life(9). In the Middle East, initiation of BF within an hour was reported among 34.3% of mothers while only 20.5% followed an exclusive BF for the first 6 months of newborn life (10). In Uganda, the prevalence of exclusive BF reached 24.6% at five months (28). In Cyprus, similar to our findings, initiation of BF was high, however, discontinuation was observed and was highest before the fourth month; additionally, the prevalence of EBF was only 5•0% at the infants` age of 6 months (31).

In the present study, the majority of mothers reported receiving health education regarding BD; the main sources were self-education, doctors and nurses. However, this history could not impact positively on both attitude towards BF as well as practicing it, which raises a question about the quality and nature of such education. Furthermore, self-education (through social media and Internet sources) and nurses were the only two ways that improved attitude towards BF, without effect on practice. In another recent Saudi study, the main sources of information about infant feeding were social media, Internet sources, friends and relatives (24). It has been reported that social media and Internet sources` information, although questionable and hard to control, are cheap, easily accessible, and widely distributed (32).

It is obvious from results of the present study that more than half of the mothers expressed a positive attitude towards BF as 72.1% of them agreed that healthcare workers encourage breastfeeding, 71.9% agreed that breastfeeding helps in weight loss, 69.9% agreed that breastfeeding is easier than artificial feeding and 61.9% disagreed that breastfeeding has a negative effect on marital relationship. However, 60.4% disagreed that work places offer suitable private places for breastfeeding. These findings are in line with previous local, (33) regional (34, 35) and international studies (36).

In the current study, the determinants for discontinuing BF were being Saudi and governmental employees, which is an alarming finding and could be attributed to the fact that most of young Saudi women nowadays are working with no appropriate facilities for BF at work places as documented in this study and also due to inadequate maternity leave at governmental workplaces. This is also confirmed by finding that women working in private places or business were more likely to continue BF, mostly due to availability of BF places and facilities at work places. The same has been observed in studies carried out in Uganda(28) and Tanzania (37).

Furthermore, in this study, higher educated women were more likely to discontinue BF, mostly because of also being engaged in work, in addition to wrong belief that artificial feeding preserves a woman's breast shape which was documented by almost one-third of women in the present study and most probably being more among higher educated women. The same has been reported by others in Saudi Arabia (12, 24, 27). It has been documented that higher education does not mean higher knowledge and a positive attitude towards breast feeding due to lack of proper breastfeeding education of younger women at schools and universities (38).

Breast feeding in the present study was more likely to be discontinued among women living in a separate house compared to others living with their own or husband`s house. This finding enforces the role played by family members in encouraging continuing breastfeeding. The same has been reported by others in Saudi Arabia (39).
In the current study, women delivered by cesarean section were more likely to discontinue breast feeding. It has been reported in many studies that women delivered by CS were less likely to initiate breastfeeding or to maintain it before hospital discharge as compared to those delivered vaginally (40-42). Moreover, it has been shown that maternal choice for the mode of delivery may affect her decision to breastfeed (43). This could be attributed to maternal reasons such as the side effect of the anesthesia drugs, (44) postpartum maternal fatigue or wound pain (45).

In accordance with others,(46, 47) the present study revealed that women having NICU admission of their newborns were more likely to discontinue breast feeding. Also, as expected, women who expressed a positive attitude towards BF were less likely to discontinue BF. The same has been reported by others (34, 38).

In the present study, commonest reported causes of discontinuation of BF among the participants were thinking that breast milk is not enough (39.9%), going back to work (38.5%) and thinking that baby will be demanding on breastfeeding (13.3%). In a similar Saudi study, the most frequent reasons for discontinuing BF was insufficient breast milk (25.9%), followed by getting pregnant (19.7%) and finally being a working mother (15.9%) (27). In Uganda, reasons associated with discontinuing BF were age of the infant, mother's work, infrequent attendance of antenatal care clinics, and improper breastfeeding practices at delivery (28). Insufficient breast milk was also reported by others as a main reason for discontinuing BF (37, 48, 49).

Strengths and limitation

Only inclusion of mothers of children aged up to two years minimized the possibility of recall bias. In addition, data of the present study explored the current practice of breast feeding in Abha city and defined the determinants of its discontinuation despite the high initiation rate. Additionally inclusion of mothers from both primary healthcare centers and outpatients clinics in children and maternity hospital ensured the best representation of various groups of people. However, the cross-sectional design applied in this study proves only association and not causality between dependent and independent variables. Also, assessment of the infant feeding history was done based on information gathered from mothers, which may overestimate the actual practice of exclusive breast feeding.

Conclusion

The study concluded that initiation of breastfeeding was very highly practiced by mothers in Abha city, Saudi Arabia. However, its discontinuation before the recommended time is also a highly reported practice. Discontinuation of breastfeeding was more frequently reported among Saudi mothers, those with higher education, governmental employees, those living in separate house, delivered by cesarean section, mothers who reported NICU admission of their newborns and those who expressed negative attitudes towards BF. The commonest reported causes of discontinuation of BF among the participants were thinking that breast milk is not enough, going back to work and thinking that baby will be demanding on breastfeeding.

Recommendations

In order to maintain the high rate of initiation of breastfeeding and following the recommendations of WHO and UNICEF, the following are recommended:

1. Creation and/or activation of breastfeeding classes for pregnant women during their antenatal visits to primary healthcare centers and hospitals.
2. Encouraging mothers to attend antenatal care visits to get information about the benefits of exclusive breastfeeding to children up to age of 6 months.
3. Providing suitable places for breastfeeding for working mothers as well as sufficient maternity leave.
4. Future study is warranted to explore the obstacles for exclusive breast feeding in more details, particularly those related to workplaces and negative attitude towards breastfeeding.

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Does test anxiety and gender have an impact on OSCE Performance among medical students?

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Abstract

Objective: to determine the association of test anxiety on OSCE performance of medical students in Taif Medical College.

Study Design: The survey research design was used to conduct the research.

Place and Duration of study: This was a comparative cross sectional study conducted on the 3rd, 4thand 5th year medical students in Taif Medical College of Taif University KSA.

Materials & Methods: A ten item questionnaire developed by Nist and Diehl (1990) for determining mild or severe levels of TA experienced by students was used in the study.

Results: A total of 518 students participated in the survey. The majority of the sample population was male 319 (61%) and 199 (39%) were females. Our results showed that a greater proportion (21%) of the male students, as compared to their counterparts, were in the group having high level of anxiety during test. It was observed that the 3rd year students performed poorly on TA and scored high on the scale. The difference observed in proportions was also statistically significant (Chi square 65.97, p value 0.000001). There was a significant negative correlation between the test anxiety and students performance in oral structured examination (OSCE). Pearson correlation coefficient of -0.45 and a p value < 0.0001 was observed.

Conclusion: We conclude that test anxiety is experienced by a large number of undergraduate medical students of Taif Medical University. Anxiety has a negative effect on overall academic performance; female students were also more affected compared to their male counterparts.

Key Words: Test anxiety, gender, medical students, academic performance

Introduction

Medical education exposes students to a highly stressful environment (1).Numerous reasons have been attributed, however tests and examinations are considered to be amongst the top stressors related to anxiety being experienced by the graduating students (2,3).

Tests, on one hand offer continuous feedback on the student's progress which provides an opportunity to improve, for both the teachers and the graduates. On the other hand examinations are considered a significant predictor of student performance and propensity, hence can result in causing test anxiety (TA) in medical students (4).

It has been argued that anxiety and stress are factors which can tremendously hinder the performance level of students whenever they are examined for their competence, promotion to higher grades and propensity irrespective of their age, and the field they are working in(3,5). An important component of test anxiety which might also influence student's performance is its behavioral aspect which alludes to the poor learning and exam taking strategies, inattention and distraction while taking exams (6).

Test anxiety (TA) is a social phobia which makes the students very doubtful about their ability. As a result, students are less able to deal with test situations (6). Exams produce an anxiety state when a student who has the knowledge is not able to recall or apply it properly. This also explains that anxiety scores and test scores are inversely related. However test associated anxiety might also play a double role where it is perceived as a factor which prepares the students for the stress they will come across subsequently later in the course of their academic career (7).

TA is considered as a persistent trait of one's personality by some, whereas for others it is the extreme reaction or anxiousness of some individuals when they are exposed to an exam situation (8). It has been argued that the extreme level of anxiety in test anxious students triggers the concerns, fears of failing and forgetfulness stored in a person's memory. The student becomes more preoccupied with the insinuations and consequences of failure to meet a situational challenge and loses their focus on the exam task thus leading to impeding their performance in the exam (6,9).

It is also worth mentioning that although test associated anxiety and stress might have a negative influence on the academic performance of some students, a moderate level of stress is considered normal, beneficial and contributes positively in successful performance (10,11). It has been identified that anxiety greatly influences the grades of the students, the type of test and their performance in it (12). TA results in disturbance and distress which can be disastrous for the students as it may impair their performance (5). TA is reported to be a common type of performance anxiety. Many countries from the Arabian peninsula have students experiencing TA due to greater stakes involved in the test scores (13,16).

In an effort to introduce excellence and accountability to medical education the use of standardized tests has increased which has also led to an increase in the TA amongst students. This anxiety can affect any student, regardless of the gender, ethnicity, socio-economic status; grade level, and intellectual capacity (17).Worldwide, women are in the majority in terms of getting admission to medical schools (18). Female medical students are competing and trying to be at par with the male medical students as regards to academic competence, clinical communication and patient-centered care. However literature shows that they are more anxious and less confident in their abilities than their male counterparts (19).

A review of literature shows that researchers have focused on the relationship between the TA and academic performance. It has been revealed that there exists a negative relationship between the two constructs. TA hinders mental and physical abilities of students which results in low scores in exams (20).

It is shown that in low test anxious students' exam associated anxiety positively influences their exam preparation and performance. Whereas in high test anxious students, TA is reported to prevent them from functioning normally (10,12). It has been reported that these students do not adopt proper study skill and also give inadequate time to their studies (12).

TA is a vigorous process and a contentious area that if not handled seriously might become severe with the passage of time (20). High test-anxious students were also found to have poorer study skills. For the high test-anxious group, quality of study habits and amount of study time were also positively related to academic performance. A negative relationship between TA and academic performance has also been reported (20).

Findings from a study have indicated that level of TA did not differ much in students exposed to different systems of education (21). However some studies done to determine the relationship of gender with TA highlighted greater TA levels in female students. One of the main reasons for this high TA could be the different role expected of females to play causing them to face some very conflicting situations (22).

The introduction of objective structured clinical examinations (OSCEs) in medical schools led the researchers to investigate the differences in performance of male and female OSCE examinees and the anxiety level of these students. In this regard little data is available that can identify the gender impact on clinical and communication skills during OSCE (23,24). However from the available data it could be summarized that the effect of gender on the anxiety levels and on OSCE ratings is inconsistent, with some researchers finding no gender difference in performance on the basis of their gender whereas others showing a definitive difference (25,27). The finding of this study will be noted for the benefit of society considering that medical students are assuming a vital part in society. The more noteworthy interest for

more sensible and effective teaching methodology and the approach towards the assessment results. Medical colleges adopting the recommended approach derived from the results of this study will be able to better train their medical students thus producing more confident and competent graduates.

The findings of the study will also suggest several ways for medical educators that can be adopted to minimize the detrimental effect of TA and also propose possible directions for future research in the area.

Research Questions

The current research explores the following research questions:

i. Is there any gender difference in TA and academic performance of medical students?

ii. Is there any difference in TA level of medical students of different academic years (3rd, 4th, 5th years).

iii. What is the relationship between TA and academic performance of medical students?

The present study therefore attempts to enrich the understanding of TA in the local context by examining the nature of TA and medical students' attainment of education goals in Taif, Saudi Arabia.

Hypothesis

i. There is a significant difference in association of TA and OSCE scores between male and female medical students.

ii. There is a significant difference in anxiety levels among 3rd, 4th and 5th year medical students

iii. There is a significant negative association of TA with performance of students in OSCE.

Method

Research Design

The survey research design was used to conduct the research.

Sample and Sampling Strategy

A convenience sampling method was used to select study participants from each stratum.

Inclusion Criteria

Students with the following criteria were recruited in this study

- Age greater than 20 years
- Currently enrolled in 3rd, 4th or 5th year in Taif Medical College
- Agreeing to participate in the study.

Exclusion Criteria

- Medical students with speech defects which considerably affects the clarity and content of the speech

Research Design and Setting

This was a comparative cross sectional study conducted on the 3rd, 4th and 5th year medical students in Taif Medical College of Taif University, KSA. Using a convenience sampling technique a total of 450 medical students (sample size calculated using the finding of the study by Fallahzadeh, 2011) were included in the study. 75 students each from both genders (total 150) meeting the inclusion criteria were enrolled.

TA level of 450 students was measured using a TA questionnaire. Medical student's performance was identified using the marks scored by them in the OSCEs of the last high stakes examination (modules). Statistical analysis was done to test all hypotheses. P value < 0.05 was considered significant to accept or reject the null hypothesis.

Instrument:

Test anxiety questionnaire

A ten item questionnaire developed by Nist and Diehl (1990) for determining mild or severe levels of TA experienced by students was used in the study. Student's responses were calculated based on a 5 point rating scale with 1, 2, 3, 4 and 5 points allocated to Never, Rarely, Sometimes, Often, and Always respectively.

Scores obtained on the ten item questionnaire ranged from 10 – 50. A score of <10 was considered as having no test anxiety, a score ranging from 10 to 19 was graded as low, 20 to 35 as moderate and that from 36 to 50 as a high test anxiety level.

Academic grades:

Marks scored by the students in the OSCEs of the last two modules (final semester) were considered for comparison with their TA levels. The modules included were Psychiatry & Surgery 1 for 3rd year, Obstetrics & Gynaecology 1 and Family medicine for 4th year and Surgery 2 and Obstetrics & Gynaecology 2 for 5th year, respectively.

Operational definitions:

Test –Anxiety

TA is defined as a state of uneasiness and distress before and during a test that often lowers performance.

Academic performance

Student's academic performance was based on cumulative marks scored by them in the OSCEs conducted at the end of the final semester.

Ethical Procedure:

Research ethics committee of Taif University KSA approved the study. After an informed consent participants (both male and female) were asked to fill in a TA questionnaire. Anonymity and confidentiality was maintained throughout the research.

Participants' OSCE scores were then compared with their anxiety levels. The effect of anxiety on both male and female medical students of 3rd, 4th and 5th year was also analyzed.

Statistics:
Descriptive statistics were performed. Categorical/ Qualitative variables were presented as frequencies and percentages while quantitative variables were presented as Mean ± Standard deviation.

Correlation analysis was carried out to identify the association between anxiety and its domains with academic performance.

- Hypothesis one was tested by t-test.
- Hypothesis two was tested by one-way ANOVA.
- Hypothesis three was tested by Pearson correlation.

P value < 0.05 was considered to accept or reject the null hypothesis.

Results

199 (39%) were females. The mean age of the students was 23 years SD+ 1.3 years (Table 1). Almost an equal proportion of students from third year (n=204, 39%) 4th year (n= 137, 26%) and final year (n= 177, 34%) participated in the study.

Table 1: Demographic characteristics of study participants

Age	23 years	SD± 1.3 years
Gender		
Male	319	61.58%
Female	199	38.42%
Level of study		
3rd year students	204	39.38%
4th year students	137	26.45%
5th year students	177	34.17%
TOTAL	518	100.00%

The mean academic scores (OSCE) among three levels of undergraduate students were closer to each other. The 3rd year scored 80+ 7, 4th year students scored a mean score 83 + 6 and final year scored 83.1 + 9.

Table 2: Academic performance among different levels of study

OCSE Score * year	No.o.s	Mean	StdDev
3rd	204	80.4081	7.0024
4th	137	83.0266	6.2002
5th	177	83.1727	9.0322

The reliability index measured by Cronbach's alpha on 10 items is 0.85 which showed a good reliability of scale.

Our results showed that a greater proportion (21%) of the male students as compared to their counterparts were in the group having high level of anxiety during test. The findings were however statistically insignificant (Chi 7.2, p value 0.06). Therefore, anxiety scores do not vary by gender.

Table 3: TA levels among male and female students

Gender/TA Level	No TA<10	Low TA (11-20)	Moderate TA (21-35)	High TA (36-50)	Total	P-Value
Male	27(8.5)	99(31)	126(39.5)	67(21)	319	
Female	15(7.5)	63(31.7)	96(48.2)	25(12.6)	199	
Total	42(8.1)	162(31.3)	222(42.9)	92(17.8)	518	0.064

To find out the effect of level of study on student's anxiety level it was observed that the 3rd year students performed poorly on TA and scored high on scale. The difference observed in proportions was also statistically significant (Chi square 65.97, p value 0.000001).

Table 4: Distribution of TA scores among different years of education

Academic levels	No TA <10	Low TA (10-19)	Moderate TA (21-35)	High TA (36-50)	Total	P-Value
3th year	9(4.4)	53(26)	100(49)	42(20.6)	204	<0.0001
4th year	20(14.6)	67(48.9)	49(35.8)	1(0.7)	137	
5th year	13(7.3)	42(23.7)	73(41.2)	49(27.7)	177	
Total	42(8.1)	162(31.3)	222(42.9)	92(17.8)	518	

Effect of anxiety levels on academic performance was also tested and there was a significant negative correlation between the anxiety and students' performance in academics. Pearson correlation coefficient of -0.45 and a p value < 0.0001 was observed.

Figure 1:Relationship of anxiety levels on academic performance

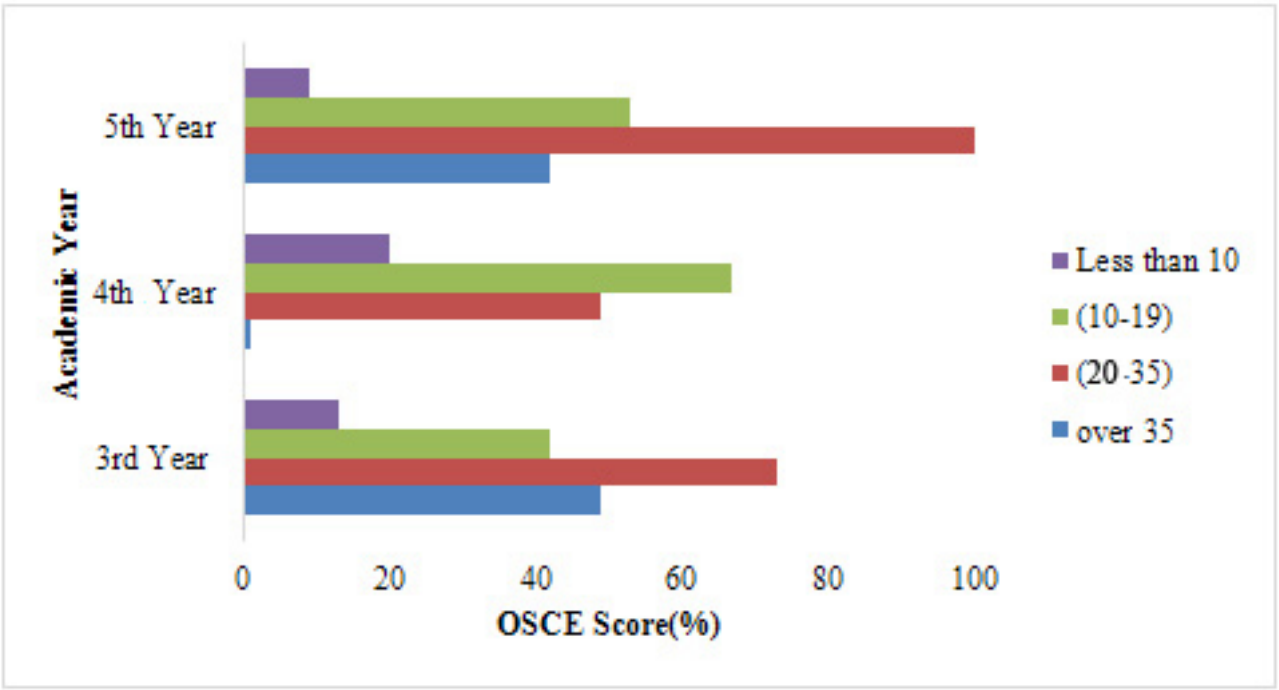

Table 5: Pearson's Correlation Analysis

Coefficient	T Statistic	P-Value
-0.4597	11.7579	<0.0001

Correlation Coefficient: r^2 = 0.21

Discussion

Our study found multiple aspects interplay in stress of examination on student's performance. This study conducted on three levels of undergraduate students of Taif University-KSA showed that all the students, irrespective of their level of study, faced anxiety when taking examinations. Though varying levels were observed and also the level of anxiety also differed, every level of studentship was facing stress. This finding is in line with many of the studies from around the world. The reason being the students perceive examination as a source of anxiety (28). Studies from around the world and from across all disciplines explained this phenomenon (29,30).

To have a deeper understanding the study looked into the differences of anxiety level among various parameters like level of study, across gender and direct impact on academic performances. When observing the anxiety levels across genders we found that the medical college female students were more commonly stressed before and during examination when tested on the scale. This difference is observed in other studies also (30). The reason for this is females are emotionally more vulnerable to fall prey to anxiety than their male counterparts (31,32). This explains careful and planned interventions for mitigating the stress must focus on females particularly.

The pattern of distribution of stress when observed across the level of study showed that its effects were marked in juniors i.e. the 3rd year students were more severely affected by stress. The reason may be that seniors are more tuned in to type of assessment i-e OSCE examination and its pattern. Their previous exposures in previous levels have oriented them and hence their severity was not as extreme as the juniors. The fact is supported by a study on medical students (33) where they were asked about management of test anxiety, where students described that after experiencing the anxiety they devise their own strategies for coping with it hence proving that previous exposures may lead to lower levels of anxiety as evident in our study. This explains that strategies to mitigate this stress must focus on earlier level students and freshmen.

This study also explored the direct effect of test anxiety on academic performance of students and not surprisingly supported the hypothesis that anxiety has a significant and profound negative impact on student's performance. The overthinking, negative emotions and depression associated with test anxiety lead to an overall decreased academic performance and limits students' critical thinking ability especially in those who are severely affected. The literature also supports this observation where a study from Iran described the role of motivation and positive emotions on academic performance (34).

Conclusion and Recommendations

• We conclude that test anxiety is experienced by a large number of undergraduate medical students of Taif Medical University.
• We also conclude that anxiety has a negative effect on overall academic performance of medical students.
• The female students were also more affected as compared to their male counterparts.
• Stress was predominantly more apparent in the third year students. They experienced moderate to high level of stress.
The alarming levels of TA prevalent in students of all levels of medical studentship are worrisome. The contributing factors other than reported in our study must be carefully determined. Targeted mitigation strategies must be implemented by the university to help students overcome their TA and demonstrate their true achievement.

Limitations:
• The study only analyzed the relationship between TA and students' academic performance i.e. apparent competencies as opposed to an insight built.
• Impact of individual's anxiety measurements and other instructive develop were also not measured.

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Clinical Efficacy and Cholesterol-Lowering Effects of Inclisiran

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Abstract

Inclisiran, a drug developed by Novartis, is a recent medication designed to alleviate cardiovascular disease symptoms through improving low-density lipoprotein cholesterol levels. Mechanistically, inclisiran is a chemically synthesized small interfering RNA (siRNA) molecule targeting serine protease proprotein convertase subtilisin-kexin type 9 (PCSK9), resulting in degradation of the LDL receptor. Positive, large-scale clinical trials on the use of inclisiran demonstrate the drug's efficacy in reducing LDL cholesterol levels in patients afflicted with cardiovascular disease. Moreover, Novartis and the National Health Services (NHS) of the UK have very recently come to an agreement (September 1st, 2021) on the drug's utility, as the NHS has enabled inclisiran's use in more than 300,000 patients with a history of cardiovascular disease. However, despite the promising clinical trials on inclisiran as well as its use in the UK, the U.S. Food and Drug Administration (FDA) has yet to approve the drug as a treatment strategy for cardiovascular disease. This review will analyze and discuss the clinical efficacy of inclisiran based on the recent clinical evidence for its pharmacological use in the treatment of cardiovascular diseases.

Key words: Inclisiran, efficacy, cholesterol-lowering

Introduction

For many years, cardiovascular disease (CVD) has been one of the leading causes of death globally, and in 2017 alone it accounted for 17.8 million deaths across the world (1). A significant risk factor for the development of CVD is hyperlipidemia or hypercholesterolemia, which is typically defined as an elevation in total fasting cholesterol levels (and possibly elevated triglycerides as well) (2). Importantly, lipids are insoluble in plasma and are instead transported via substances known as lipoproteins, which can then be measured to determine an individual's lipid status. Low density lipoprotein (LDL-C) is frequently measured, with values between 130-159mg/dL suggesting hyperlipidemia and values above 190mg/dL considered severely high and treatment (in the form of statins, lifestyle changes, etc.) is necessary (3). Thus, modifying cholesterol uptake or metabolism throughout the body may be one mechanism to improve hyperlipidemia and reduce the incidence of CVD.

Interestingly, a new class of drugs known as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have recently been developed to achieve this goal. Research in the early 2000's showed that mutations in the PCSK9 gene resulted in autosomal dominant hypercholesterolemia, and subsequent work demonstrated the protein is involved in the regulation and catabolism of the LDL-receptor (4,5). Specifically, PCSK9 degrades LDL-receptors resulting in diminished LDL-receptor recycling and LDL uptake. Due to this activity, pharmacological inhibition of PCSK9 has been proposed as a possible method to improve hyperlipidemia by preventing catabolism of the LDL-receptor and increasing cholesterol uptake. Recent clinical trials have illustrated PCSK9 inhibitors are successful in reducing LDL-cholesterol levels by as much as 60% and can significantly decrease the risk of developing adverse CVD events. One of these pharmacological agents is inclisiran, a long-acting, chemically synthesized siRNA covalently linked to a ligand with three N-acetylgalactosamine (GalNAc) residues. These residues bind directly to asialoglycoprotein receptors on hepatocytes, leading to inclisiran uptake (6). Importantly, hepatocyte-specific uptake of inclisiran has been reported in multiple studies, indicating the high specificity and efficacy of the drug (7,8). Once inclisiran enters the hepatocyte, the drug has specific cleavage activity of the PCSK9 mRNA, decreasing PCSK9 protein and, ultimately, preventing LDL-receptor breakdown. This review will discuss the recent clinical and scientific evidence (namely, the recent ORION trials) for inclisiran in the treatment of hyperlipidemia and CVD.

Inclisiran in the Clinic

The first clinical investigation to assess inclisiran's effect on LDL cholesterol was funded by Alnylam Pharmaceuticals in 2014, and was also the first study to successfully show that an siRNA drug can be used to clinically validate an endpoint (9). The study was a randomized, single-blind, placebo-controlled phase I dose-escalation study on 32 healthy adults with normal serum LDL cholesterol level. 24 of the 32 participants were randomly selected to receive a single inclisiran dose (0.015mg/kg, 0.045mg/kg, 0.090mg/kg, 0.150mg/kg, 0.250mg/kg, 0.400mg/kg) and eight were given the placebo. Reports of adverse side effects were similar between the inclisiran-treated and placebo-treated groups (9). The most commonly stated side effects of the treatment and placebo groups was the presence of rashes around the injection site, and this adverse effect was particularly prevalent in the 0.400mg/kg, high-dose inclisiran group, although the data was insignificant. The researchers also discovered just a single-dose of inclisiran rapidly decreases PCSK9 protein in a dose-dependent manner, as plasma PCSK9 protein levels were reduced by 70% in the individuals given the 0.400mg/kg dose. This reduction in PCSK9 was accompanied by a 40% reduction in LDL-cholesterol from baseline values relative to placebo-treated control individuals as well, indicating the drug was not only effective at reducing PCSK9 protein, but that it has cholesterol-lowering capabilities as well. Overall, this was the first clinical investigation to show inclisiran displays a potent inhibitory effect on PCSK9 that can improve LDL-cholesterol levels, and provided a basis for further, more large-scale studies.

The ORION program consists of a sequence of clinical investigations aimed at testing the safety and efficacy of inclisiran use in hyperlipidemic or individuals with CVD. The ORION-2 investigation was a proof-of-concept study initially conducted to confirm the dose and regimen for subsequent phase-3 clinical trials using an open-label, single-arm treatment approach (10). All patients (n=5) of the study were previously diagnosed with homozygous familial hypercholesterolemia (HoFH), a genetic disorder characterized by elevated levels of LDL-cholesterol that typically results in premature atherosclerotic CVD, and the patients were also receiving statin or ezetimibe therapy as well. Patients were given a subcutaneous injection of inclisiran sodium (300mg) and monitored for 180 days. If PCSK9 levels were not suppressed by 70% or more, another dose was given either on day 90 or day 104. Interestingly, each participant receiving inclisiran experienced robust and long-term PCSK9 reductions. 3 of the patients showed a robust decline in their LDL-cholesterol levels as well, with levels declining as much as 37% from baseline at 180 days after treatment (10). One of the patients showed a notable reduction in PCSK9 protein but no reduction in LDL-cholesterol, but the authors reported this individual had a history of poor response to both of the currently marketed PCSK9-inhibiting monoclonal antibodies. The PCSK9 and LDL-cholesterol-lowering effects of inclisiran persisted at day 300 in 2 of the patients, indicating long-term efficacy after treatment with only 2 doses. One individual received only one inclisiran dose and PCSK9 levels remained suppressed for 300 days but LDL-cholesterol levels did not. Lastly, no adverse events or injection site reactions/rashes were reported by any of the study participants (10). This study, along with the aforementioned clinical trial funded by Alnylam Pharmaceuticals, provided the basis and framework for more thorough investigations which were conducted over the past couple of years.

The ORION-9, 10, and 11 clinical investigations are the 3 robust clinical trials analyzing the safety and efficacy of inclisiran for the treatment of **Homozygous familial hypercholesterolemia** (HoFH). Specifically, the ORION-9 study was a phase 3, double-blind trial on 480 adults with HoFH that were randomly assigned to either receive a subcutaneous injection of inclisiran sodium (300mg) or placebo on days 1, 90, 270, and 450 (11). The aim of the trial was to evaluate the effect of inclisiran treatment on LDL-cholesterol levels in HoFH-afflicted individuals. Median age of the patients was 56 years and 47% were male, and mean baseline levels of LDL-cholesterol amongst all participants was 153mg/dL. At day 510 of the study, LDL-cholesterol levels were measured and the inclisiran group showed a 39.7% reduction compared to an 8.2% increase in the placebo-treated individuals. Importantly, all genotypes of HoFH experienced robust reductions in LDL-cholesterol levels, and adverse events or serious side effects were similarly reported between both groups.
The ORION-10 trial was conducted in the United States on 1,561 adult participants with atherosclerotic CVD, elevated LDL-cholesterol levels (70mg/dL or higher), and who were receiving statin therapy (12). ORION-10 was a randomized, double-blind, placebo-controlled phase 3 clinical trial investigating the efficacy and safety of inclisiran use over an 18 month period. Overall, 781 patients with a mean age of ~65 years were treated with inclisiran and 780 were given the placebo, and 89.2% of these individuals were receiving high doses of statins. Mean LDL-cholesterol levels amongst all trial participants was 104.7 ± 38.3mg/dl (12). At day 510 of the study, the inclisiran-treated group demonstrated a robust 51.3% decline in LDL-cholesterol levels, compared to a 1.0% increase in the placebo-treated group, resulting in a 52.3% group difference. In terms of absolute change, inclisiran-treated participants experienced a 56.2mg/dL decline in LDL-cholesterol, while individuals given the placebo showed a modest 2.1mg/dL decline (12). This reduction in LDL-cholesterol at day 510 was concomitant with a 69.8% reduction in PCSK9 levels in the inclisiran group, compared to a 13.5% increase in the group given the placebo. Importantly, inclisiran-treated patients also displayed improvements in secondary end points at day 510 as well, including a reduction in total cholesterol, non-HDL cholesterol, and apolipoprotein B. Inclisiran-treated individuals also experienced a decrease in triglycerides and an increase in high-density lipoprotein (HDL) cholesterol (12). Concerning safety of inclisiran, 73.5% of individuals receiving the drug and 74.8% of participants given the placebo reported the presence of mild or moderate adverse events, the most common of which were similar between groups. Rash or injection-site specific side effects were more prevalent in the inclisiran group compared to those given the placebo. Finally, laboratory analysis of creatine kinase and C-reactive protein levels, liver and kidney function, and platelet counts were similar between groups.

In conjunction with the ORION-10 trials, the ORION-11 trial was a similarly run clinical trial conducted in Europe and South Africa comprised of adults with atherosclerosis CVD or atherosclerotic CVD-risk equivalent, such as type 2 diabetes, HoFH, or elevated risk of a CVD event over 10 years as determined by the Framingham Risk Score for CVD) (12). Eligibility for entry into the trial was similar to the ORION-10 trials except that patients with an elevated atherosclerotic CVD risk equivalent must have had LDL-cholesterol levels of 100mg/dL or higher, per the European Atherosclerosis Society (EAS) (12,13). Moreover, patients must have been receiving lipid-lowering therapies (statins, ezetimibe, etc.) for 30 days or more to be considered for entry into the study. The study design was similar to the ORION-10 trials as well – a total of 1,617 adult patients (mean age ~64.8) were randomized to inclisiran (284mg) or placebo treatments groups via subcutaneous injection, with injections taking place at days 1, 90, 270, and 450 (12). 810 participants were treated with inclisiran and 807 were given the placebo, and high-dose statin treatment was highly prevalent (94.7% of total study participants). After 510 days of treatment, the inclisiran-treated group showed a 45.8% decline in LDL-cholesterol concentration, compared to a 4.0% increase in participants given the placebo. The absolute change in LDL-cholesterol levels was a ~50.9mg/dL decline in the group given inclisiran, and a 1.0mg/dL increase in the placebo-treated group. Similar to the ORION-10 trial, the reduction in LDL-cholesterol in response to inclisiran treatment was accompanied by a 63.6% reduction in PCSK9 protein levels 510 days after the initial dose was given. Improvements in secondary end point factors were observed in the inclisiran-treated group as well (total cholesterol, apolipoprotein B, triglycerides, increased HDL-cholesterol, etc.). Adverse events and side effects of the ORION-11 trial were synonymous with ORION-10; no significant differences in severe or persistent side effects were identified between placebo and inclisiran-treated groups, but mild injection site-specific side effects were increased in the group treated with inclisiran (12). Together with the other ORION trials, the results of these studies indicate inclisiran is highly effective at reducing LDL-cholesterol levels in patients who are at risk of (or are already diagnosed with) CVD with minimal serious adverse complications.

Concluding remarks

Overall, the very recent inclisiran clinical trials provide promising evidence for its utility as a cholesterol-lowering pharmaceutical drug in patients with HoFH or atherosclerotic cardiovascular disease. Based on data from over 2,500 patients across 3 clinical trials (ORION 9, 10, 11), minimal adverse effects were observed, suggesting the drug's safety. However, it remains to be seen if inclisiran can improve CVD as a whole – including hypertension, coronary artery disease, or stroke, or if the drug can be used as an alternative to statins when patients do not respond well to them. Furthermore, due to 'unresolved facility inspection-related conditions,' reported in 2020, the FDA has not approved inclisiran for LDL-cholesterol lowering use, but Novartis has conveyed they are actively working to resolve this issue (14).

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Malignant Melanoma

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Abstract

A review of malignant melanima including epidemiology, risk factors, molecular and immune mechanisms, diagnosis, clinical manifestations, subtypes, dermatoscopy, histology, treatment, prognosis and prevention.

Key words: malignant melanoma

Introduction

Malignant melanoma (MM) is cancerous neoplasm of the melanocytes. It is the most aggressive type of skin cancer as it tends to metastasize early. Melanocytes reside in the basal layer of the epidermis in a ratio of 10-15 basal cells to 1 melanocyte. It can also present as non-cutaneous cancer as there are substantial numbers of melanocytes in the digestive, urogenital track and mucous glands.

Epidemiology

Melanoma is the 5th commonest cancer in the UK. It affects adults of any age but is extremely rare in children. The risk of developing malignant melanoma in the UK is 1 in 52 for men and 1 in 54 women (1).

Risk Factors

Excessive sun exposure in childhood and early adult life is the most dominant risk factor in most cases of MM. Other risks include those with skin type 1 (always burn and never tan), people with red or blonde hair, freckles, high numbers of naevi >50, and strong family history of melanoma.

Table 1: Risk Factors for Cutaneous Melanoma

High risk (>50-fold increase in risk)	Intermediate risk (~10-fold increase in risk)	Low risk (2- to 4-fold increase in risk)
Persistently changing mole Clinically atypical moles in patient with two family members with melanoma Adulthood (vs. childhood) >50 nevi ≥2 mm in diameter	Family history of melanoma Sporadic clinically atypical moles Congenital nevi (?) White ethnicity (vs. black or East Asian ethnicity) Personal history of prior melanoma	Immunosuppression Sun sensitivity or excess exposure to sun

Source: Adapted from AR Rhodes et al: JAMA 258:3146, 1987.

Molecular and immune mechanisms

The mitogen-activated protein kinase (MAPK) pathway (Ras, Raf, MEK and ERK) plays a pivotal role in regulating gene expression, cellular growth and survival (2). This regulatory apparatus is tweaked in nearly 80% of all cases of malignant melanoma which was found to be due to mutation in either NRAS or BRAF. BRAF mutation accounts for nearly 90% of these cases. The activating mutation is formed by the replacement of glutamic acid for valine at the amino acid in position 600 (V600E).

The PI3K-AKT pathway is another major regulator of cell survival, growth and apoptosis. A key inhibitor of this pathway is PTEN, and inactivation of the gene that encodes PTEN via mutations, deletions, or promoter methylation also occurs in cutaneous melanomas. Thus, there is increased activity of the PI3K-AKT signalling pathway.

Figure 1: RAS-RAF-MEK-ERK (MAPK) and PI3K-AKT signalling pathways.

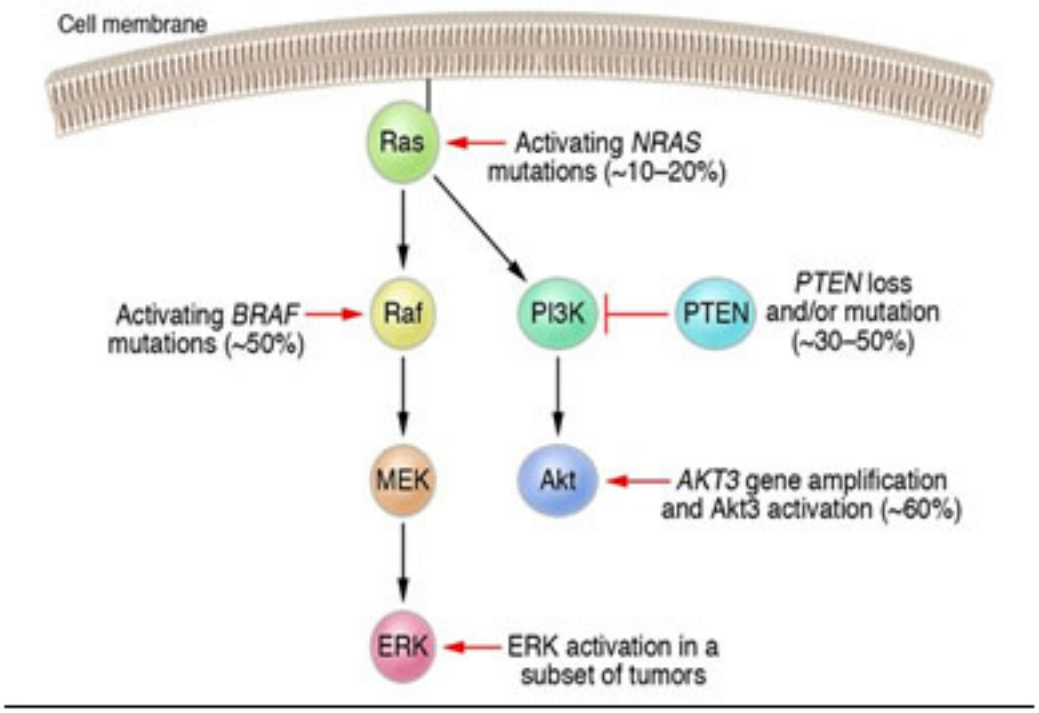
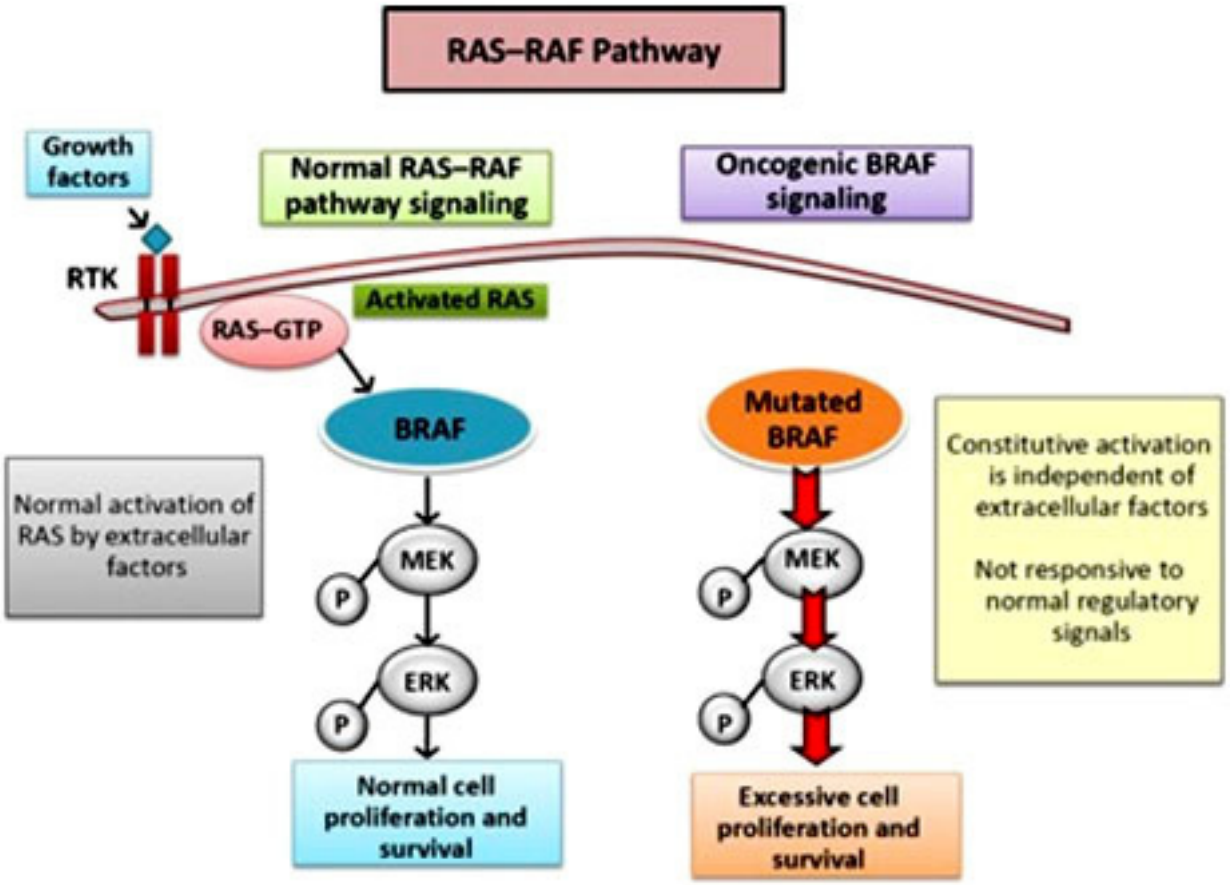


Figure 2: MAPK pathway is normally activated by growth factor binding to receptor tyrosine kinases which stimulate a cascade activation of the signalling molecules Ras, Raf, MEK and ERK. Activated ERK controls cellular proliferation.



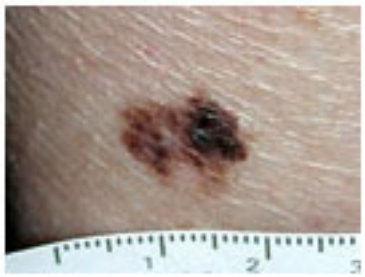
Diagnosis

A. Clinical presentation:
ABCDE is an easy reminder of the worrying changes to a pigmented lesion which should prompt a 2-week rule referral to dermatologist for biopsy and histological diagnosis. ABCDE rule is:

Asymmetry, Border irregularity, Colour irregular, Diameter >6 mm and Elevation / Enlargement of any mole over short period.

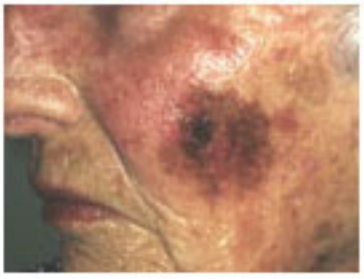
There are other symptoms as well which should raise the alarm regarding possible MM i.e. bleeding/oozing, pain, and inflammation.

B. Subtypes of cutaneous malignant melanoma:
1. Superficial spreading malignant melanoma: This is by far the commonest type of MM. It is more prevalent at sites of excessive sun exposure, i.e. on the trunk in males (40%) and the legs in females (also 40%).



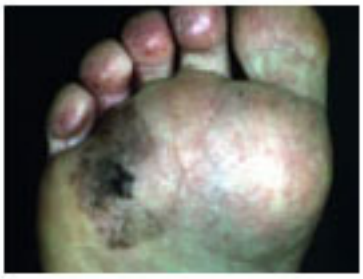
Picture 1: Typical SSMM

2. Lentigo maligna melanoma: This arises from lentigo maligna (areas of malignant transformation of melanocytes on sun damaged sites) which is still confined to the epidermis and defined as melanoma in situ. When it invades the dermis, it is call lentigo maligna melanoma.



Picture 2: Lentigo maligna melanoma

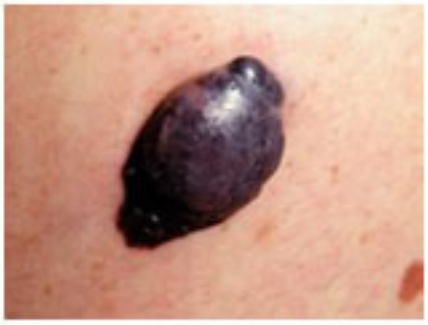
3: Acral lentiginous melanoma: This affects the palm, sole and subungual areas.



Picture 3: Acral lentiginous melanoma

4. Nodular melanoma

This type presents clinically as a rapidly **growing nodule over weeks to few months. It has the potential of early invasion and is capable of early metastasis.**



Picture 4: Nodular melanoma

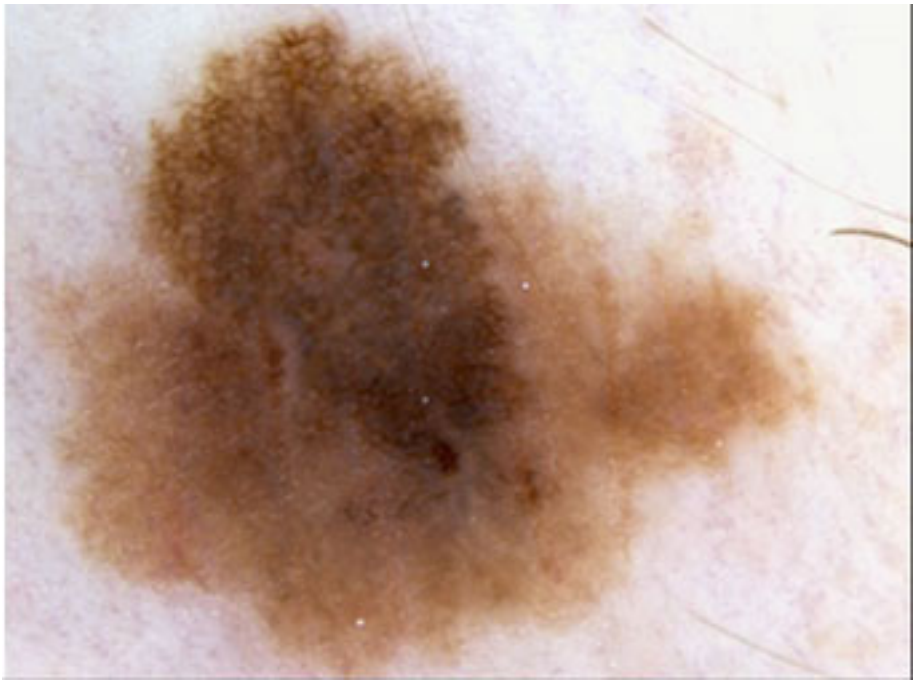
5. Amelanotic melanoma

The lesions in this type of MM have no colour and lack the typical changes in pigmentation. It is often diagnosed histologically on excisional biopsy of rapidly changing nodule or suspected BCC.

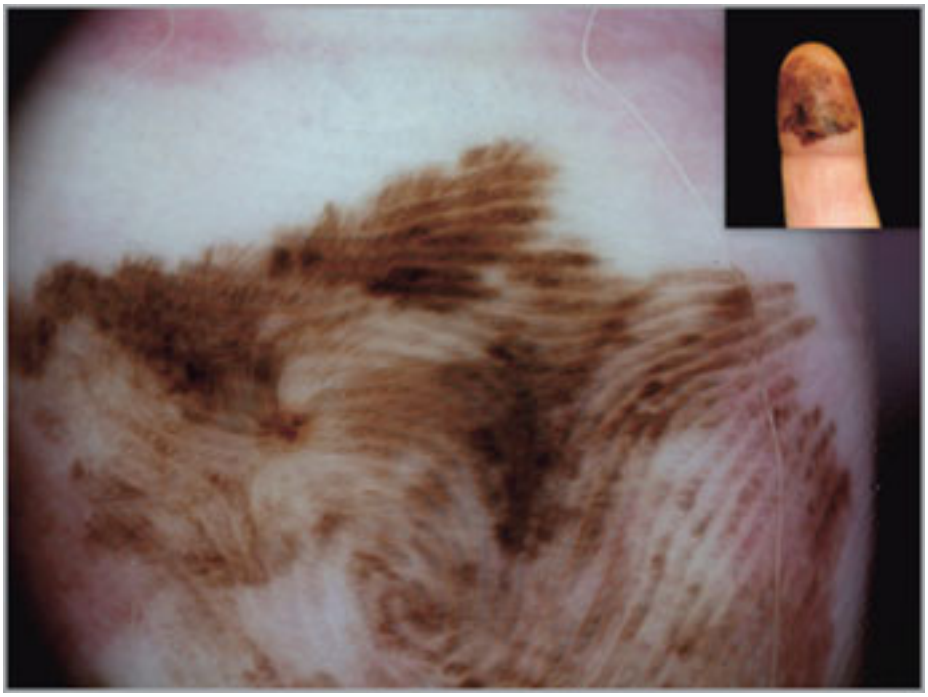
Subtype	Frequency	Common site	Key distinguishing features
Superficial spreading melanoma	70%	Trunk of men Legs of women	RGP, 1–5 years
Nodular melanoma	10–25%	Trunk of men Legs of women	RGP, 6–18 months
Acral lentiginous melanoma	5%	Palms, soles, nails	Not related to sun damage All races affected Accounts for 30–70% of melanoma in dark-skinned individuals
Lentigo maligna melanoma	<1%	Head and neck of elderly	Associated with chronic sun exposure RGP, 3–15 years
Noncutaneous melanoma	5%	Ocular, mucosal	Not associated with sun exposure Prognostic features and treatment differ from that of cutaneous subtypes

C. Dematoscopy:
This can provide quick information to differentiate common benign pigmented lesions from those which display features of MM. The following table shows some of these sinister features:

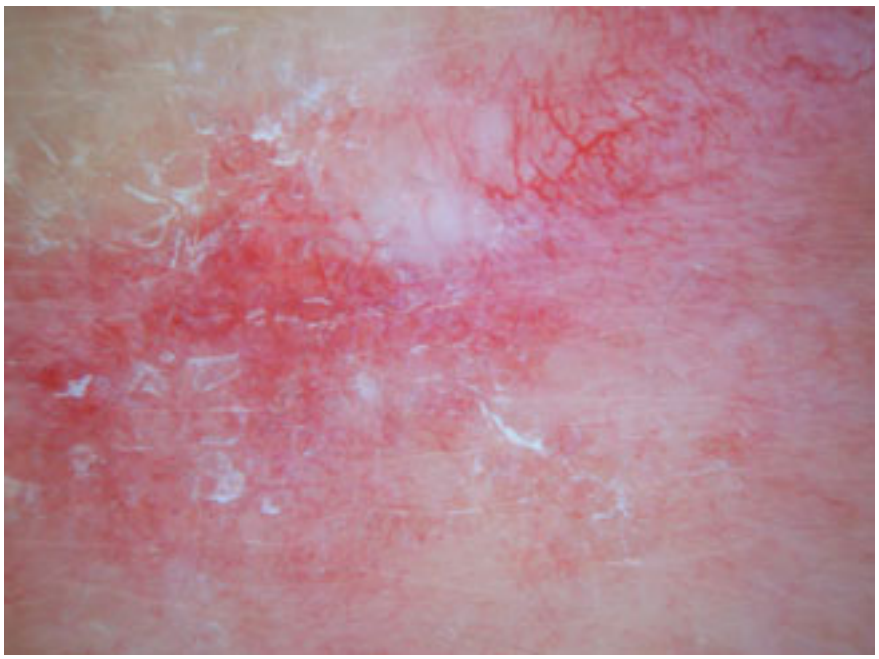
Table 2: shows dermatoscopic findings in each type of malignant melanoma. Source: www.dermnetnz.org/



Superficial melanomas and lentigo maligna melanoma
• Blue-white veil
• Radial streaming
• Scar-like depigmentation
• Peripheral black dots/globules
• Different colours
• Broad and irregular network
• Focal sharply cut-off border



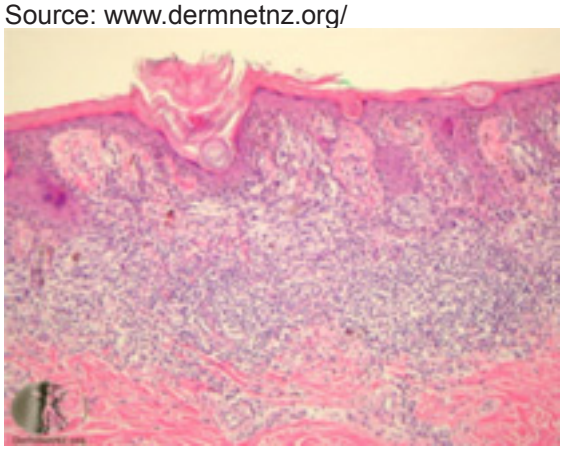
Acral melanoma
• Different colours.
• Irregular borders
• Asymmetry
• Pigmentation involving the ridges rather than the benign parallel furrow pattern.
• Destruction of sweat ducts which normally appear as white dots on the ridges (acrosyringia)



Amelanotic melanoma
This can be very tricky to diagnose by dermoscopy. Abnormal vascularity may raise the suspicion, with linear, dotted, corkscrew or polymorphous vessels. Pressing hard on the dermatoscopy may obscure the vascular pattern.

D. Histology:
The classical histological features of melanomas include destruction of the epidermis, upward spread of melanocytes, nests of atypical melanocytes with variable morphology (which may lack maturation), melanocytic invasion of lymphovascular spaces, increased apoptosis and atypical mitoses. These changes lead to architectural disturbance to the skin (3).

Figure 3: Shows the typical histological features of melanoma as described above.
Source: www.dermnetnz.org/



6. Metastasis:
Melanoma can spread via lymphatic channels or blood stream. Regional lymph nodes are a common site to find the earliest metastases hence lymphadenectomy is thought to control the disease. Haematogenous spreading usually affects the Liver, lung, bone, and brain.

7. Staging:
The following table (3) summarises the AJCC Cancer Staging Manual, 7th Edition 2010

ANATOMIC STAGE/PROGNOSTIC GROUPS							
Clinical Staging[3]				Pathologic Staging[4]			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥ N1	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

Table 3: AJCC TNM staging system 7th edition (2010): TNM categories.

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis < 1/mm^2 b: With ulceration or mitoses ≥ 1/mm^2
T2	1.01-2.00	a: Without ulceration b: With ulceration
T3	2.01-4.00	a: Without ulceration b: With ulceration
T4	> 4.00	a: Without ulceration b: With ulceration
N	**No. of Metastatic Nodes**	**Nodal Metastatic Burden**
N0	0	NA
N1	1	a: Micrometastasis* b: Macrometastasis†
N2	2-3	a: Micrometastasis* b: Macrometastasis† c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M	**Site**	**Serum LDH**
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Abbreviations: NA, not applicable; LDH, lactate dehydrogenase.
*Micrometastases are diagnosed after sentinel lymph node biopsy.
†Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

Source; Melanoma Molecular Map Project website.

8. Treatment

A. SURGICAL MANAGEMENT:

Excision: Once malignant melanoma has been confirmed by initial excision, a wide local excision should be performed to remove all cancerous cells to minimise the risk of local recurrence. Surgery can cure early disease which is still confined to the skin. The margin of this WLE will depend on Blow thickening. The current guideline from the British Association of Dermatologists recommend the following safe margin:

Melanoma in situ= 0.5 cm, <1 mm= 1cm, 1.1-2 mm= 1-2 cm, 2.1-4 mm= 2-3 cm, >4 mm= 3 cm.
This safe margin might be modified according the anatomical site of the lesion.

Sentinel lymph node biopsy:

This is considered to aid the staging of the disease.
It is indicated for patients with stage 1B–2C melanoma. It should be performed at the time of the WLE. It can helps predicting the prognosis, identify those who needs completion lymphadenectomy and those who might be eligible to participate in clinical trials of new treatments for melanoma. (4)

Completion lymphadenectomy:

This procedure should be considered when the histology result confirms the presence of cancerous cells in the sentinel lymph node (stage 3A melanoma). Although it reduces the risk of cancer recurrence in the same area, it has not shown any evidence of increasing the overall survival rate. (4)

Lymph node dissection

This is indicated for patients with stage IIIB–IIIC melanoma or nodal disease detected by imaging.

B. TREATMENT OF METASTATIC MALIGNANT MELANOMA

The aim of treatment in metastatic melanoma is to control the disease and prolong the survival rate.

• Chemotherapy and interleukin

• The main stream treatment for metastatic malignant melanoma was based on two agents (dacarbazine and interleukin-2) until recent years. No improvement was shown in the overall prognosis when using these agents (Tsao et al., 2004). Further studies have demonstrated a poor response rate from both agents (Dacarnazine - 15%-20%, interleukin 2 - 16%) (Middleton et al., 2000).

• Targeted therapies

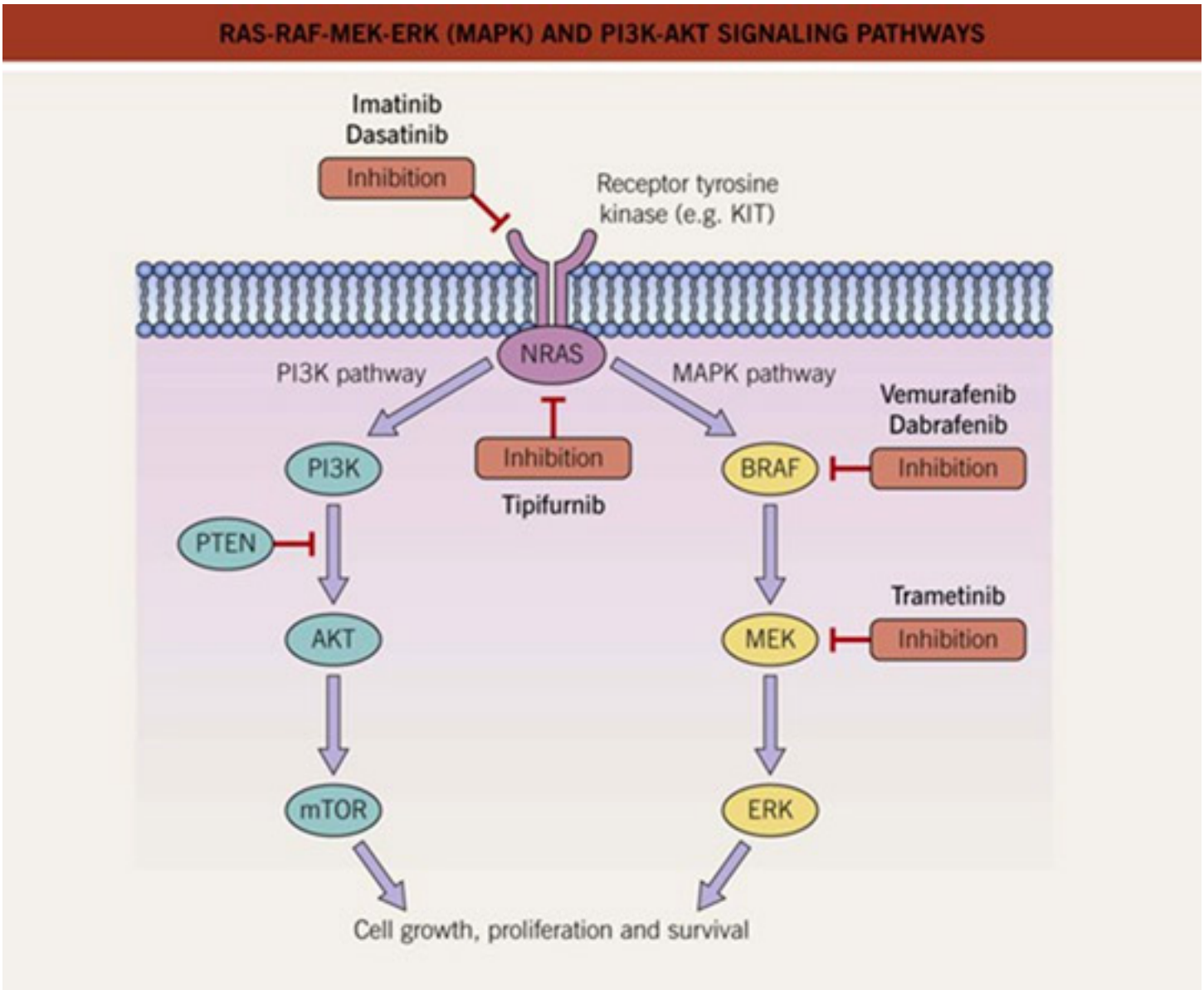
BRAF inhibitors (Vemurafenib and Dabrefenib): these drugs selectively inhibit mutant BRAF protein in patients with V600E mutation. Using BRAF inhibitors alone can result in resistance (5).

MEK inhibitors (Trametinib and cobimetinib): these drugs inhibit MEK, the MAPK node immediately downstream of RAF, which have shown to increase disease-free survival and reduce resistance rate when used in combination with BRAF inhibitors (5).

• Immunotherapy

• Tumour cells can escape the body's own immunity by expressing ligands to activate CTLA-4 and PD-1, inhibitory T-cell receptors, by that downregulating T-cell activity. To rectify this, therapeutic monoclonal antibodies (mAb) targeting these receptors have been researched and developed.

1. CTLA-4 inhibitors (ipilimumab and tremelimumab): these drugs help to overcome immune evasion by blocking tumour activation of CTLA-4, which acts as an inhibitory signal in CD4+ and CD8+ Tcells.
2. PD-1 inhibitors (nivolumab): Activation



Adapted from Eggermont AM, Robert C. Melanoma in 2011: A new paradigm tumor for drug development. Nat. Rev. Clin. Oncol. 2012;9:74–76.

9. Prognosis

This is based on the survival rate in 5 year after diagnosis
Stage 0 (Tumour in situ) this can be cured with surgical excision.
Stage 1: 90% survival rate.
Stage 2: 80%
Stage 3: 50%
Stage 4: 10% of men and around 25% of women will survive their cancer for 5 years or more after diagnosis.
These statistics are based on patients treated around 10 years ago. Currently, there are new biological treatments available for patients with stage 4 melanoma. Hence, the survival rate is likely to be better than the figures above (6).

10. Follow-up

Stage 0 (melanoma in situ / lentigo maligna) - no follow-up is needed
Stage 1A: Review every 3-4 months for one year and then discharge. As part of the follow up all patients will be advised about self-examination, sun protection and red flags.
Stage 1B – IIIA: Review every 3-4 months for the first three years then twice yearly for another two years. They might be discharged after 5 years if they remain disease free.
Stage IIIB and upwards: Review every 3-4 months for the first three years then twice yearly to five years then annually to ten years (6).

11. Psychosocial impact:
A diagnosis of melanoma can have variable psychosocial impact in different patients and caregivers alike. Holistic needs assessment HNA is used as a universal measure to assess all patients for a variety of physical, psychological, social, spiritual and information needs. This should be carried out and repeated throughout the patient's journey from the diagnosis, assessment, and treatment phases (7).

12. Prevention:
Sun protection, self-examination and improving melanoma awareness are the key factors to achieve a reduction of the rising MM trend globally.

Conclusion

Malignant melanoma is the most serious skin malignancy. Historically metastatic melanoma had a very poor prognosis but thanks to the advances in understanding the pathogenesis and immunological mechanisms, new and novel treatments have been introduced leading to a better outcome. This area is developing fast and hopes are rising regarding reducing morbidity and mortality associated with metastatic disease.

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Non-surgical options to treat androgenic alopecia

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Abstract

Androgenic alopecia (AGA) is the commonest cause of hair loss in men and women. It is attributed to genetic and hormonal factors. This paper aims to discuss three non-surgical options to assess their use and effectiveness in treating AGA. This will include the following treatments: Minoxidil, Finasteride and low-level laser therapy (LLLT).

Key words: Androgenic alopecia, Minoxidil, Finasteride, low-level laser therapy (LLLT

Introduction

Androgenic alopecia (AGA) is the commonest cause of hair loss in men and women [1]. It is attributed to genetic and hormonal factors. A major factor identified, so far, is the effect of Dihydrotestosterone (DHT) on the scalp hair follicles. DHT is formed by the conversion of Testosterone to DHT when it is activated by the enzyme 5-α reductase which is found in type 2 receptors on the scalp hair follicles. The result of this activation is miniaturization (thinning) and shortening of the growth phase (anagen) in the hair cycle [1].

This paper aims to discuss three non-surgical options to assess their use and effectiveness in treating AGA. This will include the following treatments: Minoxidil, Finasteride and low-level laser therapy (LLLT).

Formulation of the three-part BET question:
[Non-surgical treatment] is [Effective and safe] at [treating androgenic alopecia]

- Patient group: Patients with androgenic alopecia
- Defined question: can non-surgical, minoxidil, finasteride and LLLT treat androgenic alopecia
- Relevant outcome: improve androgenic alopecia (AGA)

Clinical scenario: A patient with androgenic alopecia presented to the clinic. He/she wanted to discuss the available non-surgical options to treat his/her AGA as he/she has needles phobia and is not keen on surgery or injections.

Search strategy:
Medline search using PubMed (restricted to publications from 2005-2020). Also, a manual search in Google scholar was conducted.

Search outcome:
Initial PubMed search resulted in 26 publications; among these, three papers were found to be relevant to this topic. Three more papers were manually searched in Google scholar (Olsen et al., Kaufman et al. and Lee et al).

Relevant papers: Low-level laser table

Author, date & country	Patient Group	Study type (level of evidence)	Outcomes	Key Results	Study weaknesses
A.K Gupta et al. Efficacy of non-surgical treatments for androgenetic alopecia: a systematic review and network meta-analysis 2018 Canada	15,888 participants (88% males), average age 36.0 ± 7.3	1a Systematic review	LLLT is superior to placebo in treating AGA	5 RTCs showed that LLLT has the highest effect in increasing average hair count compared to placebo among all non-surgical options. (the difference in hair count = 66.70)	All 5 trials were funded by the device manufacturer or they had an affiliation to the authors.
Evan Darwin et al. Low-level laser therapy for the treatment of androgenic alopecia: a review 2017 USA	13 RCTs	1a systematic review	LLLT is safe and effective in treating AGA. LLLT can be used alone or in combination with finasteride 1mg or topical minoxidil 5%. Overall LLLT is safe, however, in 5 trials AEs were reported i.e., urticaria, skin dryness, acne, headache and mild burning sensation.	10 RCTs showed a significant statistical increase in hair count (20 hair/cm2), this is higher than the growth rate seen in both finasteride 1mg and Minoxidil 5% (13.5 and 12.3 hair/cm2 alternatively)	Early RCTs were small and lacked control, more recent RCTs were better designed.

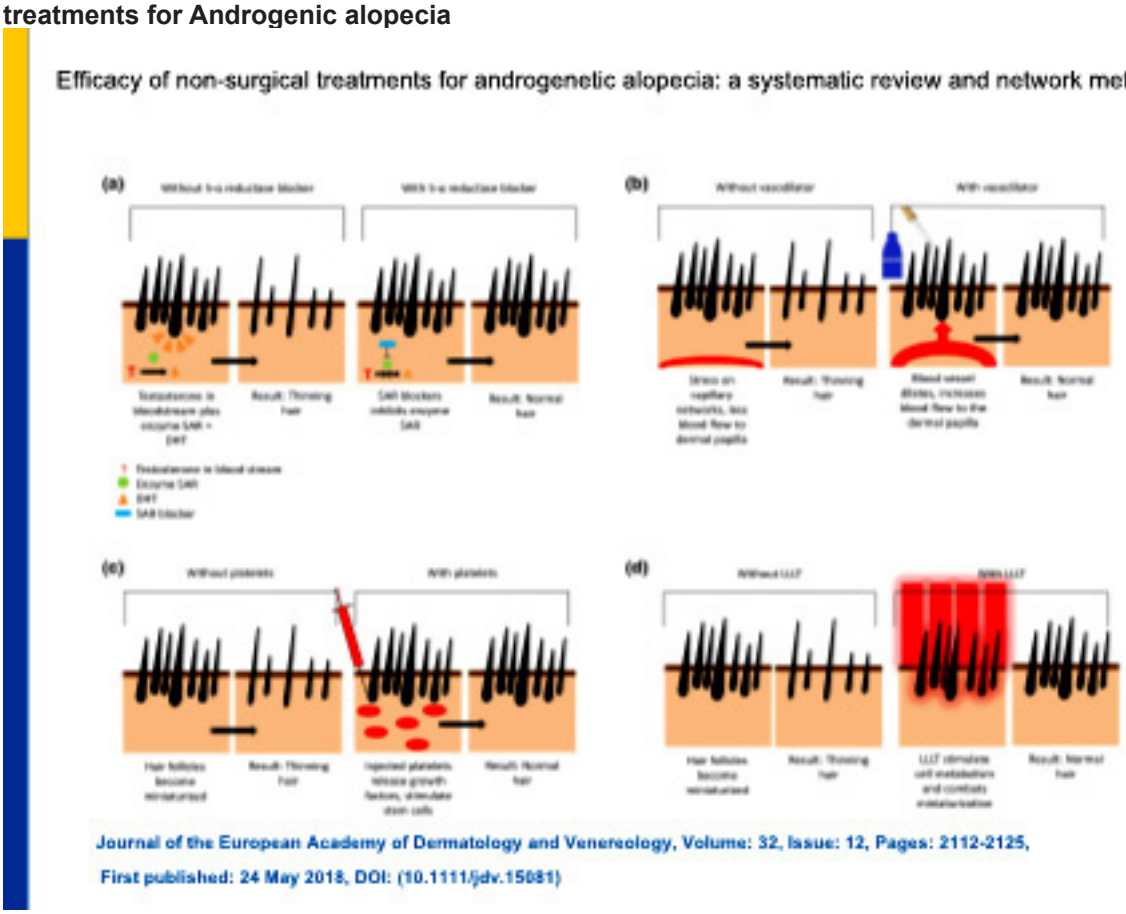
Relevant papers: Minoxidil table

Author, date & country	Patient Group	Study type (level of evidence)	Outcomes	Key Results	Study weaknesses
A.K Gupta et al. Efficacy of non-surgical treatments for androgenetic alopecia: a systematic review and network meta-analysis 2018 Canada	15,888 participants (88% males), average age 36.0 ± 7.3	1a Systematic review	Topical Minoxidil5% and 2% were both superior to placebo in treating AGA	Minoxidil5% showed a higher average hair count when compared to Minoxidil2% (4.69 [1.35, 8.04]), however, it carries the greatest risk of adverse events (n=45)	
Olsen et al. A multicentre, randomized, placebo-controlled, double-blind clinical trial of a novel formulation of 5% minoxidil topical foam versus placebo in the treatment of androgenetic alopecia in men 2007 USA	352 men, age (average age 39 years old), 86% Caucasians(172 on placebo arm and 180 on 5% Minoxidil foam)	1c RCT	At 16 weeks there was a statistically significant rise in hair count with minoxidil 5% foam compared to placebo (hair count 20.9 vs 4.7 respectively) (p<0.001	Subjectively participants reported a 70.6% improvement in hair growth compared to 42.4% in the placebo arm. Overall, there were less Adverse Events AEs seen in comparison to minoxidil solution (less than 1%) including irritation, headache, acne	Short duration for the study, only involved male patients and there was no data collection beyond 16 weeks. Some authors received funding or were employed by Pfizer.
Zhou et al. The effectiveness of combination therapies for androgenetic alopecia: A systematic review and meta-analysis 2020 China	1172 participants	1a Meta-analysis and systematic review of 15 RCTs	The combined therapy of topical minoxidil 5% with finasteride or LLLT is more effective than monotherapy. There was not an increase in adverse effects compared to monotherapy.	Statistically significant increase in hair count with combined treatment for AGA compared to monotherapy. (p <0.05)	

Relevant papers: Finasteride table

Author, date & country	Patient Group	Study type (level of evidence)	Outcomes	Key Results	Study weaknesses
A.K Gupta et al. Efficacy of non-surgical treatments for androgenetic alopecia: a systematic review and network meta-analysis 2018 Canada	15,888 participants (88% males), average age 36.0 ± 7.3	1a Systematic review	Finasteride 1mg (male) is superior to placebo in treating AGA	5 RCTs showed an increase in average hair count of 17.37 compared to the placebo	
Kaufman et al. Long-term treatment with finasteride 1 mg decreases the likelihood of developing further visible hair loss in men with androgenetic alopecia (male pattern hair loss) 2008 USA	1553 participants	1a systematic review of 2 phase 3 trials of men with AGA who received finasteride 1mg vs placebo for up to 5 years.	There is significant statistical evidence that supports the continued use of finasteride 1mg to maintain improvement in hair count and coverage ($p<0.001$)	93% of patients who received finasteride 1mg for 5 years reported no further hair loss compared to placebo ($p<0.001$)	Only included male patients.
Lee et al. Adverse Sexual Effects of Treatment with Finasteride or Dutasteride for Male Androgenetic Alopecia: A Systematic Review and Meta-analysis. 2019	4,495 male participants	1a systematic review of 15 RCTs	In general, 5α-reductase inhibitors increase the risk of sexual dysfunction by 1.57-fold (95% CI) 1.19–2.08).	Finasteride carries a higher relative risk of sexual dysfunction when compared to Dutasteride (1.66 and 1.37 respectively)	Regarding Dutasteride, only 5 papers were meta-analysed as it a newer intervention, hence not many adverse effects were recorded compared to finasteride

Figure 1: summarises the current hypotheses regarding the mechanism of action of different non-surgical treatments for Androgenic alopecia



Comments

This paper looked into the three FDA approved AGA treatments so far;

1. Low-level laser therapy LLLT: These devices emit red light (650–900 nm and 5 mW), which stimulates keratinocytes and fibroblasts mitosis, increases cellular metabolism, reduces nitric oxide level and inhibits inflammation in the scalp [1].

In terms of its efficacy, LLLT was approved by FDA in 2011 and it is ranked as the most effective treatment out of all non-surgical options. Clinically LLLT results in improving hair thickness and hair count by 20 hair/cm2. There were no adverse events reported by patients [1].

Different devices are FDA approved and available commercially i.e HairMax Lasercomb®, TOPHAT 655®, and the Capillus® laser caps. These devices can either be used in clinics or patients can buy them individually. Duration for use depends on the device but roughly patients have to use it for < than 30 minutes up to 3 times a week and can be used in combination of both minoxidil 5% and finasteride for an even better result [3].

2. Minoxidil: Topical minoxidil has been used in improving AGA since the 1980s and it was the first AGA treatment to get FDA approval in 1988. Although the exact mechanism is not known, it is believed that topical minoxidil promotes hair growth by improving blood supply to the hair follicles, by shortening the telogen phase and prolonging the anagen phase in the hair growth cycle [1].

In terms of efficacy minoxidil, 5% has a similar profile to Finasteride 1mg and is more effective than Minoxidil 2%. Regarding, adverse events, minoxidil 5% carries the highest risk of SE among the three FDA approved options (n=45), these AEs include dryness, irritation, acne and headache [1].

It can be used by both genders daily for up to 6 months before expecting enough improvement. Improvement reported in patients with Norwood grade 5 AGA. Commercially it is available in solution or foam forms (foam is a newer version and reported to cause fewer side effects and improved compliance in patients as it gets absorbed more quickly through the skin) [3].

The combined therapy of topical minoxidil 5% with finasteride or LLLT is safe and more effective in treating AGA than monotherapy [4].

3. 5 alfa reductase inhibitors (5-ARIs): Oral Finasteride 1 mg (Propecia) was approved by the FDA in 1997. Currently, both Finasteride 1mg and Dutasteride 0.5mg tablets (unlicensed) for up to 48 to 52 weeks are used to treat male pattern AGA. These oral medications prevent the conversion of testosterone to its active form Dihydrotestosterone (DHT), which lead to a significant drop in the scalp and serum DHT levels by 60-70% [1].

A large meta-analysis (Gupta et al.) showed a statistically significant increase in hair count in men who were treated by both Finasteride 1mg and Dutasteride compared to placebo, giving a clear indication of their efficacy in treating AGA.

Finasteride can be used safely in combination with LLLT or Minoxidil which enhances its effect and produces an even better result than monotherapy [4].

Due to its potential adverse effects on the foetus as well as endometrial and menstrual side effects, Finasteride was not licenced by the FDA for female pattern AGA. Adverse effects in men were less common than with Minoxidil but they were more significant and has a greater impact on patients. These included sexual dysfunction including erectile dysfunction, reduced libido and ejaculatory dysfunction [1].

Current data from Lee et al. estimates the overall risk of 5-ARIs in causing sexual dysfunction at 1.57 folds. Finasteride carries a slightly higher risk than Dutasteride (1.66 vs 1.37 respectively). Data regarding Dutasteride are less consistent due to the lack of enough studies into its use in AGA so far. This might change with more research and studies [5].

Clinical bottom line and Conclusion

LLLT, finasteride 1mg and Minoxidil 5% are all FDA approved for the treatment of AGA. LLLT has produced the best results when used to treat AGA so far and had no reported adverse effects. Minoxidil 5% and Finasteride have similar efficacy but varies in terms of adverse effects. Minoxidil associate with a higher risk of adverse effects which are mainly dermatological, while Finasteride's main adverse effects were sexual dysfunction which can be very frightening to young men who are suffering from AGA. Thorough counselling, good patient selection and tailored treatment are paramount when offering hair loss treatment. Combined treatment is safe and offers a better result than monotherapy.

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