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Dementia Special Series

Review

Editorial

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The present collection of manuscripts reflects the breadth and depth of current clinical and public health research emerging from the Middle East, with a particular focus on Saudi Arabia. Each contribution offers unique insights into priority health issues, combining rigorous methodological approaches with an emphasis on practical implications for patient care and policy.

Attention Deficit Hyperactivity Disorder (ADHD) remains a significant concern in pediatric populations worldwide, and the study by AlGhassab et al. sheds light on the knowledge, attitudes, and practices of primary healthcare physicians in Tabuk City. Despite generally good awareness of ADHD, the findings underscore persistent misconceptions and limited direct management experience, highlighting the urgent need for enhanced training and clearer guidelines to empower primary care providers in early identification and referral.

In the realm of dementia, Abyad's comprehensive clinical review offers an invaluable synthesis of current knowledge on dementia subtypes, diagnostics, and treatment options. As the Middle East witnesses rapid population aging, such updated overviews are crucial for guiding clinicians and policymakers in building responsive care systems and advancing research in neurodegenerative

Preventive health remains a recurring theme across the collection. The cross-sectional study on herpes zoster vaccination uptake among older adults in Tabuk emphasizes both promising levels of general awareness and persistent barriers such as fear of side effects and perceived low personal risk. This research underscores the importance of physician recommendations and targeted public health messaging to improve immunization rates in vulnerable populations.

The intersection of autoimmunity and chronic disease is exemplified in the retrospective study of celiac disease prevalence among patients with type 1 diabetes mellitus. Despite a modest prevalence (2.4%), the study identifies underweight status as a potential clinical marker warranting proactive screening, reinforcing recommendations for integrated care models in endocrinology and gastroenterology.

Public health nutrition also features prominently, with Dr. Ebtisam Elghblawi's paper on the global obesity epidemicpresenting a compelling call to action. The review eloquently outlines the systemic and environmental drivers of "globesity," reminding readers that obesity is not simply a matter of individual choice but a reflection of pervasive societal and commercial pressures.

The collection further includes a thought-provoking hypothesis paper by Helvaci et al. suggesting that chronic idiopathic thrombocytopenic purpura—a condition traditionally regarded as deleterious—might paradoxically confer survival benefits by modulating platelet-driven atherosclerosis. While preliminary, this perspective contributes to the broader discourse on the complex interplay between hemostasis and vascular disease.

Finally, the cross-sectional study on sleep disorders among primary healthcare physicians provides timely insights into occupational health. Alarmingly high rates of poor sleep hygiene and daytime sleepiness were observed, strongly associated with modifiable factors such as long working hours, night shifts, and inadequate rest. These findings carry clear implications for healthcare system reform and physician well-being initiatives.

Collectively, these manuscripts illustrate a shared commitment to advancing evidence-based practice across disciplines and addressing both emerging and longstanding health challenges in the region. Whether exploring neurodevelopmental disorders, chronic disease comorbidities, vaccine hesitancy, or clinician burnout, the studies underscore the importance of context-specific data to inform local policy and improve patient outcomes.

I commend the authors for their rigorous scholarship and their contributions to enhancing our understanding of health and disease in the Middle East. This body of work offers valuable guidance for clinicians, researchers, and public health professionals committed to improving care delivery in complex and evolving healthcare landscapes.

Warm regards,
Dr. Abdulrazak Abyad
Editor-in-Chief
Middle East Journal of Family Medicine

In Memoriam


A photo of Dr. Marwan Sultan and Dr. Adnan Al-Bursh. Marwan was the director of the Indonesian Hospital and Adnan was the head of the Orthopedic department at Al- Shifa hospital. Both were brutally murdered by the occupation.

Assessment of Knowledge, Attitude and Performance of Primary Healthcare Physicians in Tabuk City, Saudi Arabia regarding Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents

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Abstract

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental disorder that affects children and adolescents, often persisting into adulthood. Primary healthcare (PHC) physicians play a crucial role in the early identification, referral, and management of ADHD, yet their knowledge, attitudes, and clinical practices may vary.

Aim: To assess the knowledge, attitudes, and performance of primary healthcare physicians in Tabuk City, Saudi Arabia, regarding ADHD in children and adolescents.

Methods: A cross-sectional study was conducted among 181 PHC physicians in Tabuk City from April to September 2024. Data were collected using a structured, self-administered questionnaire distributed via interviews and online forms. The questionnaire included sections on sociodemographic characteristics, knowledge (12 items), attitudes, and clinical practices related to ADHD. A pilot study confirmed the reliability of the questionnaire (Cronbach's alpha = 0.72).

Results: The majority of participants (82.3%) had good overall knowledge of ADHD. While most correctly identified core ADHD symptoms and its chronic nature, misconceptions persisted regarding gender differences and the need for private educational support. Attitudes were generally positive, with 80.1% supporting a role for PHC physicians in ADHD management, although 58.0% believed it is not their job. Only 33.7% reported diagnosing ADHD cases in the past year, and of those, 90.2% referred patients to specialists. Age and gender were significantly associated with knowledge levels ($p = 0.049$ and $p = 0.004$, respectively), whereas other factors showed no significant association.

Conclusion: PHC physicians in Tabuk show generally good knowledge and a positive attitude toward ADHD, yet gaps in practice and misconceptions remain. Strengthening ADHD-specific training and enhancing PHC involvement in early identification and management are recommended to improve care delivery for affected children and adolescents.

Keywords: ADHD, primary healthcare, knowledge, attitude, physicians, Tabuk, Saudi Arabia

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by hyperactivity, impulsivity, and inattention (1). It is one of the most common conditions affecting children worldwide (2), with prevalence rates varying based on location and diagnostic criteria, ranging from 1.7% to 6.7% (3). In Saudi Arabia, ADHD is particularly widespread among elementary school children, with higher rates in males (16.4%) compared to females (11.6%-13.5%) (4-8).

The condition originates from neurological dysfunction in the brain, though researchers continue to explore its physiological origins (1, 9). Genetic factors play a significant role, with a monozygotic twin concordance rate of 55%-90% (10-12). Children with ADHD parents face a 25% risk of inheriting the disorder, and males are at higher risk than females. Other contributing factors include prenatal and perinatal conditions (such as maternal stress, alcohol and tobacco use, low birth weight, and prematurity), lead exposure, and brain injuries (12, 13). Interestingly, higher parental education is associated with lower ADHD incidence (14).

Symptoms usually become evident in early childhood, particularly between ages 6 and 12, when school demands make them more noticeable (15, 16). The DSM-5 criteria remain the standard for diagnosis, classifying ADHD into four types: combined presentation, hyperactive-impulsive presentation (ADHD/HI), inattentive presentation (ADHD/I), and other specified or unspecified ADHD (17). While neuropsychological testing exists, it does not significantly enhance diagnostic accuracy.

ADHD affects daily functioning, increasing the risk of academic and professional struggles, car accidents, substance abuse, social difficulties, and legal issues (18-21). Although no cure has been reported, it can be managed through medication and behavioral therapy (22). Authoritative reports suggest stimulant medications like methylphenidate (Ritalin, Equasym) and dexamphetamine (Dexedrine) as primary treatments (23, 24).

Primary healthcare physicians play a crucial role in ADHD management but often struggle to recognize mental health conditions in children (25). Research suggests that only a third of children and adolescents with mental health issues receive specialized care (26). ADHD is one of the leading reasons for pediatric and adolescent psychiatry follow-ups (27). Compared to their peers, children with ADHD require significantly more medical visits, prescriptions, and mental health appointments, leading to more than double the yearly healthcare costs, which escalate when comorbid conditions are present (28-30).

Methodology

A cross-sectional study design was used to answer the research questions. The target population consisted of all primary healthcare physicians working in Tabuk City, with an estimated total of approximately 400 physicians. The study was conducted over a six-month period from April 1, 2024, to September 31, 2024. Data collection was carried out using a structured, self-administered questionnaire, made available in both online and interview formats to maximize response rates. The online version was distributed through WhatsApp groups via a Google Form, while additional data were gathered through face-to-face and telephone interviews. Participation was voluntary, and informed consent was obtained from all respondents. The inclusion criteria included all currently practicing primary healthcare physicians in Tabuk City. Physicians who were on leave or sabbatical during the study period or those who declined to participate were excluded. All available and accessible health care physicians were invited to participate in the study till no more new participants were included. The data collection tool was a structured questionnaire composed of three main sections. The first section captured sociodemographic and professional characteristics, including age, gender, and years of experience, nationality, and educational qualifications. The second section assessed knowledge of ADHD using 12 multiple-choice items. The third section evaluated the participants' attitudes and practices regarding the diagnosis and management of ADHD in children, including questions on their perceived roles, referral behaviors, and continuing medical education sources. Before the main data collection, a pilot study was conducted on 10 primary healthcare physicians to assess the clarity, validity, and reliability of the questionnaire. Feedback was used to refine the tool, and internal consistency was evaluated using Cronbach's alpha, which yielded a value of 0.72, indicating acceptable reliability.

Data Analysis

Data entry and statistical analysis were performed using the Statistical Package for the Social Sciences (SPSS) software, version 28 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the personal and professional characteristics of the primary healthcare physicians, as well as their knowledge, attitudes, and experience related to Attention-Deficit/Hyperactivity Disorder (ADHD). Frequencies and proportions were calculated for categorical variables. The overall knowledge score was computed by assigning one point for each correct answer to the knowledge-related items. The total score was then converted to a percentage. Physicians who scored more than 60% were classified as having good knowledge, whereas those with scores of 60% or below were categorized as having poor knowledge. To examine associations between physicians' knowledge levels and various sociodemographic and professional variables (e.g., age, gender, nationality, qualifications, years of experience, and sources of ADHD knowledge), the Chi-square test (Pearson's χ^2 test) was used. When expected cell counts were small, the Exact Probability test was applied. A p-value of less than 0.05 was considered statistically significant. Additionally, physicians' attitudes toward ADHD diagnosis and management, and their practical experience with ADHD cases in the past year, were also analyzed using descriptive statistics.

Results

Table 1 describes the personal characteristics of the 181 primary healthcare physicians who participated in the study in Tabuk City, Saudi Arabia. The largest age group was physicians under 30 years old, accounting for 92 (50.8%), followed by 67 (37.0%) aged 30–40 years, and 22 (12.2%) over 40 years. In terms of gender, 109 (60.2%) were male and 72 (39.8%) were female. Regarding nationality, a majority were non-Saudi 137 (75.7%), while 44 (24.3%) were Saudi nationals. Most participants held an MBBS degree 147 (81.2%), whereas 28 (15.5%) had a doctorate and only 6 (3.3%) had a diploma or master's degree. Experience levels were nearly evenly split, with 88 (48.6%) having less than 5 years of experience and 93 (51.4%) having more than 5 years. Finally, when assessing perceived knowledge of ADHD, 145 (80.1%) of the physicians rated their knowledge as acceptable, while 36 (19.9%) reported poor knowledge.

Table 1: Personal Characteristics of the Study Primary Healthcare Physicians in Tabuk City, Saudi Arabia (N=181)

Personal data	No	%
Age in years		
< 30	92	50.8%
30-40	67	37.0%
> 40	22	12.2%
Gender		
Male	109	60.2%
Female	72	39.8%
Nationality		
Saudi	44	24.3%
Non-Saudi	137	75.7%
Qualification		
Diploma/master's	6	3.3%
Doctorate	28	15.5%
MBBS	147	81.2%
Experience years		
< 5 years	88	48.6%
> 5 years	93	51.4%
Perceived knowledge level of ADHD		
Poor	36	19.9%
Acceptable	145	80.1%

Table 2 illustrates the responses of primary healthcare physicians regarding key knowledge items related to ADHD. A high proportion of participants correctly identified that ADHD manifests in early childhood with symptoms of hyperactivity, impulsivity, and/or inattention (181; 100%), and that it is one of the most common neuropsychiatric disorders in childhood and adolescence (171; 94.5%). Most respondents also correctly recognized that ADHD may persist into adulthood (165; 91.2%) and potentially become a lifelong condition (159; 87.8%). Furthermore, awareness was strong regarding symptoms of inattention, such as difficulty organizing tasks and being easily distracted (175; 96.7%). However, distinguished misconceptions were observed as 77 (42.5%) of the participants incorrectly believed there are no gender differences in ADHD, and 87 (48.1%) wrongly stated that ADHD is associated with only one health condition. Additionally, 107 (59.1%) believed that children with ADHD do not need support from private education.

Table 2. Knowledge of ADHD among Primary Healthcare Physicians in Tabuk City, Saudi Arabia (N = 181)

Knowledge items	True		False	
	No	%	No	%
ADHD is a disorder that manifests in early childhood with symptoms of hyperactivity, impulsivity, and/or inattention	181	100.0%	0	0.0%
ADHD is one of the most common neuropsychiatric disorders of childhood and adolescence	171	94.5%	10	5.5%
There are no gender differences in ADHD	77	42.5%	104	57.5%
ADHD is associated with 1 health condition	87	48.1%	94	51.9%
Slow reading speed and learning difficulties are frequent in ADHD	149	82.3%	32	17.7%
Children with ADHD have a low level of arithmetic (mathematic) ability	119	65.7%	62	34.3%
Children with ADHD need not be supported by private education	107	59.1%	74	40.9%
Parents of ADHD children may have psychiatric disorders	127	70.2%	54	29.8%
ADHD may become a lifelong disease	159	87.8%	22	12.2%
ADHD may be seen during adulthood	165	91.2%	16	8.8%
Difficulty in remaining seated when sitting is required and difficulty waiting turns are symptoms of inattention	153	84.5%	28	15.5%
Difficulty organizing tasks, activities, and belongings, and easily distracted by irrelevant stimuli are symptoms of inattention	175	96.7%	6	3.3%

Figure 1 shows the overall knowledge levels of ADHD among primary healthcare physicians, along with their reported sources of information. The majority of physicians (149; 82.3%) had a good level of knowledge, while a smaller proportion (32; 17.7%) had poor knowledge. When exploring sources of knowledge (Figure 2), most participants (141; 77.9%) reported gaining information through personal reading about ADHD. In contrast, only 22 (12.2%) cited the internet, and a mere 18 (9.9%) had attended continuing medical education (CME) programs on ADHD.

Figure 1: The Overall Knowledge of ADHD among Primary Healthcare Physicians in Tabuk City, Saudi Arabia (N = 181

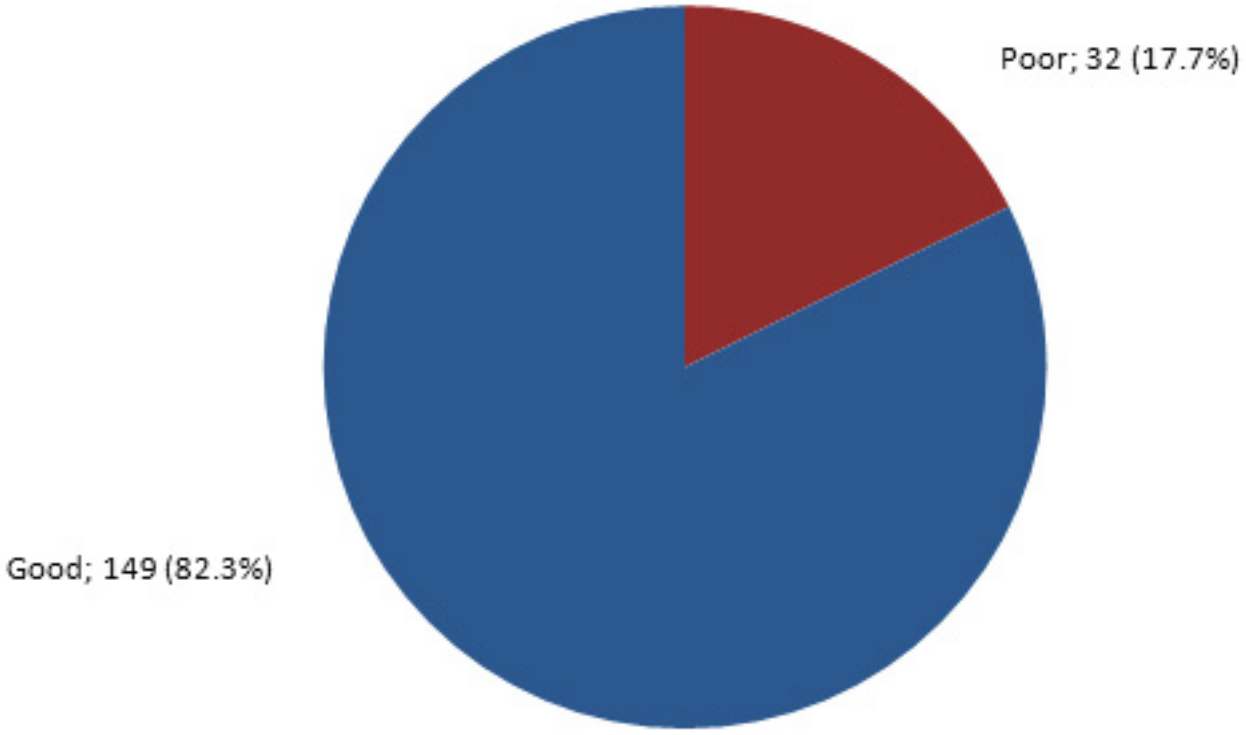

Figure 2: The source of Information about ADHD among Primary Healthcare Physicians in Tabuk City, Saudi Arabia

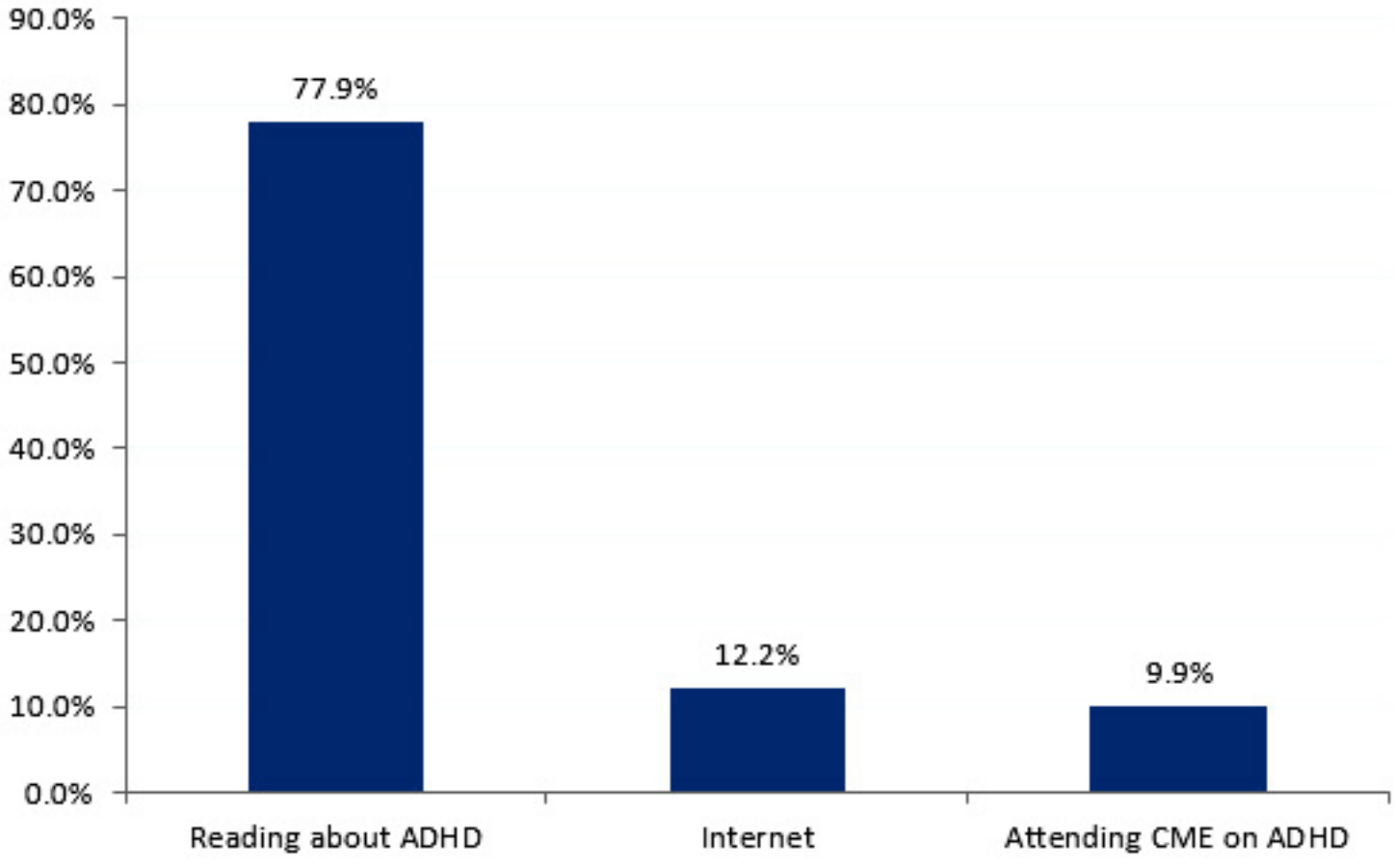

Table 3 presents the attitudes of primary healthcare (PHC) physicians toward ADHD diagnosis and management. A majority of physicians (119; 65.7%) agreed that ADHD is difficult to diagnose or manage within the PHC setting. Despite this, 145 (80.1%) believed that PHC physicians can play an active role in ADHD management, indicating a positive outlook toward their potential involvement. Interestingly, more than half of the respondents (105; 58.0%) agreed that managing ADHD is not within the job scope of PHC physicians. Consistently, 147 (81.2%) supported referring suspected ADHD cases to pediatricians.

Table 3: Attitudes of Primary Healthcare Physicians toward ADHD Diagnosis and Management in Tabuk City, Saudi Arabia (N = 181

Attitude	Agree		Disagree	
	No	%	No	%
ADHD is difficult to diagnose or manage by PHC physicians	119	65.7%	62	34.3%
PHC physicians can play an active role in the management of ADHD	145	80.1%	36	19.9%
Management of ADHD is not the job for PHC physicians	105	58.0%	76	42.0%
For the diagnosis of ADHD in children, PHC physicians should refer any suspected case to a pediatrician	147	81.2%	34	18.8%

Table 4 highlights the clinical experience of primary healthcare physicians in managing ADHD cases. Only 61 physicians (33.7%) reported diagnosing ADHD cases within the past year, while the majority (120; 66.3%) had not encountered or diagnosed any such cases. Among those who had diagnosed ADHD (n = 61), most (55; 90.2%) referred the patients to specialists, whereas only a small proportion (6; 9.8%) proceeded to prescribe treatment themselves.

Table 4. Experience of Primary Healthcare Physicians in Diagnosing and Managing ADHD Cases in the Past Year in Tabuk City, Saudi Arabia (N = 181)

	No	%
Diagnosed case(s) with ADHD in the last year		
Yes	61	33.7%
No	120	66.3%
If yes, what was done? (n=61)		
Prescribed treatment to ADHD patients	6	9.8%
Refer ADHD patients to a specialist	55	90.2%

Table 5 explores the association between various demographic and professional factors and the overall knowledge level of ADHD among primary healthcare physicians. Statistically significant associations were found with age and gender. Physicians aged over 40 years had the highest percentage of good knowledge (90.9%) compared to those under 30 (78.3%) and those aged 30–40 (85.1%) (p = 0.049). Gender differences were also significant (p = 0.004), with 89.0% of male physicians exhibiting good knowledge compared to 72.2% of female physicians. Other variables, such as nationality (p = 0.086), qualification (p = 0.459), years of experience (p = 0.863), and perceived knowledge level (p = 0.859), showed no statistically significant association with knowledge levels. Additionally, sources of knowledge, including attending CME (88.9%), internet (72.7%), and reading (83.0%), were not significantly linked to knowledge level (p = 0.374). Similarly, whether physicians had diagnosed ADHD cases in the past year did not significantly affect knowledge (p = 0.746).

Table 5: Factors Associated with PHCCs physicians Knowledge about ADHD in Tabuk

Factors	Overall knowledge level				p-value
	Poor		Good		
	No	%	No	%	
Age in years					
< 30	20	21.7%	72	78.3%	.049*
30-40	10	14.9%	57	85.1%	
> 40	2	9.1%	20	90.9%	
Gender					
Male	12	11.0%	97	89.0%	.004*
Female	20	27.8%	52	72.2%	
Nationality					
Saudi	4	9.1%	40	90.9%	.086
Non-Saudi	28	20.4%	109	79.6%	
Qualification					
Diploma/master's	0	0.0%	6	100.0%	.459^
Doctorate	6	21.4%	22	78.6%	
MBBS	26	17.7%	121	82.3%	
Experience years					
< 5 years	16	18.2%	72	81.8%	.863
> 5 years	16	17.2%	77	82.8%	
Perceived knowledge level of ADHD					
Poor	6	16.7%	30	83.3%	.859
Acceptable	26	17.9%	119	82.1%	
Sources of knowledge regarding ADHD					
Attending CME on ADHD	2	11.1%	16	88.9%	.374^
Internet	6	27.3%	16	72.7%	
Reading about ADHD	24	17.0%	117	83.0%	
Diagnosed case(s) with ADHD in the last year					.746
Yes	10	16.4%	51	83.6%	
No	22	18.3%	98	81.7%	

P: Pearson X2 test ^: Exact Probability test * P < 0.05 (significant)

Discussion

The study included 181 primary healthcare physicians, with the majority being under 30 years of age. A slightly higher proportion of participants were male, and most were non-Saudi nationals. In terms of qualifications, the vast majority held an MBBS degree, while a smaller percentage had a doctorate or higher qualifications. Years of experience were nearly evenly distributed between those with less than five years and those with more than five years. When self-assessing their knowledge of ADHD, most physicians perceived their understanding as acceptable, though a notable minority reported poor knowledge.

Regarding ADHD in children and adolescents, most physicians had a strong understanding of ADHD recognizing its early childhood onset, core symptoms (hyperactivity, impulsivity, inattention), and potential persistence into adulthood several misconceptions and knowledge deficiencies were identified, which may impact clinical practice. This high awareness of ADHD as a common neurodevelopmental disorder matches with global literature, which highlights its prevalence and long-term implications (31). The recognition of ADHD's persistence into adulthood is consistent with international studies showing that symptoms often continue beyond adolescence, affecting academic, occupational, and social functioning [32, 33]. However, the misconception that ADHD has no gender differences contradicts well-established evidence that boys are more frequently diagnosed due to differing symptom presentations, with girls often exhibiting more inattentive rather than hyperactive behaviors [34]. Additionally, the belief that ADHD is not associated with comorbid conditions is concerning, given that ADHD frequently coexists with learning disabilities, anxiety, and behavioral disorders [35]. This misconception may lead to under-diagnosis or mismanagement of associated conditions. Furthermore, the assumption that children with ADHD do not require private educational support directs the importance of individualized learning strategies, which are crucial for academic success in this population [36].

The dependence on personal reading as the primary source of ADHD knowledge, rather than structured medical education, underlines a critical gap in formal training. While self-directed learning is valuable, the low attendance in CME programs suggests that many physicians may lack exposure to updated, evidence-based ADHD guidelines. This finding is consistent with studies from other regions, where primary care providers often report insufficient ADHD training [37]. In Saudi Arabia, similar knowledge deficiencies have been observed in previous research, indicating the need for enhanced ADHD education in medical curricula and postgraduate training [38].

Compared to studies in other Saudi regions, such as Al-Khobar and Riyadh, where physicians also showed variable ADHD knowledge [39], our findings suggest that while awareness of core ADHD symptoms is strong, misconceptions about comorbidities and gender differences persist. Internationally, similar patterns have been reported, with primary care providers often lacking confidence in diagnosing and managing ADHD without specialist support [40]. The high proportion of physicians with good self-reported knowledge contrasts with some global studies where clinicians expressed uncertainty about ADHD management [41], possibly indicating cultural differences in self-assessment or varying exposure to ADHD cases.

In contrast to our study, Al-Ahmari et al (42) in Aseer Region reported that PHC physicians' knowledge about ADHD was suboptimal, but they had a positive attitude toward their role with regard to ADHD. Also, these findings have been reported in studies in several countries. In Pakistan, Jawaid et al. [34] reported that the knowledge of general practitioners on ADHD was deficient. They questioned the ability of physicians at the PHC level to screen children for ADHD. In the UK, Thapar and Thapar [44] stated that general practitioners did not have adequate knowledge to diagnose or manage ADHD. Ghanizadeh [45] also reported that general practitioners needed to be more informed about ADHD. In the USA, Goodman et al. [46] found that primary care physicians had limited knowledge and experience with ADHD.

Our study also reveals contradiction in primary healthcare (PHC) physicians' attitudes toward ADHD. While a majority acknowledged the challenges of diagnosing and managing ADHD in PHC settings, most also believed they could play an active role in its management. This suggests a willingness to engage in ADHD care despite perceived difficulties, possibly reflecting a sense of professional responsibility. However, over half of the respondents did not consider ADHD management within their job scope, and a strong preference for referral to pediatricians was evident. This discrepancy may be due to insufficient training, lack of confidence, or systemic barriers such as limited resources and unclear clinical guidelines for ADHD in primary care. The high referral tendency aligns with studies in Saudi Arabia and globally, where ADHD management remains heavily reliant on specialists.

Conclusion and Recommendations

In conclusion, this study demonstrates a good level of knowledge regarding ADHD among the study PHCC physicians in Tabuk City, especially in recognizing its core symptoms and chronic nature. However, knowledge gaps and misconceptions persist in specific areas, such as the role of gender differences and the association of ADHD with other conditions. Although most physicians expressed positive attitudes toward their role in ADHD management, a significant number still perceived it as outside their responsibilities, with limited direct involvement in diagnosis or treatment. The majority preferred referring cases to specialists rather than initiating management themselves. The findings also indicate that knowledge levels were significantly associated with age and gender, but not with other professional or educational factors. Notably,

continuing medical education (CME) on ADHD was underutilized, with most physicians relying on self-directed reading. Enhancing CME programs focusing on ADHD diagnosis and management tailored to PHC settings, with efforts to increase participation is recommended with clarification of the role of PHC physicians in ADHD care through guidelines and structured training to empower their involvement.

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Prevalence of limitations and barriers of receiving herpes-zoster vaccine among patients attending PHC in Tabuk city, 2023, cross-sectional study

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Abstract

Background: Herpes Zoster (HZ), or shingles, is a vaccine-preventable condition that disproportionately affects older adults and immunocompromised individuals. Despite the availability of the HZ vaccine, uptake remains suboptimal in many settings, potentially due to poor awareness and misconceptions.

Aim: This study aimed to assess the awareness, knowledge, attitudes, and barriers to HZ and its vaccine among residents of Tabuk City, Saudi Arabia.

Methods: A cross-sectional, quantitative study was conducted among 500 patients aged 50 years and older attending primary healthcare centers (PHCs) in Tabuk City over a six-month period. Data were collected using a validated, structured questionnaire adapted from previous literature and translated into Arabic. The questionnaire covered demographics, knowledge of HZ and its vaccine, attitudes, and sources of information. Data were analyzed using SPSS version 28, with descriptive statistics and chi-square tests to examine associations between knowledge levels and participant characteristics.

Results: Among the participants, 56.0% demonstrated good knowledge of HZ, while 44.0% had poor knowledge. Awareness of HZ (76.8%) and its vaccine (68.4%) was generally high; however, gaps remained in the recognition of symptoms and understanding of disease impact. Factors significantly associated with better knowledge included female gender ($p = .012$), non-Saudi nationality ($p = .022$), higher education ($p = .001$), employment ($p = .001$), prior infection or vaccination history ($p = .001$), and using the internet or healthcare professionals as information sources ($p = .001$). While 62.0% expressed willingness to receive the vaccine, acceptance increased to 81.4% if recommended by a physician. Fear of side effects and perceived low risk were the main barriers to vaccination.

Conclusion: Although general awareness of HZ is high among the Tabuk population, significant knowledge gaps and misconceptions persist, especially regarding symptoms and vaccine safety.

Keywords: Herpes Zoster, shingles, vaccine awareness, knowledge, attitudes, Saudi Arabia, primary healthcare, Tabuk, vaccination barriers.

Introduction

Herpes zoster (HZ), commonly known as shingles, is a painful cutaneous eruption resulting from the reactivation of latent varicella-zoster virus (VZV) in sensory ganglia, often decades after initial varicella (chickenpox) infection. Its incidence and severity increase markedly with age, particularly among individuals aged 50 years and older, as cellular immunity to VZV wanes over time [1]. Globally, it is estimated that one in three individuals will develop HZ during their lifetime, with higher rates observed in elderly and immunocompromised populations [2]. Complications such as postherpetic neuralgia (PHN), which can persist for months or years, significantly impair quality of life and daily functioning [3].

Vaccination is currently the most effective preventive measure, with recombinant zoster vaccine (RZV) representing high efficacy in reducing both HZ and PHN incidence [4]. Despite the availability of effective vaccines, awareness, acceptance, and uptake remain suboptimal in many regions, including the Middle East, where vaccine hesitancy and limited knowledge may pose barriers to implementation [5, 6].

For herpes zoster, two vaccines are currently available: the varicella vaccine, administered to prevent primary VZV infection, and the zoster vaccine, which reduces the risk of reactivation in older adults [7, 8]. The herpes zoster vaccine is especially critical for individuals aged 60 years and above, who are at higher risk of developing severe complications [9]. Despite its proven efficacy, vaccine uptake remains suboptimal globally due to barriers such as limited awareness, vaccine hesitancy, and accessibility issues [10, 11].

In Saudi Arabia, where an aging population is increasingly at risk of herpes zoster, the need to address vaccination challenges is pressing. Understanding local barriers to herpes zoster vaccine (HZV) uptake, including knowledge gaps and misconceptions, is essential for improving public health outcomes. This study focuses on assessing awareness, obstacles, and vaccine hesitancy among the population in Tabuk city, offering insights into strategies for enhancing immunization coverage and reducing the burden of herpes zoster in Saudi Arabia.

Methodology

A quantitative, observational, cross-sectional design was applied to assess the study objectives. Tabuk City, located in the northern region of Saudi Arabia, has an estimated population of approximately 657,000 as of the 2020 census. Data collection was conducted in primary healthcare centers (PHCs) under the Ministry of Health, encompassing 35 centers distributed throughout the city. The target population included patients aged 50 years and above attending these PHCs, with an estimated population size of around 200,000 individuals within this age group. The study duration extended over six months. Sample size was calculated using an online calculator based on a 95% confidence interval and a 5% margin of error, resulting in a minimum required sample size of 139 patients from a total of 384 patients visiting PHCs. Inclusion criteria encompassed male and female individuals aged 50 years and above, as well as immunocompromised patients under 50 years. Exclusion criteria included patients who had received the shingles vaccine outside Tabuk City or in hospitals, children, and pregnant women.

Data were collected using a structured, close-ended questionnaire adapted from a similar study conducted in the United Arab Emirates. The questionnaire consisted of 27 questions divided into four sections: demographics (6 questions), knowledge about HZ and its vaccine (14 questions), attitudes toward HZ and vaccination (5 questions), and vaccination practices (2 questions). Question formats included yes/no responses, multiple-choice options, and Likert scale ratings. The original English questionnaire was translated into Arabic and reviewed by a language specialist to ensure grammatical accuracy and cultural appropriateness. The validated questionnaire was distributed online using an online link for the eligible patients till no more respondents were included/ participated.

A pilot study was conducted with 15 randomly selected eligible individuals to test clarity and reliability. Feedback from the pilot helped refine ambiguous questions and reduce medical jargon to ensure participant understanding. Data from the pilot were excluded from the final analysis. Additionally, a biostatistician reviewed the questionnaire to confirm its reliability and face validity. Researchers underwent standardization sessions to minimize interviewer bias and ensure uniformity in data collection procedures.

Data Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including frequencies and percentages, were used to summarize the socio-demographic characteristics, knowledge, attitudes, and perceptions of the participants. The overall knowledge score regarding Varicella (chickenpox), shingles (Herpes Zoster), and the associated symptoms and vaccine was calculated by assigning one point for each correct response. Participants with a total knowledge score below 60% were classified as having poor knowledge, while those with scores equal to or above 60% were considered to have good knowledge. Associations between participants' knowledge level and various independent factors such as age, gender, nationality, educational level, employment status, history of Varicella or shingles, vaccination status, and sources of information were examined using the Pearson Chi-square test. When expected cell counts were low, the Exact probability test was applied to ensure validity. Statistical significance was set at $p < 0.05$.

Results

Table 1 presents the bio-demographic characteristics of the 500 patients attending primary healthcare centers (PHC) in Tabuk City, Saudi Arabia. Regarding age, 44.4% (n=222) were younger than 50 years, 13.8% (n=69) were exactly 50 years old, and 41.8% (n=209) were older than 50 years. The majority were females (71.2%, n=356), while males constituted 28.8% (n=144). Most participants were Saudi nationals (92.4%, n=462). Regarding educational level, a large proportion were university graduates (72.6%, n=363), followed by those with secondary education (14.2%, n=71), below secondary (10.6%, n=53), and no formal education (2.6%, n=13). As for employment status, 50.2% (n=251) were employees or self-employed, 28.4% (n=142) were retired, and 21.4% (n=107) were not working, or were students.

When asked about prior Varicella (chickenpox) infection, 40.0% (n=200) reported having had the disease, whereas 60.0% (n=300) had not. Among those who had Varicella, 58.0% (n=116) contracted it in childhood, 22.0% (n=44) during adolescence, 13.0% (n=26) as adults, and 7.0% (n=14) did not recall the timing. Regarding Varicella vaccination, 38.4% (n=192) reported being vaccinated, 23.6% (n=118) were not, and 38.0% (n=190) did not remember. Among those vaccinated, 44.1% (n=156) received it in childhood, 4.0% (n=14) during adolescence, 3.1% (n=11) as adults, and 48.9% (n=173) could not recall when. Finally, only 5.8% (n=29) of the participants reported a previous episode of shingles (Herpes Zoster), while the vast majority (94.2%, n=471) had not experienced it.

Table 1. Bio-Demographic Characteristics of the Study patients attending PHC in Tabuk city, Saudi Arabia (N=500)

Items	No	%
Age in years		
< 50 years	222	44.4%
Exactly 50 years	69	13.8%
> 50 years	209	41.8%
Gender		
Male	144	28.8%
Female	356	71.2%
Nationality		
Saudi	462	92.4%
Non-Saudi	38	7.6%
Educational level		
No formal education	13	2.6%
Below secondary	53	10.6%
Secondary education	71	14.2%
University graduate	363	72.6%
Work		
Not working / student	107	21.4%
Employee / free work	251	50.2%
Retired	142	28.4%
Have you had Varicella in the past?		
Yes	200	40.0%
No	300	60.0%
If yes, how old were you?		
At childhood	116	58.0%
At adolescence	44	22.0%
At adult phase	26	13.0%
I do not remember	14	7.0%
Have you been vaccinated against Varicella?		
Yes	192	38.4%
No	118	23.6%
I do not remember	190	38.0%
If yes, how old were you?		
At childhood	156	44.1%
At adolescence	14	4.0%
At adult phase	11	3.1%
I do not remember	173	48.9%
Have you had shingles in the past (Herpes Zoster)?		
Yes	29	5.8%
No	471	94.2%

Table 2 illustrates the participants' knowledge and perceptions regarding Varicella (chickenpox), shingles (Herpes Zoster), and associated symptoms and vaccine awareness. A high proportion of respondents reported awareness of Varicella (79.8%, n=399) and shingles (76.8%, n=384). Furthermore, 59.6% (n=298) stated they personally knew someone who had experienced shingles. Considering symptoms, the most commonly identified were rash (67.6%, n=338) and pain (51.8%, n=259), followed by malaise (43.4%, n=217), itching (43.2%, n=216), and headache (19.4%, n=97), while 22.4% (n=112) were not familiar with any symptoms. Regarding the nature of shingles-related pain, 37.2% (n=186) reported it as severe and potentially lasting months or years, whereas 28.0% (n=140) considered it moderate, and only 3.2% (n=16) perceived it as mild. Regarding the impact of chronic shingles pain on daily activities, 45.4% (n=227) believed it to be very relevant, 19.8% (n=99) found it relevant, and 4.8% (n=24) considered it of little relevance, while 30.0% (n=150) were unsure. Awareness of the shingles vaccine was reported by 68.4% (n=342), whereas 31.6% (n=158) were not aware of it.

Table 2. Participants' Knowledge and Perceptions Regarding Varicella (Chickenpox), Shingles (Herpes Zoster), and Its Associated Symptoms and Vaccine (N=500)

Items	No	%
Do you know the disease called Varicella (chickenpox)?		
Yes	399	79.8%
No	101	20.2%
Do you know the disease called shingles (Herpes Zoster)?		
Yes	384	76.8%
No	116	23.2%
Do you know someone who had shingles (Herpes Zoster)?		
Yes	298	59.6%
No	202	40.4%
Symptoms of shingles (Herpes Zoster)		
Pain	259	51.8%
Rash	338	67.6%
Itching	216	43.2%
Malaise	217	43.4%
Headache	97	19.4%
I do not know	112	22.4%
The pain associated with shingles (Herpes Zoster) is:		
Severe, lasting months or years	186	37.2%
Moderate, lasting a few weeks	140	28.0%
Mild, lasting a few days	16	3.2%
I do not know	158	31.6%
Can the chronic pain associated with shingles impact normal daily activities?		
Little relevance	24	4.8%
Relevant	99	19.8%
Very relevant	227	45.4%
I do not know	150	30.0%
Are you aware of the vaccine against shingles?		
Yes	342	68.4%
No	158	31.6%

Figure 1 shows the overall participants' knowledge and perceptions regarding Varicella (chickenpox), shingles (Herpes Zoster), and related symptoms and vaccine awareness. More than half of the respondents (56.0%, n=280) had a good level of knowledge, while 44.0% (n=220) showed poor knowledge. Considering source of information (Figure 2), the most frequently reported source was the internet (38.3%, n=158), followed by other unspecified sources (24.5%, n=101) and general practitioners (23.7%, n=98). Social networks such as friends or contacts (20.6%, n=85) and family members (19.9%, n=82) were also commonly reported. Mass media accounted for a smaller portion (14.3%, n=59).

Figure 1. The Overall Participants' Knowledge and Perceptions Regarding Varicella (Chickenpox), Shingles (Herpes Zoster), and Its Associated Symptoms and Vaccine

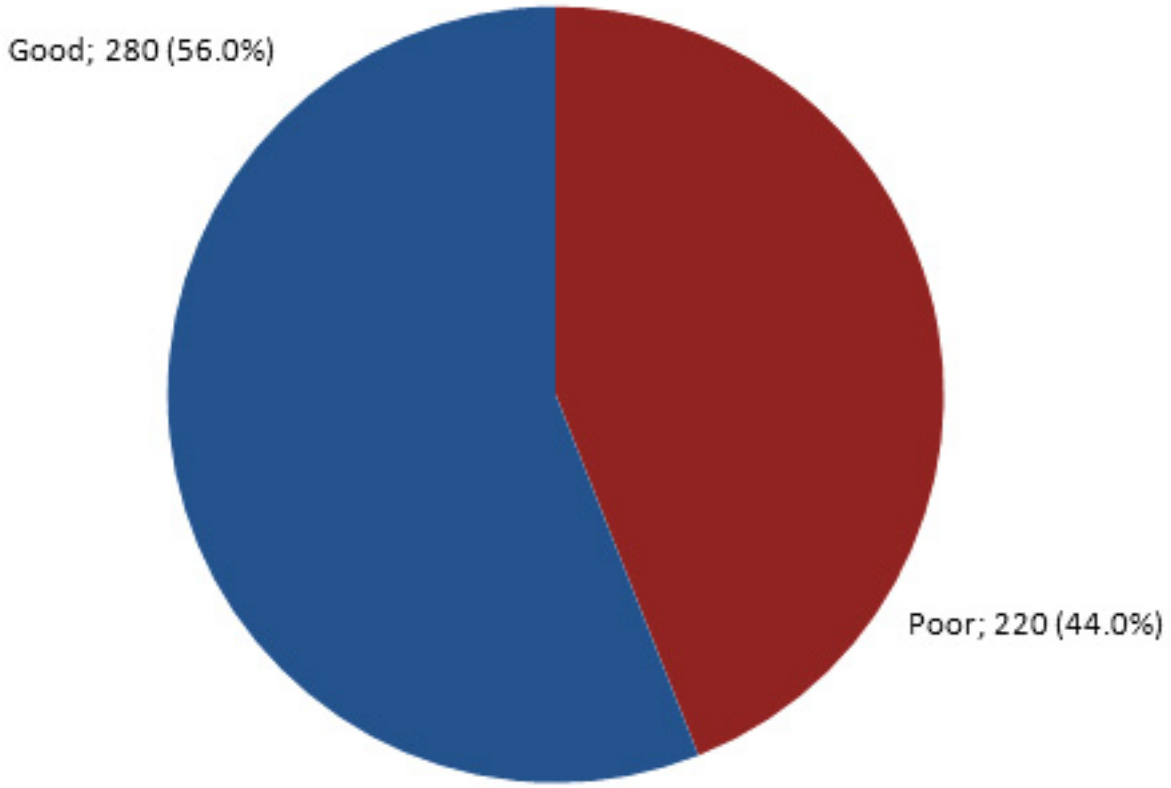

Figure 2. Source of Participants' Information about Varicella (Chickenpox), Shingles (Herpes Zoster), and Its Associated Symptoms and Vaccine

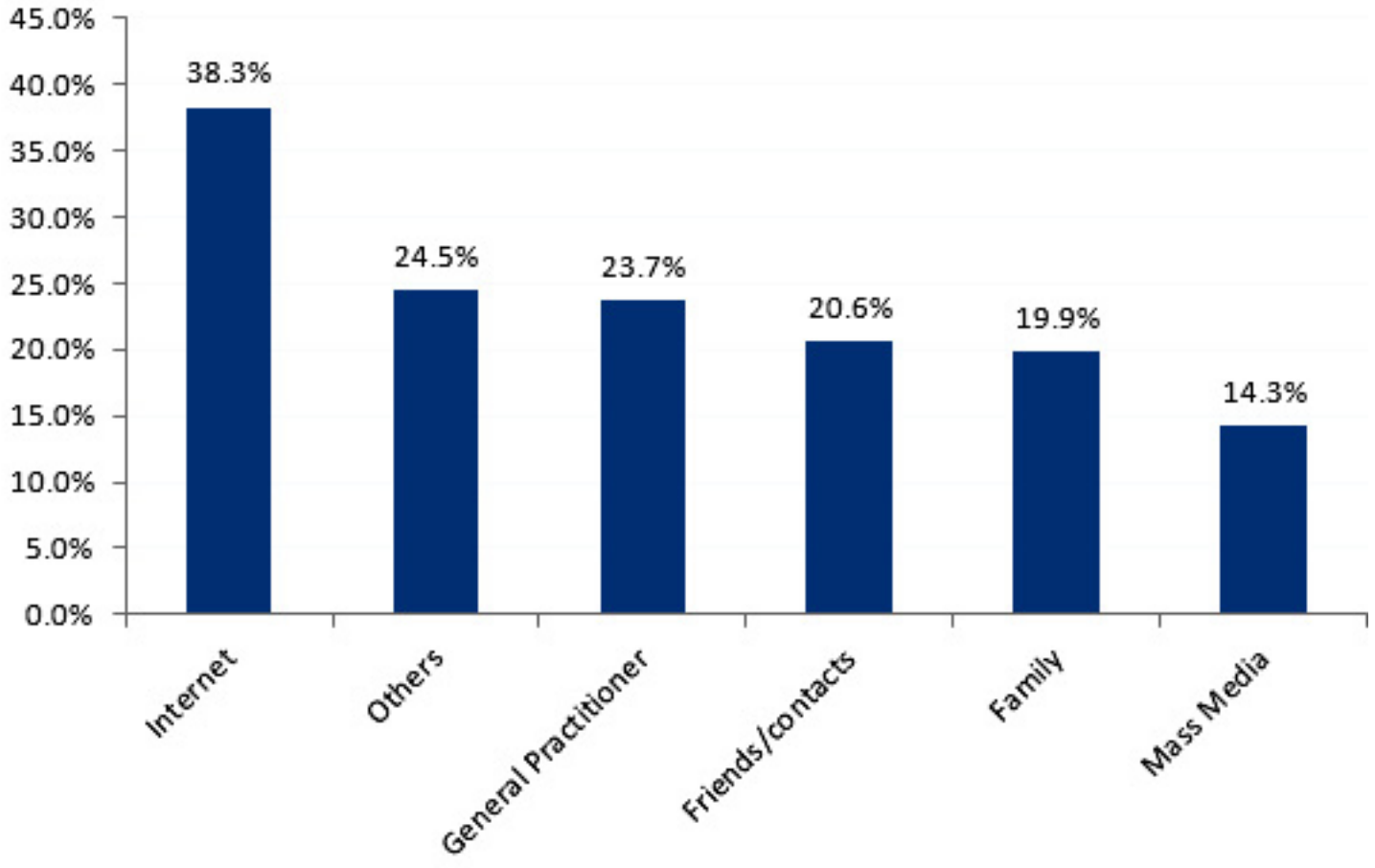

Table 3 presents the participants' attitudes and perceptions toward vaccination in general and the shingles vaccine in particular. A strong majority (88.0%, n=440) believed that vaccines are an effective tool for prevention. When asked about their willingness to receive the shingles vaccine, 62.0% (n=310) responded positively. This percentage increased to 81.4% (n=407) if the vaccine were recommended by their general practitioner. However, some concerns were evident among participants. About 41.8% (n=209) expressed worry that vaccines may interfere with other vaccines, and 47.2% (n=236) believed that vaccines could interact with other medications.

Table 3. Participants' Attitudes and Perceptions toward Vaccination and the Shingles Vaccine (N=500)

Attitude / perception	Yes		No	
	No	%	No	%
Do you think vaccines are an effective tool for prevention?	440	88.0%	60	12.0%
Would you vaccinate against shingles?	310	62.0%	190	38.0%
If your General Practitioner recommended the shingles vaccine, would you vaccinate?	407	81.4%	93	18.6%
Are you concerned that vaccines may interfere with other vaccines?	209	41.8%	291	58.2%
Do you believe that vaccines interact with other medications?	236	47.2%	264	52.8%

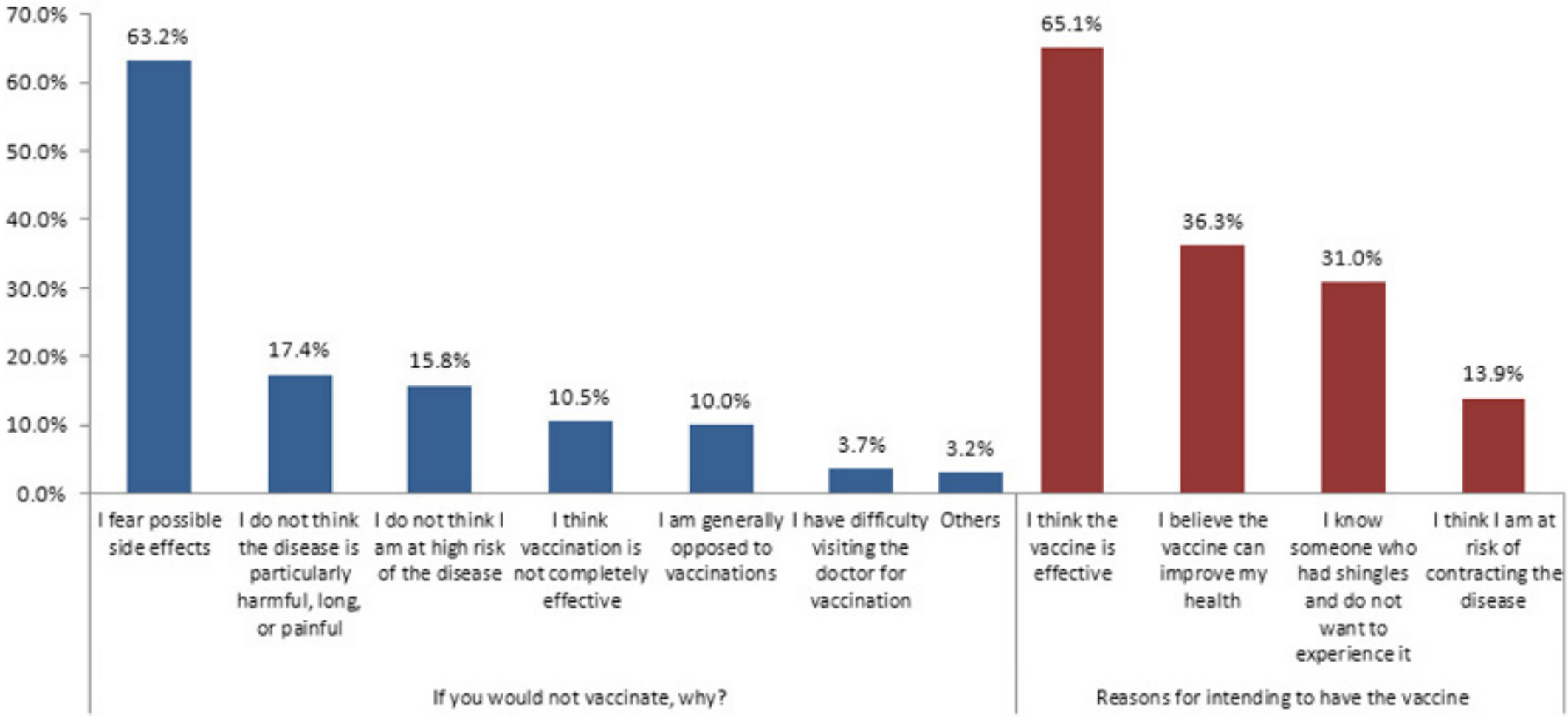

Figure 3. Reasons for Participants' Willingness or Unwillingness to Receive the Shingles Vaccine among Patients attending PHC in Tabuk city

Figure 3 presents the reasons reported by participants for either accepting or refusing the shingles vaccine. Among those unwilling to vaccinate, the most frequently reported reason was fear of possible side effects (63.2%, n=120), followed by the belief that the disease is not particularly harmful or severe (17.4%, n=33), and the perception of not being at high risk (15.8%, n=30). Other reasons included general opposition to vaccines (10.0%, n=19), doubts about vaccine effectiveness (10.5%, n=20), and difficulty accessing vaccination services (3.7%, n=7).

On the contrary, among those intending to receive the vaccine, the primary motivator was the belief in its effectiveness (65.1%, n=183). Additional reasons included the perception of being at risk for shingles (13.9%, n=39), knowing someone who had shingles (31.0%, n=87), and the belief that the vaccine would improve overall health (36.3%, n=102).

In Table 4, gender showed a significant difference, with females demonstrating higher knowledge levels than males (59.6% vs. 47.2%, p = .012). Nationality was also significant (p = .022), with non-Saudi participants showing better knowledge (73.7%) compared to Saudi participants (54.5%). Educational level was strongly associated with knowledge (p = .001), as participants with university education had higher knowledge (64.5%) than those with lower education levels, particularly those with no formal education (15.4%). Work status was another significant factor (p = .001), with employed participants having a better knowledge level (64.1%) compared to those not working or retired. Prior history of Varicella infection and vaccination were both significantly associated with higher knowledge levels (p = .001), as was a history of shingles infection, where nearly 90% (n=26) of those with past infection demonstrated good knowledge (p = .001). Regarding sources of information, those who received information from internet sources (76.6%), general practitioners (71.4%), or family and friends (over 67%) had significantly higher knowledge levels (p = .001), compared to those relying on “other” sources (46.5%). On the other hand, age did not show a statistically significant association with knowledge level (p = .546).

Table 4. Factors Associated with Participants' Knowledge and Perceptions Regarding Varicella (Chickenpox), Shingles (Herpes Zoster), and It's Associated Symptoms and Vaccine

Factors	Overall knowledge level				p-value
	Poor		Good		
	No	%	No	%	
Age in years					
< 50 years	96	43.2%	126	56.8%	.546
Exactly 50 years	27	39.1%	42	60.9%	
> 50 years	97	46.4%	112	53.6%	
Gender					
Male	76	52.8%	68	47.2%	.012*
Female	144	40.4%	212	59.6%	
Nationality					
Saudi	210	45.5%	252	54.5%	.022*
Non-Saudi	10	26.3%	28	73.7%	
Educational level					
No formal education	11	84.6%	2	15.4%	.001*
Below secondary	37	69.8%	16	30.2%	
Secondary education	43	60.6%	28	39.4%	
University graduate	129	35.5%	234	64.5%	
Work					
Not working / student	61	57.0%	46	43.0%	.001*
Employee / free work	90	35.9%	161	64.1%	
Retired	69	48.6%	73	51.4%	
Have you had Varicella in the past?					
Yes	70	35.0%	130	65.0%	.001*
No	150	50.0%	150	50.0%	
Have you been vaccinated against Varicella?					
Yes	64	33.3%	128	66.7%	.001*
No	57	48.3%	61	51.7%	
I do not remember	99	52.1%	91	47.9%	
Have you had shingles in the past (Herpes Zoster)?					.001*^
Yes	3	10.3%	26	89.7%	
No	217	46.1%	254	53.9%	
Source of information about the vaccine					
General Practitioner	28	28.6%	70	71.4%	.001*
Family	20	24.4%	62	75.6%	
Friends/contacts	28	32.9%	57	67.1%	
Mass Media	21	35.6%	38	64.4%	
Internet	37	23.4%	121	76.6%	
Others	54	53.5%	47	46.5%	

In Table 4, gender showed a significant difference, with females demonstrating higher knowledge levels than males (59.6% vs. 47.2%, p = .012). Nationality was also significant (p = .022), with non-Saudi participants showing better knowledge (73.7%) compared to Saudi participants (54.5%). Educational level was strongly associated with knowledge (p = .001), as participants with university education had higher knowledge (64.5%) than those with lower education levels, particularly those with no formal education (15.4%). Work status was another significant factor (p = .001), with employed participants having a better knowledge level (64.1%) compared to those not working or retired. Prior history of Varicella infection and vaccination were both significantly associated with higher knowledge levels (p = .001), as was a history of shingles infection, where nearly 90% (n=26) of those with past infection demonstrated good knowledge (p = .001). Regarding sources of information, those who received information from internet sources (76.6%), general practitioners (71.4%), or family and friends (over 67%) had significantly higher knowledge levels (p = .001), compared to those relying on "other" sources (46.5%). On the other hand, age did not show a statistically significant association with knowledge level (p = .546).

Discussion

In this study, the bio-demographic profile of participants attending primary healthcare centers in Tabuk City revealed a dissimilar representation across age groups, with a substantial portion aged 50 years and above. Females constituted the majority of the sample, and most participants were Saudi nationals. A notably high level of education was observed among respondents, with the majority having university degrees. Employment status varied, with many participants actively employed or self-employed, while others were retired or not working, including students.

Our study showed a significant defect in vaccination history, and disease perception related to Varicella and Herpes Zoster (HZ) among patients attending primary healthcare centers in Tabuk City. A considerable proportion of participants reported a history of Varicella infection, which matches with global patterns where Varicella remains a prevalent childhood illness, especially in regions without universal vaccination programs [12]. However, a prominent number of participants were uncertain about their history of Varicella infection or vaccination, reflecting deficiencies in personal health records and limited recall. This is consistent with findings from other populations, where poor documentation and low awareness of Varicella immunization history have been recognized as obstacles to HZ vaccine uptake [13].

Although some participants reported receiving the Varicella vaccine, nearly half were unable to recall the timing of vaccination. This observation is consistent with previous studies in Saudi Arabia and neighboring countries, which have identified challenges in vaccine documentation and public understanding of immunization schedules [14]. Furthermore, the low self-reported prevalence of HZ in this sample contrasts with international data showing increased incidence among older adults due to age-related decline in cell-mediated immunity [15]. This discrepancy may reflect underdiagnosis, misreporting, or a lack of awareness among patients' patterns observed in comparable settings where HZ is often overlooked unless severe complications occur [16].

The Varicella and Herpes Zoster (HZ) vaccination coverage observed in this study appears relatively low compared to other regions in Saudi Arabia and globally. Studies from major Saudi cities such as Riyadh and Jeddah have reported slightly higher Varicella vaccination rates, likely due to better healthcare infrastructure and awareness campaigns in urban centers [17, 18]. Globally, countries with established universal Varicella vaccination programs, such as the U.S. and parts of Europe, report significantly higher immunization rates [19]. The low HZ vaccine uptake in our study matches with trends in many middle-income nations, where barriers such as cost, lack of recommendations from physicians, and insufficient public health prioritization persist [20]. In contrast, countries like the U.S., where the HZ vaccine is routinely recommended for older adults, have achieved much higher coverage [21].

A relatively high level of awareness about Varicella (chickenpox) and Herpes Zoster (HZ) among participants was assessed with most respondents recognizing the names of both diseases. However, significant defects continue in the recognition of symptoms and the understanding of disease severity, which may affect timely healthcare-seeking behavior and vaccination decisions. While most participants reported awareness of shingles and over half knew someone who had been affected, only one-fifth could not identify any symptoms. Rash and pain were the most frequently recognized features, consistent with previous studies showing that visible symptoms are more readily recalled than systemic ones [22, 23]. Fewer participants associated HZ with malaise, itching, or headache, indicating a limited understanding of its broader clinical presentation, which has similarly been reported in other populations [15]. Remarkably, more than one-third of participants understood that shingles-related pain could be severe and long-lasting, yet fewer were uncertain about its potential to disrupt daily life, indicating a partial awareness of the debilitating nature of postherpetic neuralgia. Such misconceptions are known to contribute to delayed diagnosis and underutilization of preventive measures like vaccination [24]. Although two-thirds of participants were aware of the shingles vaccine, this awareness did not necessarily correspond to high vaccination rates, a pattern consistent with other research showing that awareness alone does not lead to action, particularly when issues of trust, access, or perceived need exist [25]. Alarmingly, the internet was cited more often than healthcare professionals as a source of information, raising concerns about misinformation,

especially in regions where online content is not always reliable. Previous studies in Saudi Arabia have highlighted the growing role of social media and informal sources in shaping public health perceptions, often at the expense of accurate knowledge [26-28]. Generally, the distribution of knowledge scores revealed that more than half of respondents had good knowledge.

Our study also showed that fear of side effects is the dominant barrier to shingles vaccine uptake, consistent with global trends where vaccine hesitancy is often driven by safety concerns [29]. A notable proportion also underestimated shingles severity or perceived them as low-risk, reflecting gaps in public awareness of the disease's potential complications. Similar reasons have been reported in Saudi and international studies, where misconceptions about susceptibility and harm contribute to low vaccination rates [30-32].

On the other hand, belief in vaccine effectiveness was the strongest motivator for acceptance, aligning with findings that confidence in vaccines drives uptake [33]. Personal exposure to shingles and perceived health benefits also played key roles, suggesting that direct experience with the disease may enhance vaccine willingness. However, the low influence of healthcare provider recommendations (not a top-cited factor) indicates missed opportunities for physician-driven advocacy, a known facilitator in high-coverage regions like the U.S. and Europe.

Conclusion and Recommendations

This study highlights both encouraging trends and significant gaps in the awareness and understanding of Varicella and Herpes Zoster (HZ) among patients attending primary healthcare centers in Tabuk City. While general awareness of these conditions and their vaccines was relatively high, substantial proportions of participants particularly those with lower education levels, limited prior infection history, or inadequate access to accurate information had poor knowledge. Only slightly more than half of respondents showed a good knowledge score, and misconceptions about disease severity, symptoms, and vaccine interactions were common. Internet sources were the most relied-upon channel for health information, more than general practitioners, which raises concerns about the quality and accuracy of public knowledge. Socio-demographic factors such as gender, nationality, education, and employment status were significantly associated with knowledge levels. Targeted educational interventions should be implemented, especially for older adults and those with lower education or no history of infection, to address knowledge gaps about HZ and its prevention. Also, primary healthcare providers must be empowered and encouraged to play a more prominent role in patient education, as their recommendations were shown to greatly influence vaccine acceptance. Public health campaigns to deliver accurate, culturally tailored messages, countering misinformation were commonly found online.

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Chronic idiopathic thrombocytopenic purpura may even prolong survival in human beings in general

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Abstract

Background: Atherosclerosis may be the major cause of aging and death, and the role of platelets (PLT) is well-known in the terminal consequences of atherosclerosis.

Methods: All patients with sickle cell diseases (SCD) were included.

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

Conclusion: As a prototype of accelerated atherosclerosis, hardened RBC-induced capillary endothelial damage initiating at birth terminates with multiorgan failures in much earlier ages in the SCD. Excess fat tissue may be much more important than smoking and alcohol for atherosclerosis, and CHD and stroke may be the terminal causes of death in both genders at the moment. Although the possibility of some severe bleedings in rare cases, we have just seen two mortile cases due to the chronic idiopathic thrombocytopenic purpura (ITP) in our 25 years of experience. Due to the well-known roles of PLT during the terminal atherosclerotic consequences, chronic ITP may even prolong the survival in human being in general.

Key words: Chronic idiopathic thrombocytopenic purpura, platelets, sickle cell diseases, systemic atherosclerosis, coronary heart disease, stroke, vascular endothelial inflammation, excessive fat tissue, smoking, alcohol

Introduction

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

Material and Methods

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

the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 222 males and 212 females with similar ages (30.8 vs 30.3 years, p>0.05, respectively), and there was no patient above the age of 59 years in both genders. Prevalences of associated TM were similar in both genders, too (72.5% vs 67.9%, p>0.05, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were higher in males (p<0.001 for both) (Table 1). Transfused units of RBC in their lives (48.1 vs 28.5, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), CRD (9.9% vs 6.1%, p<0.05), COPD (25.2% vs 7.0%, p<0.001), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males (Table 2). On the other hand, mean ages of the other atherosclerotic consequences in the SCD were shown in Table 3.

Table 1: Characteristic features of the study patients

Variables	Males with the SCD*	*p*-value	Females with the SCD
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated TM‡	72.5% (161)	Ns	67.9% (144)
Smoking	***23.8% (53)***	***<0.001***	***6.1% (13)***
Alcoholism	***4.9% (11)***	***<0.001***	***0.4% (1)***

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Thalassemia minors

Table 2: Associated pathologies of the study patients

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

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

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

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

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

Discussion

Excess weight may be the most common cause of disseminated vasculitis all over the world at the moment, and it may be one of the terminal endpoints of the metabolic syndrome, since after development of excess weight, nonpharmaceutical approaches provide limited benefit either to improve excess weight or to prevent its complications. Excess fat tissue may lead to a chronic and low-grade inflammation on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess fat tissue in all age groups (19). The low-grade chronic inflammation may also cause genetic changes on the epithelial cells, and the systemic atherosclerotic process may decrease clearance of malignant cells by the immune system, effectively (20). Excess fat tissue is associated with many coagulation and fibrinolytic abnormalities suggesting that it causes a prothrombotic and proinflammatory state (21). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (22, 23). For example, elevated C-reactive protein (CRP) levels in serum carry predictive power for the development of major cardiovascular events (24, 25). Overweight and obesity are considered as strong factors for controlling of CRP concentration in serum, since fat tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines (26, 27). On the other hand, individuals with excess fat tissue will have an increased circulating blood volume as well as an increased cardiac output, thought to be the result of increased oxygen demand of the excess fat tissue. In addition to the common comorbidity of atherosclerosis and HT, the prolonged increase in circulating blood volume may lead to myocardial hypertrophy and decreased compliance. Beside the systemic atherosclerosis and HT, fasting plasma glucose (FPG) and serum cholesterol increased and high density lipoproteins (HDL) decreased with increased body mass index (BMI) (28). Similarly, the prevalences of CHD and stroke, particularly ischemic stroke, increased parallel with the elevated BMI values in another study (29). Eventually, the risk of death from all causes including cardiovascular diseases and cancers increased throughout the range of moderate and severe excess fat tissue for both genders in all age groups (30). The excess fat tissue may be the most common cause of accelerated atherosclerotic process all over the body at the moment, the individuals with underweight may even have lower biological ages (30). Similarly, calorie restriction extends lifespan and retards age-related chronic diseases (31).

Smoking may be the second most common cause of disseminated vasculitis all over the world at the moment. It may cause a systemic inflammation on vascular endothelium terminating with an accelerated atherosclerosis-induced multiorgan insufficiencies in whole body (32). Its atherosclerotic effect is the most obvious in the COPD and Buerger's disease (33). Buerger's disease is an obliterative vasculitis characterized by inflammatory changes in the small and medium-sized arteries and veins, and it has never been documented in the absence of smoking. Its characteristic findings are acute inflammation, stenoses and occlusions of arteries and veins, and involvements of hands and feet. It is usually seen in young males between the ages of 20 and 40 years. Claudication may be the most common initial symptom in Buerger's disease. It is an intense pain caused by insufficient blood flow during exercise in feet and hands but it may even develop at rest in severe cases. It typically begins in extremities but it may also radiate to more central areas in advanced cases. Numbness or tingling of the limbs is also common. Raynaud's phenomenon may also be seen in which fingers or toes turn a white color upon exposure to cold. Skin ulcerations and gangrene of fingers or toes are the final consequences. Gangrene of fingertips may even need amputation. Unlike many other forms of vasculitis, Buerger's disease does not keep other organs with unknown reasons, yet. Similar to the venous ulcers, diabetic ulcers, leg ulcers of the SCD, digital clubbing, onychomycosis, and delayed wound and fracture healings of the lower extremities, pooling of blood due to the gravity may be important in the development of Buerger's disease, particularly in the lower extremities. Angiograms of upper and lower extremities are diagnostic for Buerger's disease. In angiogram, stenoses and occlusions in multiple areas of arms and legs are seen. In order to rule out some other forms of vasculitis by excluding involvement of vascular regions atypical for Buerger's disease, it is sometimes necessary to perform angiograms of other body regions. Skin biopsies are rarely required, since a biopsy site near a poorly perfused area will not heal, completely. Association of Buerger's disease with tobacco use, particularly cigarette smoking is clear. Although most patients are heavy smokers, some cases with limited smoking history have also been reported. The disease can also be seen in users of smokeless tobacco. The limited smoking history of some patients may support the hypothesis that Buerger's disease may be an autoimmune reaction triggered by some constituent of tobacco. Although the only treatment way is complete cessation of smoking, the already developed stenoses and occlusions are irreversible. Due to the clear evidence of inflammation in this disorder, anti-inflammatory dose of aspirin plus low-dose warfarin may probably be effective to prevent microvascular infarctions in fingers or toes at the moment. On the other hand, FPG and HDL may be negative whereas triglycerides, low density lipoproteins (LDL), erythrocyte sedimentation rate, and CRP may be positive acute phase reactants indicating such inflammatory effects of smoking on vascular endothelium (34). Similarly, it is not an unexpected result that smoking was associated with the lower values of BMI due to the systemic inflammatory effects on vascular endothelium (35). In another definition, smoking causes a chronic inflammation in human body (36). Additionally, some evidences revealed an increased heart rate just after smoking even at rest (37). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (38). According to an animal study, nicotine may lengthen intermeal time,

and decrease amount of meal eaten (39). Smoking may be associated with a postcessation weight gain, but the risk is the highest during the first year, and decreases with the following years (40). Although the CHD was detected with similar prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher prevalences of white coat hypertension, BMI, LDL, triglycerides, HT, and DM in females (41). Beside that the prevalence of myocardial infarction is increased three-fold in men and six-fold in women who smoked at least 20 cigarettes per day (42). In another word, smoking may be more dangerous for women about the atherosclerotic endpoints probably due to the higher BMI in them. Several toxic substances found in the cigarette smoke get into the circulation, and cause the vascular endothelial inflammation in various organ systems of the body. For example, smoking is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis in the literature (43). There may be several underlying mechanisms to explain these associations (44). First of all, smoking may have some antidepressant properties with several potentially lethal side effects. Secondly, smoking-induced vascular endothelial inflammation may disturb epithelial functions for absorption and excretion in the gastrointestinal and genitourinary tracts which may terminate with urolithiasis, loose stool, diarrhea, and constipation. Thirdly, diarrheal losses-induced urinary changes may even cause urolithiasis (45). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the gastrointestinal and genitourinary tracts terminating with the IBS and urolithiasis. Eventually, immunosuppression secondary to smoking-induced vascular endothelial inflammation may even terminate with the gastrointestinal and genitourinary tract infections causing loose stool, diarrhea, and urolithiasis, because some types of bacteria can provoke urinary supersaturation, and modify the environment to form crystal deposits in the urine. Actually, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infections with the bacteria producing urease. Parallel to the results above, urolithiasis was detected in 17.9% of cases with the IBS and 11.6% of cases without in the other study ($p<0.01$) (43).

CHD, together with the stroke, may be the terminal causes of death in every body with every disease for both sexes all over the world at the moment. The most common triggering event is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade. The plaque is a gradual and unstable collection of lipids, fibrous tissue, and white blood cells (WBC), particularly the macrophages in arterial wall in decades. Stretching and relaxation of arteries with each heart beat increases mechanical shear stress on atheromas to rupture. After the myocardial infarction, a collagen scar tissue forms in its place. This scar tissue may also cause potentially life threatening arrhythmias since the injured heart tissue conducts electrical impulses more slowly than the normal heart tissue. The difference in conduction velocity between the injured and uninjured tissue can trigger re-entry or a feedback loop that is believed to be cause of many lethal arrhythmias. Ventricular fibrillation is the most serious arrhythmia that is the leading cause of sudden cardiac death. It is an extremely fast and chaotic heart rhythm. Another life threatening arrhythmia is ventricular tachycardia that may also cause sudden cardiac death. Ventricular tachycardia usually results in rapid heart rates which prevent effective pumping. Cardiac output and BP may fall to dangerous levels which can lead to further coronary ischemia and extension of infarct. This scar tissue may even cause ventricular aneurysm, rupture, and sudden death. Physical inactivity, sedentary lifestyle, emotional stress, animal-rich diet, excess fat tissue, smoking, alcohol, chronic infection and inflammations, and cancers are important in atherosclerotic plaque formation in time. Physical inactivity is important since moderate physical exercise is associated with a 50% reduced incidence of CHD (46). Probably, excess fat tissue may be the most important cause of CHD. There are approximately 20 kg of excess fat tissue between the lower and upper borders of normal weight, 35 kg between the lower borders of normal weight and obesity, 66 kg between the lower borders of normal weight and morbid obesity (BMI ≥ 40 kg/m2), and 81 kg between the lower borders of normal weight and super obesity (BMI ≥ 45 kg/m2) in adults. In fact, there is a significant percentage of adults with a heavier fat mass than their organ plus muscle masses in their bodies. This excess fat tissue brings a heavy stress on liver, lungs, kidneys, brain, and of course on the heart.

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (6). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being, and increased prevalence of excess fat tissue all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it became the most common cause of chronic liver disease even at childhood, nowadays (47). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (47). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases (48). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (49). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCD (50). Probably smoking also takes role in the inflammatory process of the capillary endothelium in liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (39). Increased oxidative stress, inactivation of antiproteases, and release of proinflammatory mediators may terminate with the systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much

more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious or inflammatory processes and cancers may also terminate with an accelerated atherosclerosis in whole body (51). For instance, chronic hepatitis C virus (HCV) infection raised CIMT, and normalization of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (51, 52). As a result, cirrhosis may also be another atherosclerotic consequence of the SCD.

Acute painful crises are the most disabling symptoms of the SCD. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stress are the most common precipitating factors of the crises (53). The increased basal metabolic rate during such stresses aggravates the sickling, capillary endothelial damage, inflammation, edema, tissue hypoxia, and multiorgan insufficiencies. So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with the following crises by leaving significant sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with sudden multiorgan failures and death during a final acute painful crisis that may even be silent, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCD. Unfortunately, most of the deaths develop just after the hospital admission, and majority of them are patients without hydroxyurea therapy (54, 55). Rapid RBC supports are usually life-saving for such patients, although preparation of RBC units for transfusion usually takes time. Beside that RBC supports in emergencies become much more difficult in terminal cases due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBC complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBC transfusions should be kept just for acute events and emergencies in the SCD (54, 55). According to our experiences, simple and repeated transfusions are superior to RBC exchange in the SCD (56, 57). First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBC suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their relatives since RBC transfusions probably have the strongest analgesic effects during the crises (58). Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation all over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices. On the other hand, pain is the result of complex and poorly understood interactions between RBC, WBC, platelets (PLT), and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes is unknown. The adverse actions of WBC on endothelium are of particular interest with regard to the cerebrovascular diseases in the SCD. For example, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCD (59), and it was associated with the risk of stroke in a cohort of Jamaican patients (60). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Because of the severity of pain, narcotic analgesics are usually required to control them (61), but according to our practice, simple and repeated RBC transfusions may be highly effective both to relieve pain and to prevent sudden death that may develop secondary to multiorgan failures on the chronic inflammatory background of the SCD.

Hydroxyurea may be the only life-saving drug for the treatment of the SCD. It interferes with the cell division by blocking the formation of deoxyribonucleotides by means of inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the suppression of leukocytosis and thrombocytosis by blocking the DNA synthesis in the SCD (62, 63). By this way, the chronic inflammatory and destructive process of the SCD is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As in the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' own WBC and PLT. So suppression of proliferation of them may limit the endothelial damage-induced edema, ischemia, and infarctions in whole body (64). Similarly, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels (65). The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with the SCA, and compared the results of patients treated with hydroxyurea or placebo (66). The study particularly researched effects of hydroxyurea on painful crises, ACS, and requirement of blood transfusion. The outcomes were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was initiated for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations (66). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (66). But this study was performed just in severe SCA cases alone, and the rate of

painful crises was decreased from 4.5 to 2.5 per year (66). Whereas we used all subtypes of the SCD with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7 per year (p<0.000) with an additional decreased severity of them (7.8/10 vs 2.2/10, p<0.000) in the previous study (54). Parallel to our results, adult patients using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period (67). Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may also decrease severity of disease and prolong survival (67). The complications start to be seen even in infancy in the SCD. For example, infants with lower hemoglobin values were more likely to have a higher incidence of clinical events such as ACS, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them (68). Hydroxyurea therapy in early years of life may protect splenic function, improve growth, and prevent multiorgan insufficiencies. Blood transfusions can also reduce all of the complications, but carry many risks such as infections, iron overload, and development of allo-antibodies causing subsequent transfusions much more difficult.

Aspirin is a member of nonsteroidal anti-inflammatory drugs (NSAID) used to reduce pain, fever, inflammation, and acute thromboembolic events. Although aspirin has similar anti-inflammatory effects with the other NSAID, it also suppresses the normal functions of PLT, irreversibly. This property causes aspirin being different from other NSAID, which are reversible inhibitors. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin inactivates the COX enzyme, irreversibly, which is required for prostaglandins (PG) and thromboxanes (TX) synthesis. PG are the locally produced hormones with some diverse effects, including the transmission of pain into the brain and modulation of the hypothalamic thermostat and inflammation in the body. TX are responsible for the aggregation of PLT to form blood clots. In another definition, low-dose aspirin use irreversibly blocks the formation of TXA2 in the PLT, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLT (8-9 days). Since PLT do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin has inhibited the enzyme. The antithrombotic property of aspirin is useful to reduce the incidences of myocardial infarction, transient ischemic attack, and stroke (69). Heart attacks are caused primarily by blood clots, and low-dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction (70). According to the literature, aspirin may also be effective in prevention of colorectal cancers (71). On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Due to the risk of Reye syndrome, the US Food and Drug Administration recommends that aspirin or aspirin-containing products should not be prescribed for febrile patients under the age of 12 years (72). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (73). Reye syndrome is a rapidly worsening brain disease (73). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (74). The syndrome mostly affects children, but it can only affect fewer than one in a million children a year (74). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (73). Although the liver toxicity typically occurs in the syndrome, jaundice is usually not seen with it, but the liver is enlarged in most cases (73). Although the death occurs in 20-40% of affected cases, about one third of survivors get a significant degree of brain damage (73). The cause of Reye syndrome is unknown (74). It usually starts just after recovery from a viral infection, such as influenza or chicken pox. About 90% of cases in children are associated with an aspirin use (74, 75). Inborn errors of metabolism are also the other risk factors, and the genetic testing for inborn errors of metabolism became available in developed countries in the 1980s (73). When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% in rates of Reye syndrome was seen (74). Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling (74). Due to the very low risk of Reye syndrome but much higher risk of death, aspirin should be added both into the acute and chronic phase treatments with an anti-inflammatory dose in childhood in the SCD (76).

Warfarin is an anticoagulant, and first came into large-scale commercial use in 1948 as a rat poison. It was formally approved as a medication to treat blood clots in human being by the U.S. Food and Drug Administration in 1954. In 1955, warfarin's reputation as a safe and acceptable treatment was bolstred when President Dwight David Eisenhower was treated with warfarin following a massive and highly publicized heart attack. Eisenhower's treatment kickstarted a transformation in medicine whereby CHD, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. Warfarin is found in the List of Essential Medicines of WHO. In 2020, it was the 58th most commonly prescribed medication in the United States. It does not reduce blood viscosity but inhibits blood coagulation. Warfarin is used to decrease the tendency for thrombosis, and it can prevent formation of future blood clots and reduce the risk of embolism. Warfarin is the best suited for anticoagulation in areas of slowly running blood such as in veins and the pooled blood behind artificial and natural valves, and in blood pooled in dysfunctional cardiac atria. It is commonly used to prevent blood clots in the circulatory system such as DVT and pulmonary embolism, and to protect against stroke in people who have atrial fibrillation (AF), valvular heart disease, or artificial heart valves. Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery. The warfarin initiation regimens are simple, safe, and suitable to be used in ambulatory and in patient settings (77). Warfarin should be initiated with a

5 mg dose, or 2 to 4 mg in the very elderly. In the protocol of low-dose warfarin, the target international normalised ratio (INR) value is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR value is between 2.5 and 3.5 (78). When warfarin is used and INR is in therapeutic range, simple discontinuation of the drug for five days is usually enough to reverse the effect, and causes INR to drop below 1.5 (79). Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Blood products should not be routinely used to reverse warfarin overdose, when vitamin K1 could work alone. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticlotting protein C and protein S are also inhibited, but to a lesser degree. A few days are required for full effect to occur, and these effects can last for up to five days. The consensus agrees that patient self-testing and patient self-management are effective methods of monitoring oral anticoagulation therapy, providing outcomes at least as good as, and possibly better than, those achieved with an anticoagulation clinic. Currently available self-testing/self-management devices give INR results that are comparable with those obtained in laboratory testing. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is low with a yearly rate of 1-3% (80). All types of bleeding may occur, but the most severe ones are those involving the brain and spinal cord (79). The risk is particularly increased once the INR exceeds 4.5 (80). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (81). But thirteen publications from 11 cohorts including more than 48.500 total patients with more than 11.600 warfarin users were included in the meta-analysis (82). In patients with AF and non-end-stage CRD, warfarin resulted in a lower risk of ischemic stroke ($p= 0.004$) and mortality ($p<0.00001$), but had no effect on major bleeding ($p>0.05$) (82). Similarly, warfarin resumption is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (83). Death occured in 18.7% of patients who resumed warfarin and 32.3% who did not resume warfarin ($p= 0.009$) (83). Ischemic stroke occured in 3.5% of patients who resumed warfarin and 7.0% of patients who did not resume warfarin ($p= 0.002$) (83). Whereas recurrent ICH occured in 6.7% of patients who resumed warfarin and 7.7% of patients who did not resume warfarin without any significant difference in between ($p>0.05$) (83). On the other hand, patients with cerebral venous thrombosis (CVT) those were anticoagulated either with warfarin or dabigatran had low risk of recurrent venous thrombotic events (VTE), and the risk of bleeding was similar in both regimens, suggesting that both warfarin and dabigatran are safe and effective for preventing recurrent VTE in patients with CVT (84). Additionally, an INR value of about 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted in no increase in the number of men ever reporting minor bleeding episodes, although rectal bleeding occurs more frequently in those men who report this symptom (85). Non-rheumatic AF increases the risk of stroke, presumably from atrial thromboemboli, and long-term low-dose warfarin therapy is highly effective and safe in preventing stroke in such patients (86). There were just two strokes in the warfarin group (0.41% per year) as compared with 13 strokes in the control group (2.98% per year) with a reduction of 86% in the risk of stroke ($p= 0.0022$) (86). The mortality was markedly lower in the warfarin group, too ($p= 0.005$) (86). The warfarin group had a higher rate of minor hemorrhage (38 vs 21 patients) but the frequency of bleedings that required hospitalization or transfusion was the same in both group ($p>0.05$) (86). Additionally, very-low-dose warfarin was a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer (87). The warfarin dose was 1 mg daily for 6 weeks, and was adjusted to maintain the INR value of 1.3 to 1.9 (87). The average daily dose was 2.6 mg, and the mean INR was 1.5 (87). On the other hand, new oral anticoagulants had a favourable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding (88). Interestingly, rivaroxaban and low-dose apixaban were associated with increased risks of all cause mortality compared with warfarin (89). The mortality rate was 4.1% per year in the warfarin group, as compared with 3.7% per year with 110 mg of dabigatran and 3.6% per year with 150 mg of dabigatran ($p>0.05$ for both) in patients with AF in another study (90). On the other hand, infections, medical or surgical emergencies, or emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths in the SCD (91). So lifelong aspirin with an anti-inflammatory dose plus low-dose warfarin may be a life-saving treatment regimen even at childhood both to decrease severity of capillary endothelial inflammation and to prevent thromboembolic complications in the SCD (92).

COPD is the third leading cause of death with various underlying etiologies in whole world (93, 94). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, male gender, excess fat tissue, chronic inflammations, prolonged infections, and cancers may be the major underlying causes. Atherosclerotic effects of smoking may be the most obvious in the COPD and Buerger's disease, probably due to the higher concentrations of toxic substances in the lungs and pooling of blood in the extremities. After smoking, excess fat tissue may be the most significant cause of COPD all over the world due to the excess fat tissue-induced systemic atherosclerotic process in whole body. After smoking and excess fat tissue, regular alcohol consumption may be the third leading cause of the systemic accelerated atherosclerotic process and COPD, since COPD was one of the most common diagnoses in alcohol dependence (95). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (96). Probably an

accelerated atherosclerotic process is the main structural background of functional changes that are characteristics of the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may actually be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD (25, 97). For example, there may be close relationships between COPD, CHD, PAD, and stroke (98). Furthermore, two-third of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (99). When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again (99). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (100). On the other hand, COPD may be the pulmonary consequence of the systemic atherosclerotic process caused by the hardened RBC in the SCD (93).

Leg ulcers are seen in 10% to 20% of the SCD (101), and the ratio was 13.5% in the present study. Its prevalence increases with aging, male gender, and SCA (102). Similarly, its ratio was higher in males (19.8% vs 7.0%, p<0.001), and mean age of the leg ulcer cases was higher than the remaining patients (35.3 vs 29.8 years, p<0.000) in the present study. The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (101). Similar to Buerger's disease, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow (101). The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes (102). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC-induced venous insufficiencies may also accelerate the process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also be important for the development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood may be the cause of delayed wound and fracture healings in the lower extremities, again. Smoking and alcohol may also have some additional atherosclerotic effects on the leg ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCD (103). It is an orally-administered, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (11). Its main action may be the suppression of hyperproliferative WBC and PLT in the SCD (104). Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems in the SCD. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of tissue damage and pain (65). Prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBC and PLT counts-induced exaggerated capillary endothelial inflammation and edema instead of the terminal fibrosis alone.

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (105). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (106). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, and hepatic diseases and smoking which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect their functions in a short period of time. On the other hand, digital clubbing is also common in the SCD, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, p<0.001) may also show some additional role of male gender in the systemic atherosclerotic process.

CRD is also increasing all over the world that can also be explained by aging of the human being, and increased prevalence of excess weight all over the world (107). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, excess fat tissue, smoking, alcohol, inflammatory or infectious processes, and cancers may be the major causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts (108). Excess fat tissue-induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause tissue inflammation and immune cell activation (109). For example, age (p= 0.04), high-sensitivity CRP (p= 0.01), mean arterial BP (p= 0.003), and DM (p= 0.02) had significant correlations with the CIMT (107). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess fat tissue (110). Excess fat tissue also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (110).

However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (111). With prolonged excess fat tissue, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in cases with excess fat tissue, CRD progresses much more easily (110). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (112). Although some authors reported that alcohol was not related with the CRD (112), various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the renal vascular endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature (111). Although CRD is due to the atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (113, 114). For example, the most common cause of death was the cardiovascular diseases in the CRD again (115). The hardened RBC-induced capillary endothelial damage in the renal vasculature may be the main cause of CRD in the SCD. In another definition, CRD may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCD, again (116).

Stroke, together with the CHD, may be the terminal causes of death at the moment. Both of them develop as an acute thromboembolic event on the chronic atherosclerotic background in most of the cases. Aging, male gender, smoking, alcohol, excess fat tissue, chronic inflammations, prolonged infections, cancers, and emotional stresses may be the major accelerating causes of the systemic process. Stroke is also a common complication of the SCD (117). Similar to the leg ulcers, stroke is particularly higher in the SCA and cases with higher WBC counts (118). Sickling-induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial inflammation, edema, and fibrosis (119). Probably, stroke may not have a macrovascular origin in the SCD, and diffuse capillary endothelial inflammation, edema, and fibrosis may be much more important. Infections, inflammations, medical or surgical emergencies, and emotional stresses may precipitate stroke by increasing basal metabolic rate and sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed due to the increased WBC and PLT counts-induced exaggerated capillary inflammation and edema (120).

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder of hemostasis characterized by low PLT counts in the absence of other causes. Depending on which age group is affected, ITP causes two distinct clinical syndromes: an acute form (resolving within two months) observed in children and a chronic form (persisting for longer than six months) in adults. Nevertheless, the pathogenesis of ITP is similar in both syndromes involving antibodies against various PLT surface antigens. Impaired production of the glycoprotein hormone, thrombopoietin, which is the stimulant for PLT production, may also be a contributing factor to the reduction of circulating PLT. The stimulus for auto-antibody production in ITP is probably abnormal T cell activity. Preliminary findings suggest that these T cells can be influenced by medications that target B cells, such as rituximab. Signs of ITP include the spontaneous formation of purpura and petechiae, particularly on extremities. In cases where PLT counts drop to extremely low levels (less than 5.000 per microliter), serious and potentially fatal complications including subarachnoid or intracerebral hemorrhage may arise. In general, patients with ITP will rarely have life-threatening bleedings and the long-term prognosis of ITP is benign even in refractory cases (121). Most patients ultimately have lower, but stable PLT counts, which are still hemostatic for the patients (122). With rare exceptions, there is usually no need to treat based on PLT counts in ITP. PLT which have been found by antibodies are taken up by macrophages in the spleen, and so removal of the spleen reduces PLT destruction. Even though there is a consensus regarding the short-term efficacy of splenectomy, findings on its long-term efficacy and side-effects are controversial (123). Durable remission following splenectomy is achieved just in 60-80% of ITP cases (124). Additionally, this procedure is potentially risky due to increased risks of infections in the future due to the asplenism. The male to female ratio in the adult group varies from 1:1.2 to 1.7 in most age ranges and the median age of adults at the diagnosis is 56-60 years (125). Although, it was reported that ITP causes an approximately 60% higher rate of mortality compared to sex-and age-matched subjects without ITP, and 96% of reported ITP-related deaths were patients with the ages of 45 years and higher (126), we have just seen two mortile cases due to chronic ITP in our 25 years of experience up to now.

As a conclusion, hardened RBC-induced capillary endothelial damage initiating at birth terminates with multiorgan failures in much earlier ages in the SCD. Excess fat tissue may be much more important than smoking and alcohol for atherosclerosis, and CHD and stroke may be the terminal causes of death in both genders at the moment. Although the possibility of some severe bleedings in rare cases, we have just seen two mortile cases due to the chronic ITP in our 25 years of experience. Due to the well-known roles of PLT during the terminal atherosclerotic consequences, chronic ITP may even prolong the survival in human being in general.

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Prevalence of celiac disease among Type 1 diabetes mellitus in Diabetic center of Tabuk City, Saudi Arabia 2024: a cross sectional retrospective medical record-based study

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Abstract

Background: Celiac disease (CD) is an autoimmune enteropathy triggered by gluten ingestion in genetically susceptible individuals. It is frequently associated with other autoimmune conditions, particularly type 1 diabetes mellitus (T1DM). Early identification of CD in T1DM patients is essential to prevent complications and improve outcomes.

Objective: To determine the prevalence of celiac disease among patients with T1DM at the Diabetic Center in Tabuk City, Saudi Arabia, and to identify associated risk factors, common symptoms, and diagnostic patterns.

Methods: A cross-sectional, retrospective study was conducted based on medical records of 373 patients with T1DM attending the Diabetic Center of King Fahad Hospital in Tabuk City between May and August 2024. Data were collected using a structured and validated form covering demographic, clinical, and diagnostic details. Statistical analysis was performed using SPSS version 18, with descriptive statistics and inferential tests including Fisher's Exact Test, t-tests, and ANOVA. A p-value < 0.05 was considered statistically significant.

Results: The prevalence of diagnosed celiac disease among T1DM patients was 2.4% (n=9). All cases were diagnosed using anti-tTG antibodies, and common presenting symptoms included abdominal pain (44.4%) and diarrhea (33.3%). A significant association was found between CD and being underweight ($p = 0.049$). Other variables such as age, gender, insulin dosage, and DKA frequency showed no significant correlation with CD. However, males and patients diagnosed with T1DM at an older age were found to have a significantly later diagnosis of CD ($p = 0.001$).

Conclusion: Celiac disease is relatively uncommon but clinically relevant among T1DM patients in Tabuk City. Underweight status may serve as a useful clinical indicator for CD screening. Given the variable presentation of CD, universal screening in T1DM patients remains important for early diagnosis and management.

Keywords
Celiac disease, Type 1 diabetes mellitus, Prevalence, Risk factors, Saudi Arabia, Gluten, Anti-tTG antibodies.

Introduction

Celiac disease [CD] is an immune-mediated systemic disorder triggered by the ingestion of gluten a protein found in wheat, rye, and barley in genetically susceptible individuals [1]. It involves both intestinal and extra intestinal manifestations, with hallmark features including small intestinal mucosal injury, malabsorption, and specific serologic autoantibodies such as anti-tissue transglutaminase [anti-tTG] [2]. Clinically, CD can present with classical gastrointestinal symptoms like diarrhea and weight loss or with non-classical features such as anemia, delayed puberty, and fatigue [3].

Diagnosis of CD requires a combination of clinical assessment, serologic testing, and confirmation by duodenal biopsy [4]. A positive anti-tTG test followed by evidence of villous atrophy is considered diagnostic. In selected cases, HLA typing for DQ2 or DQ8 may support the diagnosis [5]. Effective treatment consists of lifelong adherence to a strict gluten-free diet [GFD], which typically leads to symptom resolution, histological improvement, and normalization of antibody levels [6]. However, GFD poses challenges such as nutritional deficiencies, psychological burdens, and increased costs, making routine dietary counseling essential [7].

Delayed diagnosis of CD may elevate the risk of certain malignancies, including lymphoma, though recent studies suggest a potentially reduced risk for colorectal cancer, possibly due to altered fat metabolism [8]. Immunologically, CD shares characteristics with autoimmune diseases like type 1 diabetes mellitus [T1DM], including HLA associations and autoantibody production [9].

T1DM is a prevalent autoimmune endocrine disorder in children and adolescents, characterized by insulin deficiency due to autoimmune destruction of pancreatic β-cells [10]. It typically presents in youth and requires lifelong insulin therapy. Despite advancements in diabetes care such as insulin pumps and continuous glucose monitoring T1DM is still associated with reduced life expectancy and serious long-term complications. In Saudi Arabia, the prevalence of T1DM has risen markedly, particularly among younger age groups, consistent with global trends in autoimmune disorders [11]. The current study aimed to measure prevalence of celiac disease among individuals with type 1 diabetes mellitus in a Diabetic center of Tabuk City.

Methodology

A cross-sectional, retrospective medical record-based study was conducted to assess the prevalence of celiac disease [CD] among individuals with type 1 diabetes mellitus [T1DM] attending the Diabetic Center of King Fahad Hospital in Tabuk City, Saudi Arabia. The center provides comprehensive diabetic services, including routine clinical care, health education, diabetic foot care, and retinopathy screening. The study population included all registered patients diagnosed with T1DM in the center. A total population of 12,460 T1DM patients was identified, and the minimum required sample size was calculated to be 373 patients, using a 95% confidence level, 5% margin of error, and assuming a prevalence of 50%. The finite population formula was applied for this calculation. All patients with a confirmed diagnosis of type 1 diabetes who were receiving care at the Diabetic Center were eligible for inclusion. Records not meeting these inclusion criteria were excluded. Data were collected retrospectively over a three-month period, from May 2024 to August 2024.

Patient data were extracted from medical records using a previously validated data collection form. The tool was structured into three main sections. The first section included socio-demographic data such as age, gender, weight, and height. The second section focused on diabetes-related clinical information, including age at T1DM diagnosis, diagnostic methods, total daily insulin dose, and frequency of diabetic ketoacidosis [DKA] episodes. The third section addressed information on celiac disease, including diagnostic methods [anti-tissue transglutaminase [anti-tTG] antibodies or endoscopic biopsy], age at CD diagnosis, and presenting symptoms and signs.

Data Analysis

The collected data were coded, entered, and statistically analyzed using the Statistical Package for the Social Sciences [SPSS] software, version 18 [SPSS Inc., Chicago, IL, USA]. Descriptive statistics were used to summarize the bio-demographic and clinical characteristics of the study participants. Frequencies and numbers were presented for categorical variables, while means and standard deviations were calculated for continuous variables. To explore associations between categorical variables, such as the presence of celiac disease and other demographic or clinical factors, the exact probability test [Fisher's Exact Test] was applied when appropriate, particularly in the presence of small cell counts. For comparisons involving continuous variables, such as age at celiac disease diagnosis across different patient subgroups, independent samples t-tests were used when comparing two groups and one-way analysis of variance [ANOVA] was used when comparing more than two groups. A p-value of less than 0.05 was considered statistically significant in all analyses.

Results

The study included 373 patients with type 1 diabetes attending the diabetic center in Tabuk City, Saudi Arabia. The majority were adolescents and young adults, with 50.7% aged 15–30 years [n=189], and 49.3% aged 0–14 years [n=184]. Females constituted a slightly higher proportion than males, accounting for 53.4% [n=199] and 46.6% [n=174], respectively. Most participants had a body weight of less than 50 kg [81.8%, n=305] and a height of less than 150 cm [79.6%, n=297]. Regarding BMI, 46.1% [n=172] were underweight, 38.6% [n=144] had normal weight, while 12.9% [n=48] were obese and only 2.4% [n=9] were overweight. The most common age at diagnosis was 10–12 years [42.9%, n=160], with a mean age of diagnosis of 12.6 ± 3.0 years. In terms of insulin therapy, more than half of the patients [51.2%, n=191] used less than 20 international units daily, with an average dose of 22.6 ± 13.4 IU. Diabetic ketoacidosis [DKA] was reported at least once in all participants, with 50.7% [n=189] experiencing it once, 25.7% [n=96] twice, and 18.0% [n=67] three times. A smaller proportion had four [2.9%, n=11] or five [2.7%, n=10] DKA episodes.

Figure 1 illustrates the prevalence of celiac disease among patients with type 1 diabetes mellitus at the Diabetic Center in Tabuk City, Saudi Arabia, in 2024. Out of 373 patients, only 9 [2.4%] were known cases of celiac disease, while the vast majority, 364 patients [97.6%], had no history of the condition.

Figure 1. The Prevalence of celiac disease among Type 1 diabetes mellitus in Diabetic center of Tabuk City, Saudi Arabia 2024 (N=373)

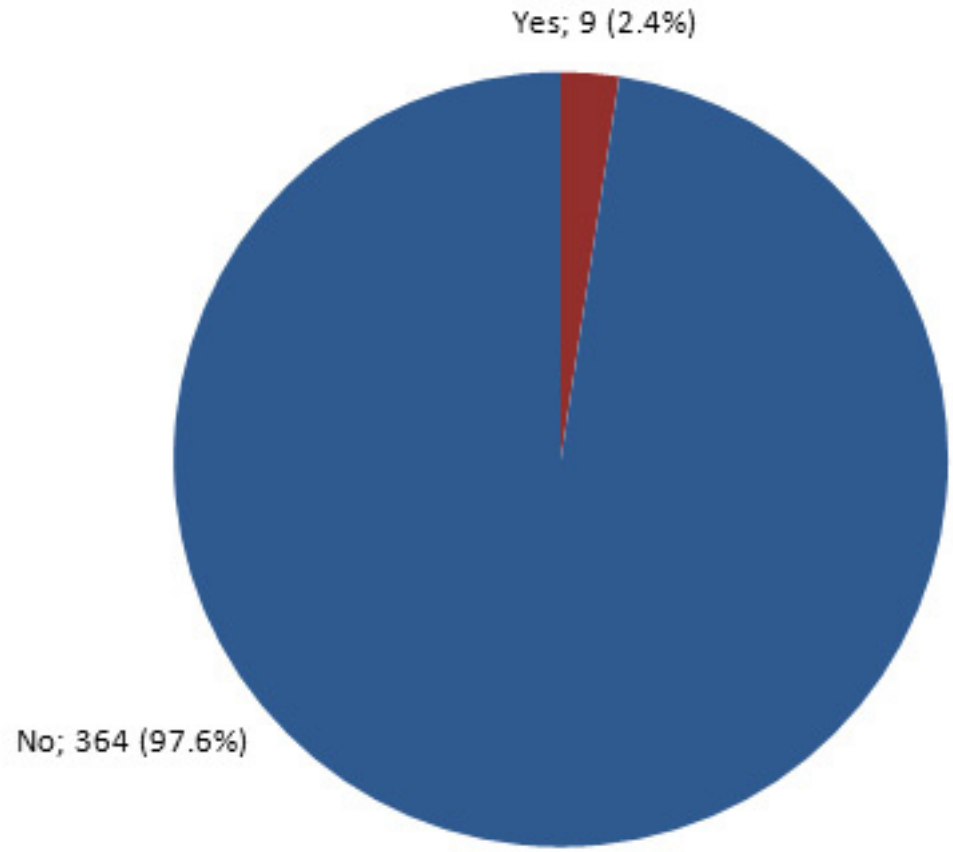

Table 1. Bio-Demographic Characteristics of Type 1 Diabetic Patients in Diabetic center of Tabuk City, Saudi Arabia 2024 (N=373)

Bio-demographics	No	%
Age in years		
0-14	184	49.3%
15-30	189	50.7%
Gender		
Male	174	46.6%
Female	199	53.4%
Weight in Kg		
< 50 Kg	305	81.8%
> 50 Kg	68	18.2%
Height in cm		
< 150 cm	297	79.6%
> 150 cm	76	20.4%
Body mass index		
Underweight	172	46.1%
Normal weight	144	38.6%
Overweight	9	2.4%
Obese	48	12.9%
Age of type 1 diabetes mellitus diagnosis		
7-9 years old	63	16.9%
10-12 years old	160	42.9%
13-16 years old	98	26.3%
17-18 years old	52	13.9%
Mean ± SD	12.6 ± 3.0	
Total daily insulin Doses		
< 20 iu	191	51.2%
20-30 iu	124	33.2%
> 30 iu	58	15.5%
Mean ± SD	22.6 ± 13.4	
Frequency of DKA		
1 time	189	50.7%
2 times	96	25.7%
3 times	67	18.0%
4 times	11	2.9%
5 times	10	2.7%

Table 2 presents the clinical and diagnostic characteristics of the 9 patients with type 1 diabetes mellitus who were also diagnosed with celiac disease at the Diabetic Center in Tabuk City. The age at diagnosis varied, with the majority being diagnosed at 12 and 17 years [33.3% each], followed by 10 years [22.2%] and 18 years [11.1%]. Regarding presenting symptoms, abdominal cramping or pain was the most commonly reported [44.4%], followed by diarrhea [33.3%] and bloating [22.2%]. Notably, all patients were reported to be in a "well" physical condition at the time of diagnosis [100%]. Glycemic control, as reflected by HbA1c levels at the time of celiac disease diagnosis, ranged from 7.0% to 8.0%, with most patients falling between 7.0% and 7.3%. Serological testing using anti-tTG antibodies were utilized in all cases for diagnosis [100%].

Table 2. Clinical and Diagnostic Characteristics of Type 1 Diabetic Patients Diagnosed with Celiac Disease at the Diabetic Center of Tabuk City, Saudi Arabia (N=9)

Items	No	%
Age diagnosis of celiac disease		
10 years	2	22.2%
12 years	3	33.3%
17 years	3	33.3%
18 years	1	11.1%
Celiac disease symptoms at time of diagnosis		
Abdominal Cramping / pain	4	44.4%
Bloating	2	22.2%
Diarrhea	3	33.3%
Physical examination at time of diagnosis		
Well	9	100.0%
HGA1C at time of celiac disease diagnosis:		
7.0%	2	22.2%
7.10%	3	33.3%
7.3%	3	33.3%
8.0%	1	11.1%
Diagnostic tests used for celiac disease		
anti-tTG	9	100.0%
Other autoimmune diseases		
No	9	100.0%

Table 3 explores the factors associated with the presence of celiac disease among patients with type 1 diabetes mellitus at the Diabetic Center in Tabuk City. Overall, none of the demographic or clinical variables showed statistically significant associations with celiac disease, except for body mass index [BMI], which demonstrated a significant relationship [p = 0.049]. Among underweight patients, 4.7% had celiac disease compared to 0% in the normal weight and overweight groups, and 2.1% in the obese group. Other factors, including age group [p = 0.705], gender [p = 0.893], weight [p = 0.575], and height [p = 0.485], did not show statistically significant associations. For example, 2.7% of children aged 0–14 years and 2.1% of those aged 15–30 years had celiac disease. Males and females had similar prevalence rates [2.3% vs. 2.5%, respectively]. Likewise, no significant associations were found between celiac disease and age at diabetes diagnosis [p = 0.226], daily insulin dose [p = 0.094], or frequency of diabetic ketoacidosis [DKA] episodes [p = 0.215], though higher celiac prevalence was observed among those who had experienced DKA three times [6.0%].

Table 3. Factors Associated With Celiac Disease among Type 1 Diabetic Patients Diagnosed with Celiac Disease at the Diabetic Center of Tabuk City, Saudi Arabia (N=9).

Factors	Patient known case of celiac?				p-value
	Yes		No		
	No	%	No	%	
Age in years					
0-14	5	2.7%	179	97.3%	.705
15-30	4	2.1%	185	97.9%	
Gender					
Male	4	2.3%	170	97.7%	.893
Female	5	2.5%	194	97.5%	
Weight in Kg					
< 50 Kg	8	2.6%	297	97.4%	.575
> 50 Kg	1	1.5%	67	98.5%	
Height in cm					
< 150 cm	8	2.7%	289	97.3%	.485
> 150 cm	1	1.3%	75	98.7%	
Body mass index					
Underweight	8	4.7%	164	95.3%	
Normal weight	0	0.0%	144	100.0%	.049*
Overweight	0	0.0%	9	100.0%	
Obese	1	2.1%	47	97.9%	
Age of type1 diabetes mellitus diagnosis					
7-9 years old	0	0.0%	63	100.0%	.226
10-12 years old	5	3.1%	155	96.9%	
13-16 years old	4	4.1%	94	95.9%	
17-18 years old	0	0.0%	52	100.0%	
Total daily insulin Doses					
< 20 iu	2	1.0%	189	99.0%	.094
20-30 iu	6	4.8%	118	95.2%	
> 30 iu	1	1.7%	57	98.3%	
Frequency of DKA					
1 time	2	1.1%	187	98.9%	
2 times	3	3.1%	93	96.9%	.215
3 times	4	6.0%	63	94.0%	
4 times	0	0.0%	11	100.0%	
5 times	0	0.0%	10	100.0%	

P: Exact probability test
* P < 0.05 (significant)

Table 4 presents the distribution of the age at celiac disease diagnosis among type 1 diabetic patients according to various bio-demographic and clinical factors [n=9]. The results show statistically significant associations between age of celiac diagnosis and both gender [p = 0.001] and age at type 1 diabetes mellitus [T1DM] diagnosis [p = 0.001]. Males were diagnosed with celiac disease at a significantly older age [mean = 17.3 ± 0.5 years] compared to females [mean = 11.2 ± 1.1 years]. Similarly, patients who were diagnosed with T1DM at ages 13–16 were found to have a later celiac diagnosis [mean = 17.3 ± 0.5 years] compared to those diagnosed with T1DM at 10–12 years [mean = 11.2 ± 1.1 years].

Other factors, such as BMI [p = 0.204], total daily insulin dose [p = 0.080], and frequency of DKA [p = 0.069], did not reach statistical significance, although trends were noted. Underweight patients were diagnosed with celiac disease at a mean age of 13.4 years, while obese patients were diagnosed later at 18.0 years. Similarly, patients using >30 IU insulin daily or experiencing three DKA episodes also tended to receive a later diagnosis [18.0 and 17.3 years, respectively].

Table 4. Distribution of age of celiac diseases diagnosis by type 1 diabetic patients bi-demographic characteristics (n=9)

Factors	Age diagnosis of celiac disease		p-value
	Mean	SD	
Gender			
Male	17.3	0.5	.001*#
Female	11.2	1.1	
Body mass index			
Underweight	13.4	3.1	.204#
Obese	18.0	0.0	
Age of type1 diabetes mellitus diagnosis			
10-12 years old	11.2	1.1	.001*#
13-16 years old	17.3	0.5	
Total daily insulin Doses			
< 20 iu	10.0	0.0	.080
20-30 iu	14.5	2.7	
> 30 iu	18.0	0.0	
Frequency of DKA			
1 time	10.0	0.0	.069
2 times	12.0	0.0	
3 times	17.3	0.5	

P: One-Way ANOVA # Independent samples t-test* P < 0.05 (significant)

Discussion

The study assessed 373 patients with type 1 diabetes at a diabetic center in Tabuk City, Saudi Arabia. Most were adolescents and young adults, with nearly equal numbers between ages 0–14 and 15–30. Slightly more females than males were included. The majority had a low body weight and short height, and almost half were underweight, while only a small portion was overweight or obese. Most were diagnosed around ages 10–12, with the average age of diagnosis being around 12–13 years.

When it came to insulin use, over half took less than 20 units per day. All patients had experienced diabetic ketoacidosis [DKA] at least once, with many having one to three episodes, and a few having up to five.

The high rate of DKA across all patients highlights how common this serious complication is, possibly pointing to difficulties in diabetes control or delayed diagnosis. The insulin doses used were relatively low, which might reflect the younger age and lower body weight of the group. The finding that over half of the patients used less than 20 units of insulin daily aligns with studies on type 1 diabetes in younger populations, where lower insulin requirements are common due to lower body weight and residual beta-cell function in early disease stages [12]. However, the average dose [22.6 ± 13.4 IU] appears slightly lower than reported in some Western cohorts, possibly due to differences in body composition or dietary habits [13]. The universal history of DKA in this study contrasts with global data, where DKA rates at diagnosis vary widely [20–70%] but are not universally present in all patients [14]. The high recurrence of DKA [up to five episodes in some cases] reflects challenges in diabetes management, consistent with studies from regions with limited access to continuous glucose monitoring or insulin pumps [15]. Similar patterns of frequent DKA episodes have been reported in other Middle Eastern populations, possibly due to delayed diagnosis or socioeconomic barriers to optimal care [16].
With regard to celiac disease prevalence, our study found that 2.4% of type 1 diabetes [T1DM] patients at the Diabetic Center in Tabuk City had a confirmed diagnosis of celiac disease [CD]. This prevalence is substantially lower than global and regional estimates. A large meta-analysis by Elfström et al. [2014] involving 26,605 T1DM patients across multiple countries reported a pooled CD prevalence of 6.0%, with higher rates in Europe compared to North America and Asia [17]. This suggests that our observed prevalence in Tabuk is below the global average, possibly due to regional genetic differences, lower screening rates, or environmental factors such as dietary habits.

However, studies from Saudi Arabia generally report much higher CD prevalence in T1DM patients than our findings. For instance, Aljulifi et al. [2021] found that 11.5% of T1DM patients in Riyadh were seropositive for CD, though only 2.4% had biopsy-confirmed disease [18]. Similarly, Saadah et al. [2012] reported 21.2% seropositivity and 11.2% biopsy-proven CD in Jeddah, indicating that the western region of Saudi Arabia may have particularly high CD-T1DM overlaps [19]. A national meta-analysis by Safi et al. [2018] estimated a 12.0% biopsy-confirmed CD prevalence among Saudi T1DM patients double the global average [20]. Even in southwestern Saudi Arabia [Aseer region], Al-Hakami [2014] found that 10.4% of T1DM patients had CD [21].

The lower prevalence in Tabuk could be attributed to several factors including underdiagnosis due to limited screening: If CD testing was not routine, asymptomatic cases may have been missed and regional variations; Genetic susceptibility or dietary gluten exposure, may differ across Saudi Arabia. Also, there may be Methodological differences as some studies relied on serological screening [which overestimates prevalence], whereas our study only included previously diagnosed cases.

Our study also found that most demographic and clinical factors were not significantly associated with celiac disease (CD) among patients with type 1 diabetes mellitus (T1DM), except for body mass index (BMI), where underweight patients had a significantly higher prevalence of CD ($p = 0.049$). Although other variables like age, gender, and DKA frequency showed no significant associations, a higher CD rate was noted in those with recurrent DKA. The limited number of CD cases (n = 9) may have influenced the statistical outcomes. These findings highlight BMI as a potential clinical indicator for CD screening, though broader screening remains important due to the variable presentation of CD in T1DM patients.

Conclusion and Recommendations

In conclusion, this study found that the prevalence of celiac disease (CD) among patients with type 1 diabetes mellitus (T1DM) in the Diabetic Center of Tabuk City was relatively low (2.4%). Most patients were adolescents and young adults, with nearly half being underweight. While most demographic and clinical factors were not significantly linked to CD, being underweight was a notable exception and was significantly associated with a higher likelihood of having CD. Additionally, males and those diagnosed with T1DM at an older age tended to receive a later CD diagnosis. Based on these findings, we recommend maintaining routine screening for celiac disease in all patients with T1DM, especially those who are underweight or have recurrent DKA episodes. Early detection through serological testing such as anti-tTG remains crucial to prevent long-term complications. Clinicians should also be aware of the variable symptoms of CD and consider it even in well-appearing patients.

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Prevalence of sleep disorders among primary healthcare physicians in Tabuk City, Saudi Arabia 2024

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Abstract

Background: Sleep disorders are highly prevalent among healthcare professionals and are linked to occupational stressors, irregular work hours, and poor lifestyle habits. Understanding sleep quality and its risk factors in primary healthcare physicians is critical for improving physician well-being and patient care quality.

Objectives: To assess the prevalence of poor sleep hygiene and excessive daytime sleepiness among primary healthcare physicians in Tabuk City, Saudi Arabia, and to identify associated demographic, occupational, and behavioral risk factors.

Methods: A cross-sectional study was conducted in 2024 among 146 primary healthcare physicians in Tabuk using a structured online questionnaire. Data were collected on sociodemographic and occupational characteristics, the Epworth Sleepiness Scale (ESS) for daytime sleepiness, and the Pittsburgh Sleep Quality Index (PSQI) for sleep hygiene. Descriptive statistics, Chi-square tests, and Fisher's exact tests were performed using SPSS version 28. A p-value < 0.05 was considered statistically significant.

Results: A total of 59.6% of physicians were classified as poor sleepers (PSQI score >7), and 93.8% reported some level of excessive daytime sleepiness. Moderate to severe sleepiness was significantly more common among poor sleepers (p = 0.001). Significant risk factors for poor sleep hygiene included age 26–45 years (p = 0.001), working more than 40 hours/week (p = 0.001), smoking (p = 0.028), night shifts (p = 0.001), staying awake more than 19 hours (p = 0.004), sleeping less than 6 hours in 24 hours (p = 0.031), and lack of sufficient rest breaks and consecutive days off (p < 0.05). Marital status and total rest time per day were not significantly associated with sleep hygiene.

Conclusion: Poor sleep hygiene and daytime sleepiness are prevalent among primary healthcare physicians in Tabuk. These outcomes are strongly influenced by modifiable work-related factors. Institutional interventions, such as optimizing shift schedules, ensuring adequate rest, and promoting sleep health are urgently needed to safeguard physician well-being and healthcare quality.

Keywords
Sleep hygiene, Daytime sleepiness, Primary healthcare physicians, Saudi Arabia

Introduction

Sleep disorders represent a group of conditions that disrupt the quality, timing, and duration of sleep, with profound effects on health, safety, and overall quality of life [1, 2]. These disorders are widely prevalent and are associated with considerable morbidity across different populations [3, 4]. Among healthcare professionals, especially primary healthcare physicians, the risk of sleep disturbances may be heightened due to occupational factors such as irregular work schedules, extended working hours, and the emotional burden of patient care [5, 6]. In the context of Saudi Arabia's rapidly evolving healthcare system, investigating the prevalence and determinants of sleep disorders among primary care physicians is vital for promoting physician well-being and ensuring the consistent delivery of high-quality healthcare services [7, 8].

Specific types of sleep disorders, including insomnia, obstructive sleep apnea, and shift work sleep disorder, have been found to impair both cognitive performance and physical functioning [9]. Insomnia, often characterized by difficulties initiating or maintaining sleep, is frequently observed in physicians, likely as a result of work-related stress and nontraditional working hours [10]. Obstructive sleep apnea, which involves repeated upper airway obstructions during sleep, may be more prevalent in this population due to risk factors such as a sedentary lifestyle and elevated body mass index [11]. Additionally, shift work sleep disorder, a condition caused by chronic misalignment between a person's circadian rhythm and their work schedule is particularly relevant for physicians involved in night or rotating shifts [12, 13].

Although global studies have demonstrated high rates of sleep disturbances among healthcare workers [8], region-specific data from Saudi Arabia remain scarce especially in the context of primary healthcare physicians practicing in Tabuk. This professional group faces not only intense job demands but also cultural and environmental influences unique to the region, underscoring the need for focused research. Understanding the prevalence and associated risk factors of sleep disorders in this group is essential for several reasons. First, it provides the foundation for developing targeted interventions aimed at improving sleep health, such as work schedule modifications, stress reduction programs, and educational initiatives to promote sleep hygiene. Second, identifying socio-demographic and occupational predictors such as age, marital status, smoking, and extended working hours can inform preventative strategies. Lastly, enhancing sleep health among physicians is closely linked to improved well-being, increased job satisfaction, and better patient care outcomes.

Methodology

This study adopted a cross-sectional design to assess the prevalence and risk factors associated with sleep disorders among primary healthcare physicians in Tabuk City, Saudi Arabia. Tabuk, located in the northwestern region of the country, has a growing healthcare system with numerous primary healthcare centers that serve as frontline units for patient care. These centers are staffed by primary healthcare physicians, who were the focus of this research due to their exposure to occupational stressors that may influence sleep patterns. The study population consisted of primary healthcare physicians actively practicing in various primary healthcare centers within Tabuk during the year 2024. Inclusion criteria required participants to be residents of Tabuk City and willing to complete the study questionnaire. Physicians who met these criteria were invited to participate through a structured online survey. A sample size of 146 physicians was determined using a standard formula for prevalence studies, taking into account the population size, an acceptable margin of error, and a confidence level represented by the Z-score. This sample size was selected to ensure statistical adequacy while remaining feasible within the study's time and resource constraints.

Data collection was carried out using a structured online questionnaire, which was disseminated to eligible participants via email. The questionnaire was divided into three key sections. The first section collected sociodemographic data, including age, marital status, work hours, and smoking habits. The second section included the Epworth Sleepiness Scale (ESS)*, a validated tool composed of 8 items rated from 0 to 3. The total score ranges from 0 to 24, and the scale categorizes daytime sleepiness as follows: 0–5 (normal), 6–10 (higher normal), 11–12 (mild), 13–15 (moderate), and 16–24 (severe) excessive daytime sleepiness [1]. The third section included the Pittsburgh Sleep Quality Index (PSQI)** – Arabic version – which assesses sleep quality over the past month using 19 items across seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each component is scored from 0 to 3, with a global score >7 indicating poor sleep quality and ≤7 indicating good sleep quality [2]. The questionnaire link was distributed via email, accompanied by a brief explanation of the study's objectives and significance. Informed consent was obtained electronically before participants proceeded with the survey. To maximize participation, reminder emails were sent periodically throughout the data collection period. All data were collected anonymously to maintain confidentiality and ensure ethical compliance.

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Data Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the socio-demographic characteristics and key variables. Frequencies and percentages were calculated for categorical variables, while means and standard deviations were used to describe continuous variables such as PSQI scores. To examine associations between sleep hygiene status (categorized as good or poor) and various socio-demographic and occupational factors, as well as sleep characteristics, Pearson's Chi-square (χ^2) test was employed for categorical variables. When the expected cell counts were less than 5, Fisher's exact test (denoted in tables as Exact probability test) was applied to ensure statistical validity. A p-value less than 0.05 was considered statistically significant.

Results

The socio-demographic profile of the 146 primary healthcare physicians in Tabuk City in 2024 was obtained. Considering age distribution, the majority of participants (108 physicians, 74.0%) were between 26 and 45 years old, followed by 33 physicians (22.6%) aged 18–25 years and only 5 participants (3.4%) aged 46–60 years. Regarding marital status, the majority were unmarried (123, 84.2%), while only 23 (15.8%) were married. Concerning working hours per week, most physicians (103, 70.5%) reported working less than 40 hours, whereas 43 (29.5%) worked more than 40 hours weekly. As for smoking habits, only a small proportion of the participants were smokers (18, 12.3%), with the majority being non-smokers (128, 87.7%).

Table 1. Socio-Demographic Characteristics of the Studied Primary Healthcare Physicians in Tabuk City, Saudi Arabia 2024 (N=146)

Socio-demographics	No	%
Age in years		
18-25 year	33	22.6%
26-45 year	108	74.0%
46-60 year	5	3.4%
Marital status		
Unmarried	123	84.2%
Married	23	15.8%
How many hours do you work per week?		
Less than 40 hours	103	70.5%
More than 40 hours	43	29.5%
Smoking		
Yes	18	12.3%
No	128	87.7%

Table 2 shows the Epworth Sleepiness Scale among the 146 primary healthcare physicians in Tabuk City and provides insights into their levels of daytime sleepiness across various situations. Exactly 68.4% reported a moderate or high chance of dozing while sitting and reading, and 73.3% reported similar levels while watching television, indicating substantial levels of sleepiness during passive activities. Additionally, 82.2% indicated at least a slight chance of dozing as a passenger in a car for an hour without a break. In more socially engaging or active contexts, like sitting and talking to someone, only 20.5% reported a moderate or high chance of dozing. However, 64.4% of participants reported a moderate to high chance of dozing after lunch while sitting quietly, which is a known time of increased physiological sleep drive.

Table 2. Distribution of Epworth Sleepiness Scale Responses among Primary Healthcare Physicians in Tabuk City, Saudi Arabia (N = 146)

Epworth sleepiness scale	Would never doze		Slight chance of dozing		Moderate chance of dozing		High chance of dozing	
	No	%	No	%	No	%	No	%
Sitting and reading	9	6.2%	37	25.3%	83	56.8%	17	11.6%
Watching television	8	5.5%	31	21.2%	76	52.1%	31	21.2%
Sitting inactive in public place as meeting	16	11.0%	67	45.9%	50	34.2%	13	8.9%
As passenger in a car for an hour without break	17	11.6%	90	61.6%	27	18.5%	12	8.2%
Lying down to rest in the afternoon	9	6.2%	34	23.3%	85	58.2%	18	12.3%
Sitting and talking to some one	15	10.3%	101	69.2%	20	13.7%	10	6.8%
Sitting quietly after lunch	9	6.2%	43	29.5%	59	40.4%	35	24.0%
In a car while stopped in traffic	33	22.6%	77	52.7%	26	17.8%	10	6.8%

Figure 1 presents the overall prevalence of daytime sleepiness among primary healthcare physicians in Tabuk City (N = 146). The majority of participants (137 physicians, 93.8%) reported experiencing some level of excessive daytime sleepiness. Specifically, 57 physicians (39.0%) had mild excessive daytime sleepiness, 45 (30.8%) experienced moderate, and 35 (24.0%) had severe excessive daytime sleepiness. In contrast, only 9 physicians (6.2%) exhibited normal daytime sleepiness.

Figure 1. The Overall Prevalence of Daytime Sleepiness among Primary Healthcare Physicians in Tabuk City, Saudi Arabia (N = 146)

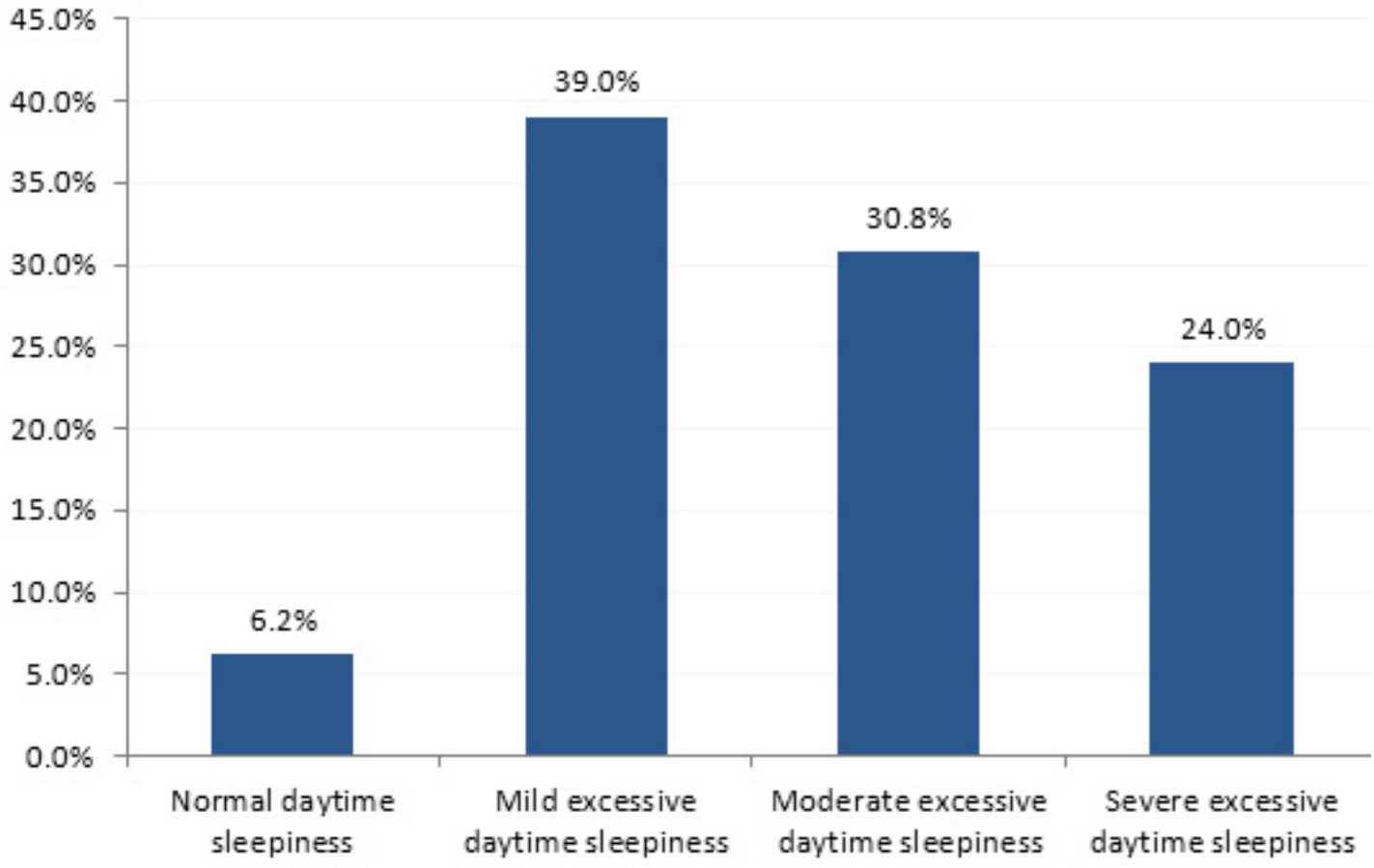

Table 3 presents the distribution of Pittsburgh Sleep Quality Index (PSQI) components among 146 primary healthcare physicians in Tabuk City. Regarding subjective sleep quality, the majority of physicians rated their sleep as either fairly good (79, 54.1%) or fairly bad (45, 30.8%), while only a small percentage (2, 1.4%) reported very good sleep quality. Sleep latency was a concern, with 52 physicians (35.6%) indicating fairly bad and 7 (4.8%) very bad latency. Considering sleep duration, most physicians (123, 84.2%) reported sleeping between 6–7 hours per night, while only 13 (8.9%) exceeded 7 hours. Short sleep duration was noted in 10 participants (6.8%) who slept less than 6 hours. Habitual sleep efficiency was relatively high among the majority (122, 83.6%) who reported efficiency between 75–84%, but only 14 (9.6%) exceeded 85%. Sleep disturbances were mostly low, with 89 physicians (61.0%) reporting fairly low and 21 (14.4%) very low disturbances, although 33 (22.6%) experienced fairly high levels. The use of sleeping medication was minimal, with 123 (84.2%) not using any, while a small proportion (10, 6.8%) used medication three or more times a week. Finally, daytime dysfunction was reported as very low by 63 physicians (43.2%) and fairly low by 52 (35.6%), but 31 physicians (21.2%) reported fairly high to very high levels of dysfunction.

Table 3. Pittsburgh Sleep Quality Index (PSQI) Components among Primary Healthcare Physicians in Tabuk City, Saudi Arabia (N = 146)

PSQI	No	%
Subjective sleep quality		
Very good	2	1.4%
Fairly good	79	54.1%
Fairly bad	45	30.8%
Very bad	20	13.7%
Sleep latency		
Very good	8	5.5%
Fairly good	79	54.1%
Fairly bad	52	35.6%
Very bad	7	4.8%
Sleep duration		
> 7 hours	13	8.9%
6-7 hours	123	84.2%
5-6 hours	5	3.4%
< 5 hours	5	3.4%
Habitual sleep efficiency		
> 85%	14	9.6%
75-84%	122	83.6%
65-74%	5	3.4%
< 65%	5	3.4%
Sleep disturbances		
Very low	21	14.4%
Fairly low	89	61.0%
Fairly high	33	22.6%
Very high	3	2.1%
Use of sleeping medication		
Not Using	123	84.2%
Less than once	12	8.2%
once or twice	1	.7%
Three or more times	10	6.8%
Daytime dysfunction		
Very low	63	43.2%
Fairly low	52	35.6%
Fairly high	26	17.8%
Very high	5	3.4%

Figure 2 illustrates the overall sleep hygiene status among primary healthcare physicians in Tabuk City based on the Pittsburgh Sleep Quality Index (PSQI). The data show that a significant majority, 87 physicians (59.6%), were classified as poor sleepers, while only 59 (40.4%) demonstrated good sleep hygiene. The global PSQI scores ranged from 3.00 to 16.00, with a mean score of 7.24 (±2.88), which exceeds the conventional cutoff point of 7, further confirming the prevalence of poor sleep quality in this population.

Figure 2. The Overall Sleep Hygiene among Primary Healthcare Physicians in Tabuk City, Saudi Arabia (N = 146)

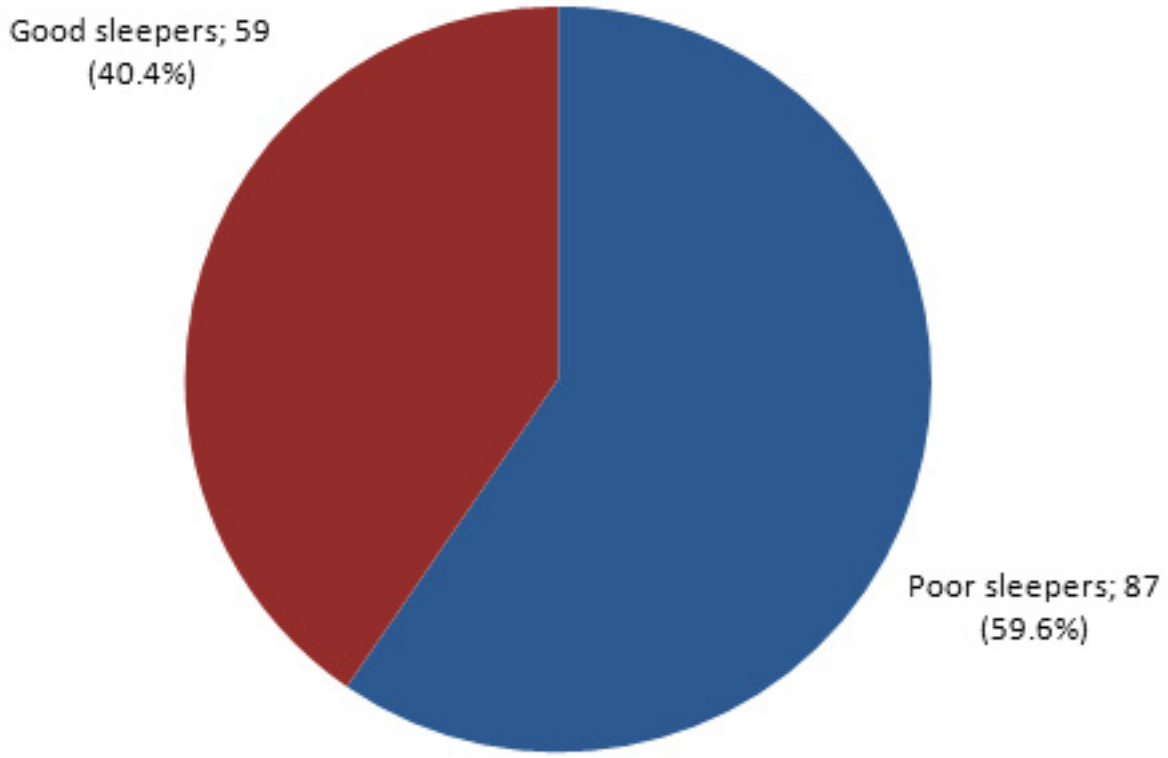

Table 4 presents the factors associated with sleep disorders among primary healthcare physicians in Tabuk City. Age was significantly associated with sleep hygiene (p = 0.001^). Physicians aged 26–45 years had the highest proportion of poor sleepers (74, 68.5%), whereas younger physicians (18–25 years) had a lower rate (36.4%) and those aged 46–60 years had the lowest (20.0% poor sleepers). Weekly working hours were also strongly associated with sleep hygiene (p = 0.001). Among those working more than 40 hours per week, 81.4% were poor sleepers, compared to only 50.5% of those working less than 40 hours. Smoking was another significant factor (p = 0.028). A higher percentage of smokers (83.3%) were poor sleepers compared to non-smokers (56.3%). On the other hand, marital status did not show a statistically significant association with sleep hygiene (p = 0.430).

Table 4. Factors Associated with Sleep Disorders among Primary Healthcare Physicians in Tabuk City, Saudi Arabia (N = 146)

Factors	Sleep hygiene				p-value
	Poor sleepers		Good sleepers		
	No	%	No	%	
Age in years					
18-25 year	12	36.4%	21	63.6%	.001*^
26-45 year	74	68.5%	34	31.5%	
46-60 year	1	20.0%	4	80.0%	
Marital status					
Unmarried	75	61.0%	48	39.0%	.430
Married	12	52.2%	11	47.8%	
How many hours do you work per week?					
Less than 40 hours	52	50.5%	51	49.5%	.001*
More than 40 hours	35	81.4%	8	18.6%	
Smoking					
Yes	15	83.3%	3	16.7%	.028*
No	72	56.3%	56	43.8%	

P: Pearson X2 test ^: Exact probability test * P < 0.05 (significant)

Table 5 shows the risk factors associated with poor sleep hygiene among primary healthcare physicians in Tabuk City. Physicians who stayed awake for more than 19 hours were significantly more likely to be poor sleepers (87.0% vs. 13.0%, p = 0.004). Similarly, those who worked night shifts between 12 am and 6 am had a high prevalence of poor sleep (86.7% vs. 13.3%, p = 0.001). Having less than six hours of continuous sleep in 24 hours was also significantly associated with poor sleep hygiene, with 81.0% of those affected classified as poor sleepers (p = 0.031). Another strong predictor was having less than two consecutive nights of good sleep, where 76.7% were poor sleepers compared to 23.3% good sleepers (p = 0.001). Moreover, those who worked continuously for five hours with less than a 30-minute break were significantly more likely to report poor sleep (82.8%, p = 0.001). Experiencing unrefreshing or interrupted sleep was also highly correlated, with 81.7% of these participants being poor sleepers (p = 0.001). Additionally, the lack of regular breaks during work was significantly associated with poor sleep hygiene (75.9%, p = 0.001), as was having less than two consecutive days off per week, where all affected individuals were poor sleepers (100%, p = 0.039). In contrast, factors such as working shifts exceeding 14–16 hours, total rest time of less than 8 hours per day, and working more than 64 hours in seven days did not show significant associations with sleep hygiene (p > 0.05).

Table 5. Risk Factors of Sleep Disorders among Primary Healthcare Physicians in Tabuk City, Saudi Arabia (N = 146)

Factors	Sleep hygiene				p-value
	Poor sleepers		Good sleepers		
	No	%	No	%	
Do you work a total hours of shift exceeding 14-16 hrs?					.241^
No	85	59.0%	59	41.0%	
Yes	2	100.0%	0	0.0%	
Do you stay a wakeful exceeding 19 hrs?					.004*
No	67	54.5%	56	45.5%	
Yes	20	87.0%	3	13.0%	
Do you work between 12 am and 6 am?					.001*
No	61	52.6%	55	47.4%	
Yes	26	86.7%	4	13.3%	
Do you have less than six hours of continuous sleep in 24 hrs?					.031*
No	70	56.0%	55	44.0%	
Yes	17	81.0%	4	19.0%	
Is your rest time <8 hrs./24 hours?					.487^
No	80	58.8%	56	41.2%	
Yes	7	70.0%	3	30.0%	
Do you have continuous work beyond 64 hours in seven-days?					.863^
No	82	59.4%	56	40.6%	
Yes	5	62.5%	3	37.5%	
Do you have less than two consecutive nights of good sleep?					.001*
No	21	35.0%	39	65.0%	
Yes	66	76.7%	20	23.3%	
Do you continuously work for five hours with <30 minutes break?					.001*
No	34	41.5%	48	58.5%	
Yes	53	82.8%	11	17.2%	
Do you have unrefreshing and /or interrupted sleep?					.001*
No	20	31.3%	44	68.8%	
Yes	67	81.7%	15	18.3%	
Is work performed without regular breaks?					.001*
No	43	48.9%	45	51.1%	
Yes	44	75.9%	14	24.1%	
Do you have less than 2 consecutive days off per week?					.039*^
No	81	57.9%	59	42.1%	
Yes	6	100.0%	0	0.0%	

P: Pearson X2 test ^: Exact probability test * P < 0.05 (significant)

Table 6 illustrates a statistically significant association between levels of daytime sleepiness and sleep hygiene among primary healthcare physicians in Tabuk City (p = 0.001). The majority of physicians with severe excessive daytime sleepiness were classified as poor sleepers (32, 36.8%) compared to only 3 (5.1%) among good sleepers. Similarly, moderate daytime sleepiness was more common among poor sleepers (31, 35.6%) than good sleepers (14, 23.7%). In contrast, mild excessive daytime sleepiness was more frequently reported among good sleepers (35, 59.3%) than poor sleepers (22, 25.3%), and normal daytime sleepiness was observed in only 2 (2.3%) of poor sleepers, compared to 7 (11.9%) among good sleepers.

Table 6. Association between Daytime Sleepiness and Sleep Hygiene among Primary Healthcare Physicians in Tabuk City, Saudi Arabia (N = 146)

Daytime sleepiness	Sleep hygiene				p-value
	Poor sleepers		Good sleepers		
	No	%	No	%	
Normal daytime sleepiness	2	2.3%	7	11.9%	.001*
Mild excessive daytime sleepiness	22	25.3%	35	59.3%	
Moderate excessive daytime sleepiness	31	35.6%	14	23.7%	
Severe excessive daytime sleepiness	32	36.8%	3	5.1%	

P: Pearson X2 test * P < 0.05 (significant)

Discussion

This study aimed to explore the prevalence of sleep disorders among primary healthcare physicians in Tabuk City, Saudi Arabia, in 2024. The sample predominantly consisted of young physicians. The high proportion of unmarried participants may also be relevant, as marital status can impact social support systems, stress levels, and lifestyle habits all of which are known to affect sleep quality. Work hours emerged as another important factor, with most physicians reporting fewer than 40 hours per week. While this could indicate manageable workloads, further investigation is needed to determine whether irregular shifts, on-call duties, or job-related stress still disrupt sleep patterns despite the relatively lower weekly hours. Besides, the low prevalence of smoking among participants is encouraging, as tobacco use is a known risk factor for sleep disorders.

As for the sleep disorders, the study revealed significant sleep disturbances in these participants, with 59.6% classified as poor sleepers (mean PSQI score: 7.24 ± 2.88). These results match with regional and international studies highlighting sleep disturbances among healthcare workers, though variations exist due to differing work environments and cultural factors. The high prevalence of poor sleep (59.6%) in this study is comparable to rates reported in Brazil (62%) [14] and China (56.8%) [15] among physicians. However, Western studies often report lower prevalence (30–45%) [16, 17], possibly due to better-regulated work hours. The minimal use of sleep medications (84.2% non-users) contrasts with U.S. data, where 15–20% of physicians use sleep aids [18].

Locally, our study matches results in a Riyadh study where 63% of physicians reported poor sleep quality due to work stress [19]. A higher prevalence was reported by Alamri et al [20] where the prevalence of poor sleep quality was 85.9% as median the sleep quality score was 10, range (3-21).

In more detail, the majority of physicians reported fairly good or fairly bad subjective sleep quality, with only 1.4% experiencing very good sleep. Sleep latency was problematic, with 35.6% reporting fairly badly and 4.8% very bad difficulty falling asleep. Also, most participants slept 6–7 hours, while only a few participants exceeded 7 hours. Short sleep duration (<6 hours) was lower than reports from high-stress medical fields (e.g., 20–30% among residents in the U.S.) [21]. However, sleep efficiency was relatively high contrasting with studies from India where 42% of doctors had low sleep efficiency due to erratic schedules [22].

The high prevalence of excessive daytime sleepiness (EDS) among primary healthcare physicians in Tabuk City is particularly concerning, with most participants reporting some degree of EDS (Figure 1). These results match with, but are more pronounced, than findings from a study of Saudi resident physicians, which reported 63% experiencing EDS [23]. The higher prevalence in our study may reflect differences in work schedules or the cumulative effect of chronic sleep deprivation among primary care physicians. Similar to our findings, an Oman study found 68% of physicians reported significant daytime sleepiness, though with lower rates of severe cases (15%) compared to our 24% [24]. The severity gradient observed (mild to severe EDS) reflects patterns seen in high-stress medical specialties internationally. For instance, a U.S. study of resident physicians reported 45% with moderate to severe EDS [25], while our study found 54.8% in these categories. This consistent pattern across different healthcare systems suggests that EDS may be an occupational hazard of medical practice globally, though our data indicate particularly high severity in the Saudi context. The clinical implications are significant, as EDS has been directly linked to medical errors in multiple studies [26, 27]. The finding that nearly one-quarter of physicians experience severe EDS is especially troubling given established associations between this level of sleepiness and impaired cognitive function [28].

The study revealed multiple significant risk factors associated with poor sleep hygiene among primary healthcare physicians in Tabuk City. Physicians aged 26–45 years had the highest prevalence of poor sleep compared to both younger and older colleagues. Occupational factors played a major role, with those working more than 40 hours per week showing significantly poorer sleep outcomes than their counterparts working fewer hours. Smoking was also associated with poor sleep quality, as 83.3% of smokers were classified as poor sleepers compared to 56.3% of non-smokers. Sleep and work pattern disruptions emerged as the most critical predictors. Extended wakefulness beyond 19 hours and night shift work between 12 am and 6 am were strongly linked to poor sleep. Other high-risk thresholds included getting less than 6 hours of continuous sleep in 24 hours, experiencing fewer than two consecutive nights of good sleep and working five continuous hours without sufficient breaks. Notably, all physicians who had fewer than two consecutive days off per week were poor sleepers, highlighting the importance of recovery periods.

Interestingly, factors such as shifts longer than 14–16 hours and total rest time under eight hours did not show a statistically significant relationship with sleep quality, suggesting that the pattern and quality of rest may be more impactful than total rest duration alone. These findings are consistent with global studies on physician sleep health [29-31], but offer context-specific insights relevant to the Saudi healthcare system.

Conclusions and Recommendations

In conclusion, this study reveals a high prevalence of poor sleep hygiene and excessive daytime sleepiness among primary healthcare physicians in Tabuk City. Nearly 60% of participants were classified as poor sleepers, and over 93% reported some level of excessive daytime sleepiness, with a significant portion experiencing moderate to severe symptoms. Key demographic and occupational factors such as being aged 26–45 years, working more than 40 hours per week, and smoking were significantly associated with poor sleep hygiene. Furthermore, specific work-related behaviors including extended wakefulness, night shifts, inadequate sleep duration, insufficient rest breaks, and lack of consecutive days off emerged as strong predictors of poor sleep outcomes. Importantly, poor sleep hygiene was also significantly linked with the severity of daytime sleepiness, highlighting its impact on alertness and functioning. These findings underline the urgent need for institutional and policy-level interventions aimed at improving sleep health among primary healthcare physicians. Recommendations include such as work schedule reforms, implementing regulated working hours, limiting night shifts, and ensuring physicians receive at least two consecutive days off per week to allow for adequate rest and recovery, As well as establishing structured break periods during shifts to prevent prolonged continuous work without rest, particularly during night duties. Sleep Health Promotion such as introducing educational programs on sleep hygiene and the risks of sleep deprivation, particularly tailored for healthcare workers are also mandatory.

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Alzheimer's Disease: Global Insights from Cause to Care

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Abstract

Alzheimer's disease (AD) is the most prevalent cause of dementia worldwide, accounting for 60-80% of dementia cases. Characterized by progressive cognitive decline, functional impairment, and neuropsychiatric symptoms, AD places a significant burden on individuals, caregivers, and healthcare systems. Advances in understanding its pathogenesis have centered on amyloid-beta (Aβ) plaques, tau pathology, neuroinflammation, vascular contributions, and genetic predispositions. While no definitive cure exists, emerging therapies targeting amyloid and tau pathways offer cautious optimism. This review integrates global and regional data, discusses evolving diagnostic frameworks, therapeutic progress, physician-specific challenges, vascular risk interactions, and unique considerations in the Middle East context.

Key words: Alzheimer's disease, cause, care,

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive impairment of memory, cognition, and behavior. Affecting approximately 24 million people globally in 2001, prevalence is projected to exceed 81 million by 2040, making it a profound public health challenge (1,14). The disease's escalating incidence, coupled with the high cost of care and lack of disease-modifying therapies, underscores the urgent need for continued research and improved clinical strategies. This review synthesizes current knowledge from multiple scientific perspectives, integrating epidemiological data, pathogenesis, diagnostic advancements, therapeutic updates, and regional considerations.

Epidemiology

AD prevalence rises exponentially with age, doubling roughly every five years after age 65 (4). The Delphi consensus study estimated worldwide dementia prevalence at 24.3 million in 2001, rising to 81.1 million by 2040 (1,14).

Table 1. Projected Global Prevalence of Dementia (Delphi Consensus Study)

WHO Region	Prevalence in 2000 (millions)	Prevalence in 2020 (millions)	Prevalence in 2040 (millions)
Western Europe (EURO A)	4.9	6.9	9.9
North America (AMRO A)	3.4	5.1	9.2
China and Developing Western Pacific (WPRO B/D)	6.0	11.7	26.1
Latin America (AMRO B/D)	1.8	4.1	9.1
North Africa and Middle East (EMRO B/D)	1.0	1.9	4.7
Sub-Saharan Africa (AFRO D/E)	0.5	0.9	1.6
Total Global	**24.3**	**42.3**	**81.1**

(Adapted from Ferri et al. (7,14))

Alzheimer's Disease in the Middle East

Despite aging populations, robust epidemiological data on AD in the Middle East are lacking. It's believed that prevalence is comparable to Western nations, though cultural stigmas, lack of specialized services, and limited public awareness hinder early diagnosis and care development (4).

Pathogenesis

The pathogenesis of AD is multifactorial, involving abnormal protein accumulation, genetic predispositions, neuroinflammation, and vascular contributions (1,2,14).

Amyloid Cascade Hypothesis

Central to AD research is the amyloid cascade hypothesis, proposing that overproduction or impaired clearance of Aβ peptides—particularly Aβ1-42—leads to plaque formation, synaptic dysfunction, and neuronal death (1,14). Yet, not all individuals with amyloid plaques develop cognitive decline, indicating other mechanisms are also involved (2).

Figure 1. Simplified Amyloid Cascade Hypothesis

APP (Amyloid Precursor Protein)
↓ β- and γ-secretase cleavage
Aβ peptides (Aβ1-40, Aβ1-42)
↓
Oligomer formation → Synaptic toxicity
↓
Plaque formation → Neuronal death

Tau Pathology

Hyperphosphorylated tau proteins aggregate into neurofibrillary tangles, disrupting cellular transport systems and correlating strongly with disease severity (1,14).

Figure 2. Tau Pathology Progression

Normal tau
↓ hyperphosphorylation
Tau oligomers
↓ aggregation
Neurofibrillary tangles
↓
Synaptic dysfunction, cell death

Neuroinflammation

Neuroinflammation mediated by activated microglia and astrocytes contributes to neuronal damage and may represent therapeutic targets (2).

Vascular Contributions

Vascular risk factors such as hypertension, diabetes, obesity, and smoking exacerbate AD pathology. Recent evidence suggests synergistic interactions between vascular pathology and amyloid/tau accumulation (5,18).

Genetic factors

About 70% of AD risk is attributable to genetic factors (1,14).

Table 2. Genetic Risk Factors for Alzheimer's Disease

Gene	Function/Effect	Risk Increase
APP	Alters Aβ processing; familial mutations raise Aβ42 levels	Familial AD
PSEN1/2	Components of γ-secretase; affect Aβ42 production	Familial AD
SORL1	Regulates APP trafficking	Familial/Late-onset
APOE ε4	Amyloid clearance, lipid metabolism	4–16x increased risk
CLU	Chaperone for Aβ aggregation	Small risk increase
PICALM	Endocytosis and amyloid trafficking	Small risk increase
TOMM40	Mitochondrial function, linked with APOE	Possible age effect

(Data consolidated from multiple sources (1,14,17).)

APOE ε4 remains the strongest genetic risk factor for sporadic AD, increasing risk up to sixteen-fold in homozygotes (14).

Diagnosis

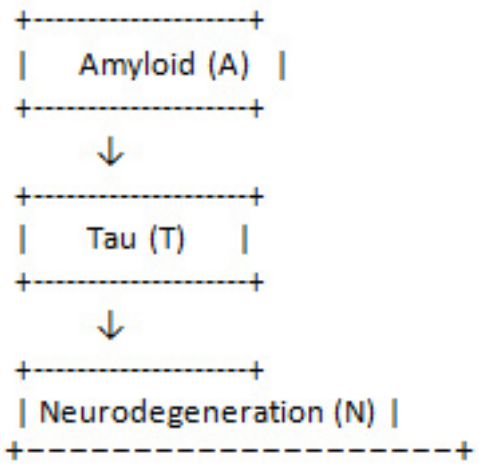
Clinical Diagnosis
Diagnosis relies on comprehensive history, cognitive testing, and functional assessments. Cognitive screening tools include MMSE (10), MoCA, Clock Drawing Test (15), and Test Your Memory (9).

Biomarkers
The 2018 NIA-AA framework defines AD biologically using the AT(N) system (2,13):

Table 3. AT(N) Biomarker Framework for AD

Biomarker Domain	Specific Biomarkers	Clinical Utility
A (Amyloid)	Low CSF Aβ42, Amyloid PET	Diagnosis of amyloid pathology
T (Tau)	CSF phosphorylated tau, Tau PET	Predicts neurodegeneration, symptoms
N (Neurodegeneration)	MRI atrophy, FDG-PET hypometabolism, Blood NfL	Severity, progression tracking

Figure 3. AT(N) Framework Visual Summary



Blood-based biomarkers, such as plasma Aβ42/40 ratios and phosphorylated tau assays, are emerging as accessible diagnostic tools (2).

Assessment Scales in Dementia

Table 4. Selected Assessment Scales in Dementia

Domain	Common Scales	Comments
Cognition	MMSE, MoCA, Mini-Cog (16), TYM (9)	Brief screens for clinical use
Function	ADL, IADL scales	Measure daily functioning
Behavior	Neuropsychiatric Inventory (NPI)	Evaluate neuropsychiatric symptoms
Quality of Life	QOL-AD (patient and proxy)	Increasingly used in trials
Depression	Geriatric Depression Scale (GDS)	Challenges in dementia diagnosis
Carer Burden	Zarit Burden Interview	Measures impact on caregivers

Effective scales must be reliable, valid, brief, and feasible in clinical practice (6,19).

Treatment

Symptomatic Treatments
Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and memantine offer symptomatic relief but do not halt disease progression (4).

Disease-Modifying Therapies

Table 5. Emerging Anti-Amyloid Therapies

Drug	Trial Highlights	Key Results	Safety Concerns
Aducanumab	EMERGE & ENGAGE trials	EMERGE met endpoint, ENGAGE did not; plaque reduction	High rates of ARIA
Lecanemab	Phase 3 trials	CDR-SB change: -0.45; ~40% achieved amyloid clearance	ARIA ~12%
Donanemab	Phase 2/3 underway	Preliminary iADRS benefit	ARIA incidence higher

(ARIA = Amyloid-Related Imaging Abnormalities) (2,13).

Despite plaque reduction, clinical benefits remain modest, and safety concerns persist (2).

Alzheimer's disease in physicians

Physicians present unique challenges (3):

Table 6. AD in Physicians – Key Challenges and Observations

Issue	Details
Underdiagnosis	High education masks deficits
Stigma	Fear of disclosure delays evaluation
Continued practice possible?	Yes, under supervision for many professionals
Referral programs	State physician health programs help manage risk

Approximately 4,600 US physicians aged ≥70 may have AD, with many able to practice safely under oversight (3).

Alzheimer's disease in the Middle East

Despite rising prevalence, AD awareness and services remain limited (4):

Table 7. AD Challenges and Needs in the Middle East

Challenge	Details
Lack of epidemiological data	No large-scale prevalence studies
Public awareness	Low; symptoms often seen as normal aging
Healthcare provider training	Limited geriatric expertise
Care systems	Heavy reliance on family caregivers
Services	Insufficient support groups and clinics

Recommendations include public education, professional training, and the development of specialized dementia care services (4).

Vascular Risk Factors and AD Progression

Vascular risk factors significantly influence AD progression (5,18).

Figure 4. Impact of Vascular Risk Factors on Cognitive Decline in AD

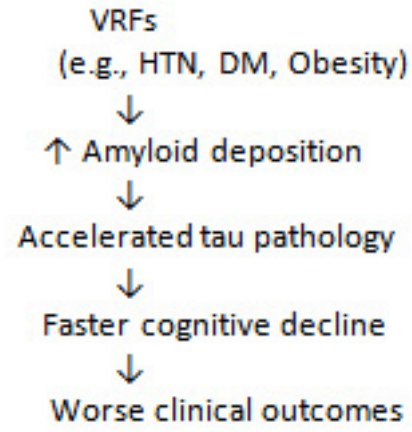


Table 8. Cognitive Decline Associated with VRFs in AD

Group	MMSE Decline	CDR-SB Increase	Significance
No VRFs	Slow	Minimal	Reference group
1-2 VRFs	Moderate	Moderate	Significant difference
≥3 VRFs	Rapid	Marked increase	Highly significant
APOE ε4 + ≥3 VRFs	Most rapid	Greatest decline	Significant synergy

Managing vascular health is crucial in mitigating cognitive decline in AD patients (5).

Future Directiions

Research priorities include:

- Precision medicine using genetic, biomarker, and lifestyle data.
- Development of blood-based biomarkers.
- Therapeutics targeting tau pathology and neuroinflammation.
- Regionally tailored strategies for under-represented populations (1,2,4).

Conclusion

Alzheimer's disease remains a formidable challenge globally. Advances in pathogenesis, diagnostics, and emerging therapeutics offer hope but require continued investment and region-specific strategies. Addressing modifiable risk factors, improving early diagnosis, and developing disease-modifying treatments are critical next steps in the fight against AD (1,14).

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Globesity and the growing nation

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Abstract

According to the World Health Organization (WHO), the prevalence of overweight and obesity is on the rise. Statistics show that American Samoa, Natru and Toketau were the top rankers with 70%. USA is 42%, followed by Qatar 41%, Australia 32%, Libya 29%, and the UK is 27%. However, the lowest in the obesity rank was Ethiopia, at 1%.

According to the World Obesity Atlas 2023 report, 38% of the global population is currently either overweight or obese. Both developed and developing countries are overwhelmed by obesity.

There is an increase in severe obesity in high- and middle-income countries, and it is projected to climb if current trends continue, from 10 to 20% between 2020 and 2035, posing a colossal peril to healthcare systems.

There is an urgent need for immediate and operational action at both population and regional levels to cease the disquieting obesity increase and its grim health risks.

Keywords: Adiposity, Body mass index, Obesity, Overweight, Prevalence, United Kingdom

Introduction

Obesity is a major public health issue, affecting all age groups, and poses a significant health problem, and it has been forecast that it's on the rise and by 2050 it is projected to affect 60% of men and 50% of women, along with 26% of under-16s in the UK (1). It is a multifactorial, complicated health issues, often relapsing, with difficult-to-treat chronic disease that poses great morbidity and mortality, that ranges from premature death to chronic ailments, like type 2 diabetes, cardiovascular diseases, stroke, metabolic syndrome (MS), non-alcoholic fatty liver disease (NAFLD), and respective malignancies, which may severely compromise patients' life expectancy and their quality of life (2). Excessive fat can aggravate existing conditions like hypertension and osteoarthritis, pressure on knees, along with reducing the quality of life and placing further pressure on healthcare facilities and the NHS. We need to unravel the driving forces for the epidemic of obesity.

Large body mass index is another risk that shows a decline in life expectancy by 2-4 years between 30-35 kg/m2, and further reduction up to 8-10 years if BMI rises above 40 kg/m2.

Not only that, it has been suggested that several obesogenic chemicals (unhealthy, dense energy food, full of refined carbohydrates, and fats) with endocrine-disrupting properties, such as plastics, fertilizers, insecticides, and additives, have gradually entered the global food chain, possibly interfering with human metabolism (2).

The environmental determinants of obesity embrace the created atmosphere, such as fast-food restaurants, supermarkets, parks, transportation facilities, and sociocultural and socioeconomic conditions, all of which either intensify or weaken the effect of global drivers on obesity tendencies (2).

The main contributing factors are increased caloric intake, alterations in the dietary composition, diminishing levels of physical activity, and shifts in the gut microbiome. Also, portion sizes have increased with substantial manufacturing of low-cost, ultra-processed, calorie-dense, tasty foods, along with increased snacking (2).

Correspondingly, lately, there has been an upsurge in leisure time with sedentary time spent in front of television and computer devices.

UK trends

The statistics are glaring, and according to the most recent data, more than 60% of adults and over 20% of children aged 10-11 are either overweight or obese. In fact, obesity has become a public health problem with serious health implications.

A nation at risk

Obesity is not just about general outlook and appearance. It poses considerable health and life-threatening implications.

Additionally, individuals with obesity face stigma, discrimination, with its mental impact and perception, all of which will cause a vicious cycle of anxiety and depression, with reverting to overeating to combat the feeling.

Evolution of obesity

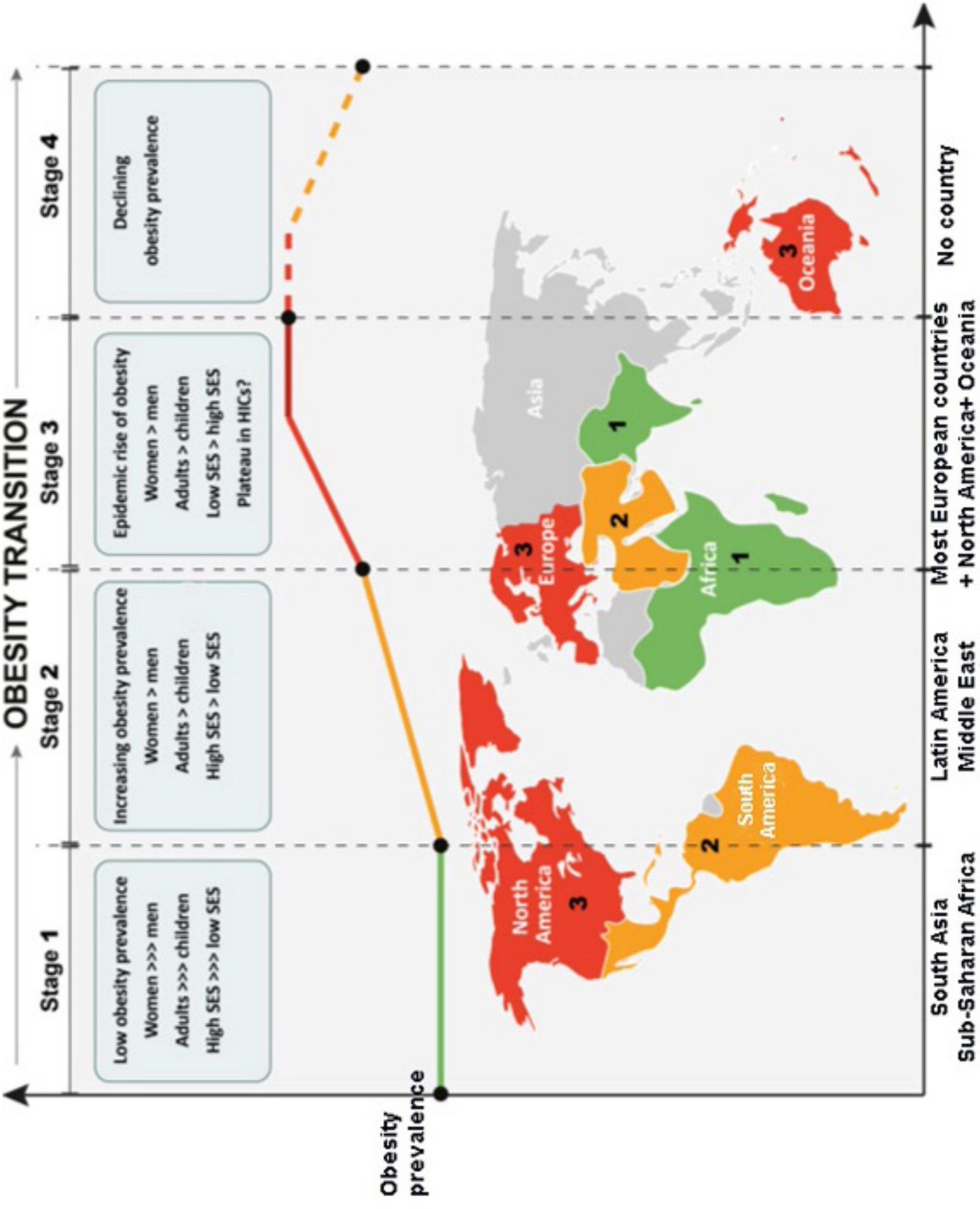
It has been suggested that obesity evolved across four stages. The first and foremost was that populations were poor and impacted by war, and overall obesity rates were low, however, obesity was growing among the wealthy nations, especially in women, and is mostly seen in many developing countries of South Asia, and sub-Saharan Africa.

In the second stage, where countries become richer, and obesity keeps increasing, men joined in and gained weight. Many Latin Americans and Middle Easterners are at this stage. In the third stage, the gap between women and men becomes narrower, where obesity keeps increasing and is seen among the lower-income group. In children and women, obesity remains stable as seen in most European nations. The last stage is where obesity prevalence starts to decline after a stabilization period, and is not seen yet in any country as none showed any projection for a decline.

The systemic factors at play

It's tempting to believe that obesity is simply about poor choices or weak willpower—but that's a painful oversimplification. The truth runs much deeper. In the UK, we're surrounded by a food environment that almost sets us up to fail. Junk food is everywhere—cheap, palatable, and deliberately made to taste tantalising, with minimal nutritional quality. Supermarket shelves are crammed with ultra-processed products, packed with sugar, salt, and unhealthy fats, while genuinely nutritious options are often harder to find and more expensive.

Figure 1 (Adapted from Current obesity report, Koliaki C et al, 2023.)



This isn't just about what we eat—it's about what we're constantly being sold. Clever marketing, especially towards children, turns sugary snacks and fizzy drinks into daily "treats." The bombardment is relentless, shaping habits from a young age. In a world like this, obesity isn't just a personal struggle—it's a battle against a system that makes healthy choices so much harder (2).

Beyond dietary factors, sedentary lifestyles have become increasingly prevalent. Many adults engage in prolonged periods of desk-based work, while children are spending more time on screens than participating in outdoor play. This reduction in routine physical activity contributes significantly to the risk of obesity. Furthermore, rising levels of poverty exacerbate these challenges by limiting access to both nutritious food and safe, affordable recreational opportunities. Together, these factors create an environment in which obesity is not merely a personal issue but a systemic and deeply rooted public health concern. Furthermore, the prevalence of severe obesity BMI> 35 kg/m2 is steadily climbing in a large number of countries (2).

How to approach sensibly:
Consultation in the primary care setting, with a caring and attentive approach, can offer a compassionate way to explore different available options for each patient. It disheartens patients if you say you are big or obese, as in fact, they do know. So, it's wise to address those problems if the patients showed interest in tackling them, especially if they saw a leaflet about obesity and its link to health problems, including knee pain due to the heavy weight imposed on the knees.

NICE 2025 guidelines devised a way for assessing and managing overweight in the primary care setting. BMI is defined by dividing the weight in kilograms by the square of the height in meters. However, this way of measuring has been criticized as some people have excess muscle mass or low body fat, where body composition is not taken into account. Also, it's not applicable to amputees and children as well, and may not represent the central obesity which is aligned with cardiovascular issues.

NICE guidelines in that condition suggest assessing health ratio risk by measuring the waist to height ratio by measuring waist circumference, above the navel, which is midway between the top of the hip and the lower chest region, dividing by the height. Any ratio lying between 0.4-0.49 is considered normal, whereas any above, as 0.5-0.59, indicates increased health risks, and >0.6 indicates further increased health risks, and those figures apply to both adults and children.

Additionally, in people older than 65 years, BMI interpretation should be assessed with care as cancer itself causes weight loss and thus a slightly higher BMI in that age would be protective.

It's essential to discuss the matter sensitively after seeking permission from the patient and probing into the patient's social, economic, and environmental factors, along with the wider determinants. The Canadian model uses 5 A's: ask, assess, advise, agree, and assist, to manage overweight and obesity.

The main determinants of overweight and obesity can be:
1. weight-linked comorbidities, and family history of weight-related comorbidities
2. weight history, and if there are any previous experiences of managing overweight or obesity
3. experiences of weight stigma, cultural stigma, and factors
4. impact of bullying and adverse childhood experiences
5. practicality of addressing weight and readiness to engage with change
6. developmental stage (for children and young people)
7. ethnicity
8. language
9. socioeconomic status and financial constraints
10. personal and family circumstances, including living arrangements and major life events
11. recent pregnancy
12. how many medicines the person is taking may affect their weight or appetite
13. current or previous experiences of eating disorders or disordered eating
14. psychosocial considerations (for example, depression, anxiety or sense of self-esteem or self-perception)
15. physical disabilities
16. the feelings and sensitivities on this subject
17. neurodevelopmental conditions and special educational needs, and disabilities (SEND)

Obesity by BMI is defined as:

Type	BMI (kg/m²)	BMI in high-risk minorities (South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean backgrounds)
Healthy weight	18.5-24.9	18.5-22.9
Overweight	25-29.9	23-27.4
Obesity class 1	30-34.9	27.5-32.4
Obesity class 2	35-39.9	32.5-37.4
Obesity class 3	≥40	≥37.5

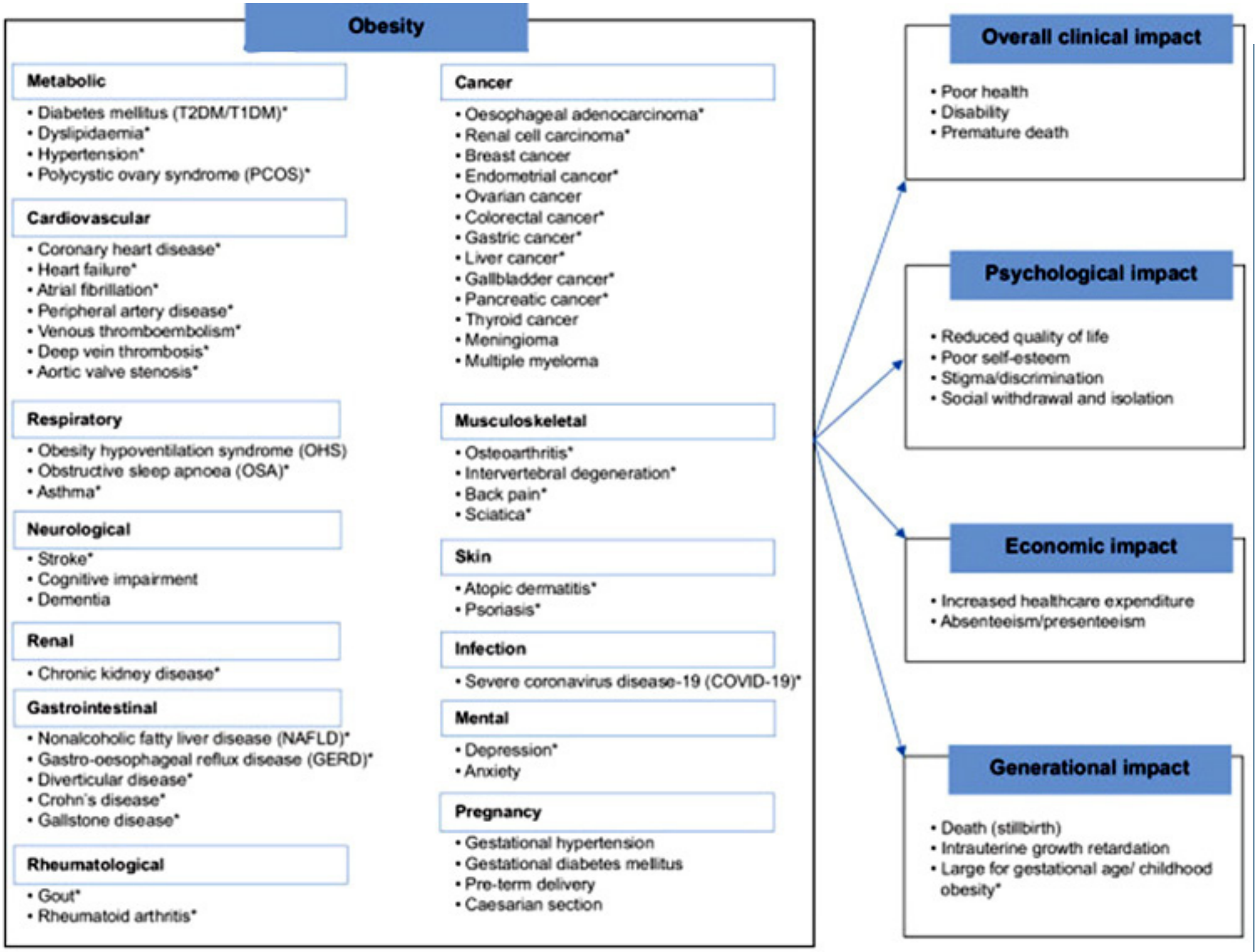


Figure 2: obesity impact, Lam BCC et al, 2023

Check behavioural intervention in the locality of the patients and their accessibility, and whether they can self-refer or it is through the GP referral route. Encourage taking physical activities even if not losing weight, as physical activity has its health benefits and improves well-being. Also, aim for healthy food, in small portions, but not restrictive, as it has not been proven to have any efficiency in the long term.
The pharmacological interventions are the last resort when the previously stated ways have failed, however the only prescribable treatment in the primary setting is orlistat. When patients are hyperglycaemic and not diabetic with cardiovascular risks, and under the specialist care for weight management, liraglutide or semaglutide (GLP-1 agonists) are offered on the NHS for obesity. It depends on the regions and services provided. The newer version, Tirzepatide which is currently offered privately, has dual GLP-1/ GIP agonist and has been approved for primary setting as well, and was only released recently in March 2025, and will roll out in June 2025 for the first 3 years, and will be monitored by new primary care weight management services rather than the GP, along with offering support in regards to nutritional and dietetic input with behavioural change interventions. In England, it is offered with certain rules in each part.

Bariatric surgery is offered only when the BMI is over 40 kg/m^2, and with significant comorbidities, and a commitment to long follow up, of at least 2 years. Weight regain is not uncommon.

The price we all pay

Obesity carries a heavy cost—not just for individuals, but for society as a whole. The NHS spends billions each year managing obesity-related illnesses, but the financial strain doesn't stop there. Lost productivity, greater demand for welfare support, and broader economic consequences all add to the burden. Despite clear and growing evidence of the scale of the problem, the response from policymakers and industry leaders remains patchy and inadequate.

What must be done

Addressing the obesity epidemic necessitates comprehensive and systematic reform. Relying solely on individual responsibility is insufficient and has proven a failure. To date, there is little evidence of successful community-based intervention. National policies of obesity prevention must aim to create health-promoting environments that support and enable individuals to make sustainable lifestyle choices by tackling environmental determinants. Only Denmark and New York City have implemented drastic restrictions on the use of trans fats in their food manufacturing by imposing regulatory legislation. Also, adopting a healthy approach to food by reducing trends in sweet drinks as for example, in Australia, in children and adolescents, and increasing fruit and fresh vegetable intake, and reducing candies, solid margarine, and breakfast eating to stagnate obesity rates in youth (3). Also increased physical activities and minimise sedentary time by less watching of TV to halt obesity, and increased media attention to local public health activities and their key role. Also, interventions such as taxing unhealthy foods or making healthy foods affordable, and encouraging behavioural changes for a better life. However, there is little research on the sociocultural determinants of food choices and physical activities to bring obesity down. Those efforts should be enforced by a stronger political will and determination (2-3).

Some strategic keys to consider:
1. Regulating food marketing and improving nutritional labelling of its sugar, calorie, and fat contents.
2. Taxing cheap sugary unhealthy food and making healthy food affordable and accessible.
3. Encourage physical activities and make initiatives of green spaces, pedestrian-friendly infrastructure, to promote and develop a healthy lifestyle.
4. Implore and introduce measures for managing weight with mental health support to facilitate long-term behavioural changes and sustained weight loss.
5. These coordinated measures are essential to create an environment in which healthy choices become the easier and more natural option for all.

A call to action

Obesity is not an inevitability; it is a challenge that can be overcome through collective effort. The government must prioritise health over industry profit, while individuals must be supported in making better choices. The tide of obesity will not be turned by blame or judgment but by compassion, education, and the creation of environments where health is the easier, more accessible option.
The time for action is now. Failure to address this growing crisis will leave generations of Britons burdened by poor health and shortened lives needlessly. We must act decisively before the weight of the nation becomes too heavy to bear.

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Gallbladder Polyps

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Abstract

Gallbladder polyps are protrusions of the mucosal lining into the lumen, most commonly identified incidentally during abdominal imaging. While the majority are benign, particularly cholesterol and inflammatory polyps, certain neoplastic types, such as adenomas and adenocarcinomas, present a risk for malignancy. Prevalence estimates range from 4% to 7%.

Risk factors include age over 60, Asian ethnicity and chronic inflammatory conditions.

Ultrasound remains the primary diagnostic tool, with polyp characteristics (size, echogenicity, and morphology) guiding risk stratification. Advanced imaging modalities are reserved for suspected malignancy. Current European guidelines (2022) recommend cholecystectomy for polyps ≥10 mm or smaller polyps in symptomatic patients or those with malignancy risk factors.

Histological analysis is essential for definitive diagnosis and to exclude cancer

Although most polyps are clinically insignificant, accurate classification and vigilance is required.

Keywords: gallbladder polyps, characteristics, abdominal imaging

Introduction

Gallbladder polyps are defined as projections from the gallbladder mucosa into the lumen. They are usually asymptomatic and found incidentally on ultrasound / CT, or after cholecystectomy but can occasionally lead to symptoms like those of cholecystitis (right upper quadrant pain, nausea and abdominal discomfort). Most polyps are not neoplastic but are hyperplastic or represent lipid deposits (cholesterolosis).

With the increased use of abdominal ultrasound, gallbladder polyps became more obvious.

However, initial imaging cannot exclude the possibility of gallbladder carcinoma or premalignant adenomas. This paper will review the classification, clinical findings, diagnosis, and management of gallbladder polyps.

Epidemiology

The causes of increased prevalence of gallbladder polyps are unclear. Studies have shown that 4% to 7% of the population may develop gallbladder polyps; the majority are cholesterol polyps. The average age of diagnosis of gallbladder polyps is 40- 50 years old. However, other studies have found the presence of polyps to be more prevalent in older patients [1].

Risk factors

There are a few risk factors associated with gallbladder polyps' formation. Some studies suggest conditions such as :

Familial polyposis, Peutz-Jeghers syndrome, and hepatitis B may be factors associated with polyp formation.

Pseudo or cholesterol polyps can develop when the cholesterol or salt content in the bile is high. This leads to condensation of cholesterol clumps which can adhere to the wall of the gallbladder. This condition may be a precursor to gallstone formation and can also at times be seen in conjunction with gallstones [1][2].

Types of gallbladder polyps

Cholesterol polyps or pseudo polyps: Are the most common type of gallbladder polyps. These account for 60% to 90% of all gallbladder polyps. They are not true neoplastic growths, but they represent a polypoid form of cholesterolosis as cholesterol deposits form as projections on the inner lumen of the gallbladder wall. Cholesterol polyps are usually asymptomatic and diagnosed incidentally on ultrasound. They are usually multiple, homogeneous, and pedunculated polypoid lesions that are more echogenic than the liver parenchyma.

(Figure 1. Ultrasound of a 41-year-old man with chest pain shows two 4-mm GB polyps)
Adenomas: Adenomas are homogeneous, isoechoic with the liver parenchyma, have a smooth surface with internal vascularity on Doppler imaging, and usually do not have a stalk.

Adenocarcinomas: Adenocarcinomas are homogeneous or heterogeneous polypoid structures that are usually isoechoic with the liver parenchyma, are vascular on Doppler imaging, and exhibit a mulberry-like surface [10]. Sessile polyp morphology with a wide base and focal thickness of the gallbladder wall of more than 4 mm are risk factors for malignancy [10]. Adenocarcinomas are usually larger than 1 cm.

Adenomayoma: In the localized type, adenomyomatosis can give the appearance of a polyp projecting from the fundus into the lumen.

Advanced imaging methods include:

Contrast-enhanced ultrasound.
Endoscopic ultrasound (EUS)
Computed tomography scan (CT)

We do not routinely obtain advanced imaging for patients with suspected benign gallbladder polyps because the use of such imaging is limited by availability, diagnostic accuracy, and/or its invasiveness (eg, endoscopic ultrasound (EUS) [10-11]. However, we obtain advanced imaging when malignancy is suspected (eg, polyps >20 mm in size, focal gallbladder wall thickening). Additional imaging evaluates the depth of invasion into the gallbladder wall and invasion into the liver. Advanced imaging may be helpful in differentiating benign from malignant lesions and differentiating tumefactive sludge from neoplastic lesions.

Figure 1: Ultrasound of a 41-year-old man with chest pain shows two 4-mm GB polyps

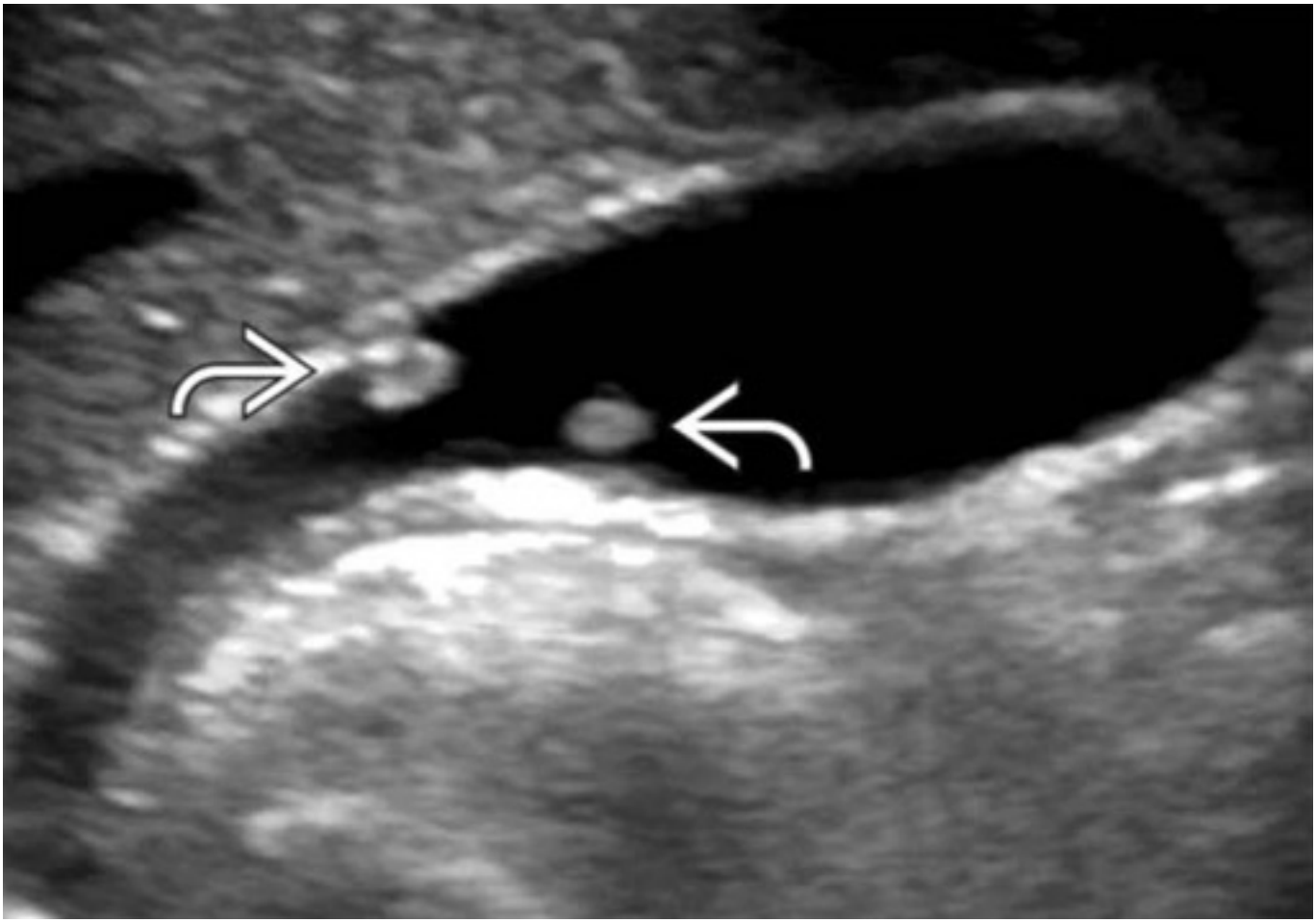
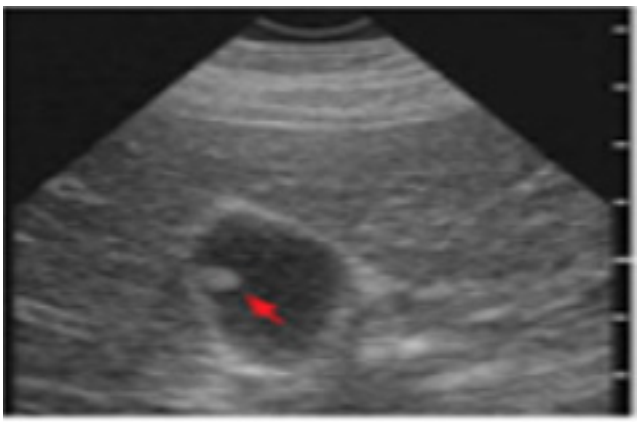


Figure 2: Gallbladder adenomatous polyp



Diagnosis

The diagnosis of a gallbladder polyp can be made with reasonable confidence based on ultrasound findings, but imaging cannot unequivocally distinguish malignant from benign polyps. Histologic evaluation also excludes malignancy.

Differential diagnosis

Gallstones
Gallbladder polyps can be differentiated from gallstones by abdominal ultrasound as the polyps are fixed and do not cast a shadow whereas gallstones move when the patient is rolled from one side to another and do not (Figure 3).

Gallbladder sludge ball mimics a gallbladder polyp but tends to be in the dependent part of the gallbladder and moves with changing the patient's position.

Gallbladder adenocarcinoma appears as a polypoid structure.

Management

European guidelines (2022)
In 2022, the joint guidelines between the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), European Association for Endoscopic Surgery and other Interventional Techniques (EAES), International Society of Digestive Surgery - European Federation (EFISDS) and European Society of Gastrointestinal Endoscopy (ESGE) were updated (12):

1-polyp ≥10 mm: cholecystectomy recommended
2-Polyp <10 mm:
a. Symptoms attributable to the gallbladder: cholecystectomy is recommended.
b. No symptoms attributable to the gallbladder:
- Polyp 6-9 mm with one or more risk factors* for gallbladder malignancy: cholecystectomy is recommended, polyp measures ≤5 mm follow-up ultrasound at 6 months, 1 year and 2 years
no risk factors for gallbladder malignancy:
polyp 6-9 mm follow-up ultrasound at 6 months, 1 year and 2 years
polyp ≤5 mm follow-up not required

***Risk factors:**
Patient age>60 years
Primary sclerosing cholangitis,
Asian ethnicity,
Sessile polyp (including focal wall thickening >4 mm).
If a polyp grows ≥2 mm within 2 years, its size should be considered along with risk factors.
Statistically, gallbladder polyps are common and gallbladder cancer is rare, so very few polyps progress to gallbladder cancer. There is also controversy regarding the development of gallbladder cancer and some suggest that polyps may not progress to cancer (10).

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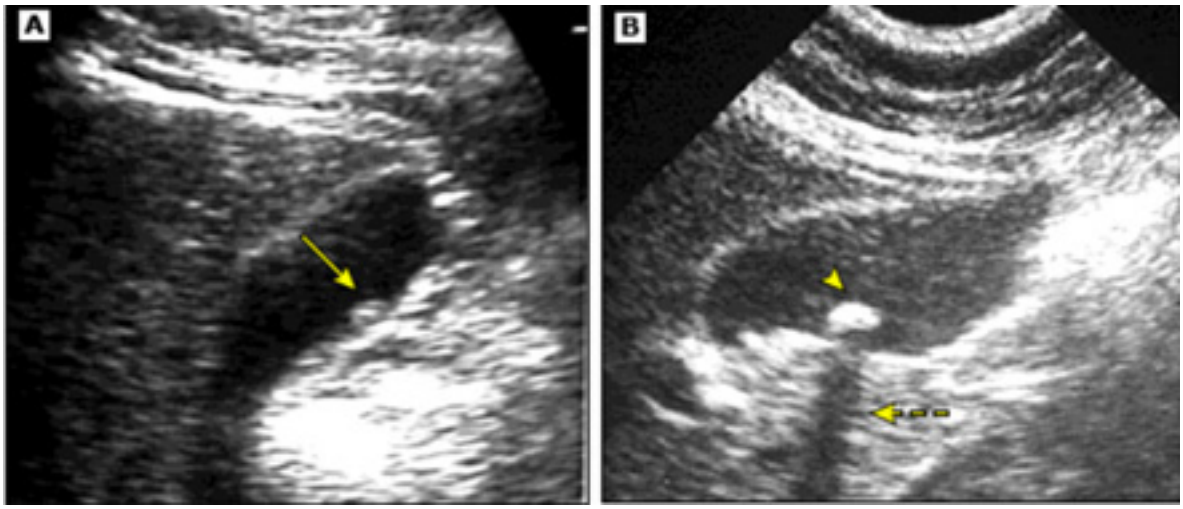
Figure 3



Ultrasound images of a gallbladder adenomatous polyp (arrow) compared with a gallstone (arrowhead). Note the shadow cast by the stone (dashed arrow) compared with the absence of a shadow behind the polyp.