World Family Medicine Journal
incorporating the Middle East Journal of Family Medicine

ISSN 1839-0188

5

July-August 2025 - Volume 23 Issue 5

Wadi Al Disah, Tabuk, Saudi Arabia

4 **Editorial**

Dr. Abdulrazak Abyad

5 **In Memoriam:** Dr Marwan Sultan and Dr Adnan Al-Bursh

Original Contribution

6 **Assessment of Knowledge, Attitude and Performance of Primary Healthcare Physicians in Tabuk City, Saudi Arabia regarding Attention De cit Hyperactivity Disorder (ADHD) in children and adolescents**
Majed Akram Al Ghassab, Rasha Ali Abdelrahman, Ahmad Raja Albalawi, Asma Ali Alharb, Nawaf Saeed Almaliki, Hamad Ibrahim Hamad Albalawi
DOI: 10.5742/MEWFM.2025.805257860

17 **Prevalence of limitations and barriers of receiving herpes-zoster vaccine among patients attending PHC in Tabuk city, 2023, cross-sectional study**
Nagham Alkrissi, Ahmed Raja Albalawi, Wejdan Mohammad Alshehri, Wejdan Abdullah Alshehri, Arub Albalawi, Asmaa Alharbi
DOI: 10.5742/MEWFM.2025.805257861

30 **Chronic idiopathic thrombocytopenic purpura may even prolong survival in human beings in general**
Mehmet Rami Helvaci, Hulya Halici, Kevser Erdogan, Murat Albayrak, Alper Sevinc, Celaletdin Camci, Abdulrazak Abyad, Lesley Pocock
DOI: 10.5742/MEWFM.2025.805257862

Population and Community Studies

46 **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**
Hamad Ibrahim Albalawi , Majed Akram AlGhassab, Nawaf Almalki, Nada Awad Dabi Al Suhaimi, Rasha Hassan, Ahmad Raja Saeed Albalawi
DOI: 10.5742/MEWFM.2025.805257863

55 **Prevalence of sleep disorders among primary healthcare physicians in Tabuk City, Saudi Arabia 2024**
Nawaf Saeed Almalki, Majed Akram Ali AlGhassab, Hamad ibrahim hamad albalawi, Raneem Abdulrahman Al Johani, Hoda Mohamed elhady, Marwa Gamal Mohamed, Rasha Hassan Ali, Hussam Ahmed Eid
DOI: 10.5742/MEWFM.2025.805257864

Dementia Special Series

69 **Alzheimer s Disease: Global Insights from Cause to Care**
A Abyad
DOI: 10.5742/MEWFM.2025.805257866

Review

77 **Globesity and the growing nation**
Ebtisam Elghblawi
DOI: 10.5742/MEWFM.2025.805257881

83 **Gall Bladder polyps**
Soliena Alnakaw
DOI: 10.5742/MEWFM.2025.805257883

Editorial

Chief Editor:
A. Abyad
MD, MPH, AGSF, AFCHSE
Email::
aabyad@cyberia.net.lb
Mobile: 961-3-201901

Publisher
Lesley Pocock
medi+WORLD International
AUSTRALIA
Email:
lesleypocock@mediworld.com.au
publishermwi@gmail.com

The present collection of manuscripts reþects 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 Deýcit Hyperactivity Disorder (ADHD) remains a signiýcant 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 ýndings 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 identiýcation and referral.

In the realm of dementia, Abyadûs 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 exempliýed in the retrospective study of celiac disease prevalence among patients with type 1 diabetes mellitus. Despite a modest prevalence (2.4%), the study identiýes 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 Elghblawiûs paper on the global obesity epidemicpresenting a compelling call to action. The review eloquently outlines the systemic and environmental drivers of ñglobesity,ò reminding readers that obesity is not simply a matter of individual choice but a reþection 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 ð a condition traditionally regarded as deleterious ð might paradoxically confer survival beneýts 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 modiýable factors such as long working hours, night shifts, and inadequate rest. These ýndings 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-speciýc 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 Deþcit Hyperactivity Disorder (ADHD) in children and adolescents

Majed Akram AlGhassab [1], Rasha Ali Abdelrahman [2], Ahmad Raja Albalawi [3], Asma Ali Alharbi [4], Nawaf Saeed Almaliki [2], Hamad Ibrahim Hamad Albalawi [3]

[1] Family medicine resident, Tabuk health cluster
[2] Egyptian board of family medicine, Tabuk health cluster
[3] Saudi board of family medicine and fellowship in diabetes management, Tabuk health cluster
[4] Saudi board of family medicine, Tabuk health cluster

Corresponding author
Dr. Majed AlGhassab
Family medicine resident
Mob: 0966551537733
Email: Majed4Ak@gmail.com

Received: June 2025. Accepted: July 2025; Published:July 20, 2025.
Citation: Majed Akram AlGhassab et al. Assessment of Knowledge, Attitude, and Performance of Primary Healthcare Physicians in Tabuk City, Saudi Arabia regarding Attention De cit Hyperactivity Disorder (ADHD) in children and adolescents. World Family Medicine. July-August 2025; 23(5): 6 - 16. DOI: 10.5742/MEWFM.2025.805257860

Abstract

Background: Attention-Deýcit/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 identiýcation, 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 conýrmed 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 identiýed 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 signiýcantly associated with knowledge levels ($p = 0.049$ and $p = 0.004$, respectively), whereas other factors showed no signiýcant 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-speciýc training and enhancing PHC involvement in early identiýcation 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 deýcit 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 signiýcant 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 speciýed or unspeciýed ADHD (17). While neuropsychological testing exists, it does not signiýcantly enhance diagnostic accuracy.

ADHD affects daily functioning, increasing the risk of academic and professional struggles, car accidents, substance abuse, social difýculties, 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 signiýcantly 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 ýrst section captured sociodemographic and professional characteristics, including age, gender, and years of experience, nationality, and educational qualiýcations. The second section assessed knowledge of ADHD using 12 multiple-choice items. The third section evaluated the participantsû 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 reýne the tool, and internal consistency was evaluated using Cronbachûs 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-Deýcit/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 classiýed as having good knowledge, whereas those with scores of 60% or below were categorized as having poor knowledge. To examine associations between physiciansû knowledge levels and various sociodemographic and professional variables (e.g., age, gender, nationality, qualiýcations, years of experience, and sources of ADHD knowledge), the Chi-square test (Pearsonûs 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 signiýcant. Additionally, physiciansû 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 30ï40 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 masterîs 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 identiýed 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 difýculty 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

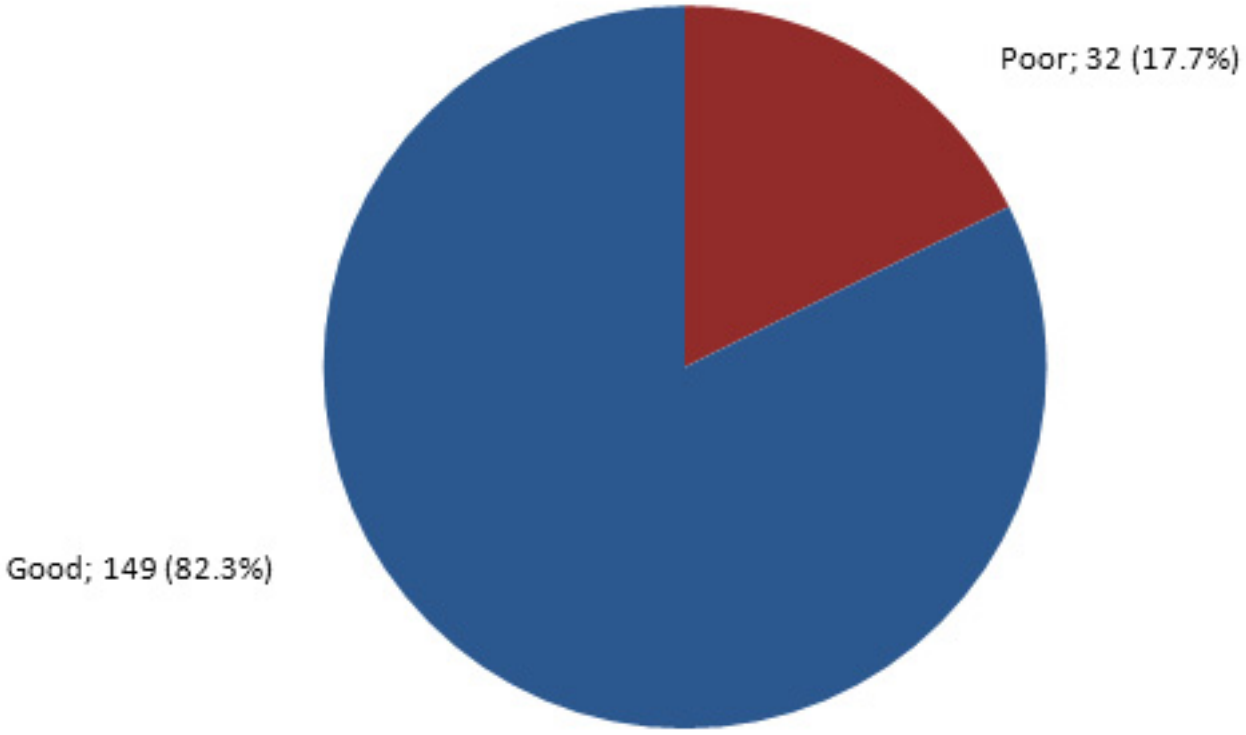

Figure 2: The source of Information about ADHD among Primary Healthcare Physicians in Tabuk City, Saudi Arabia

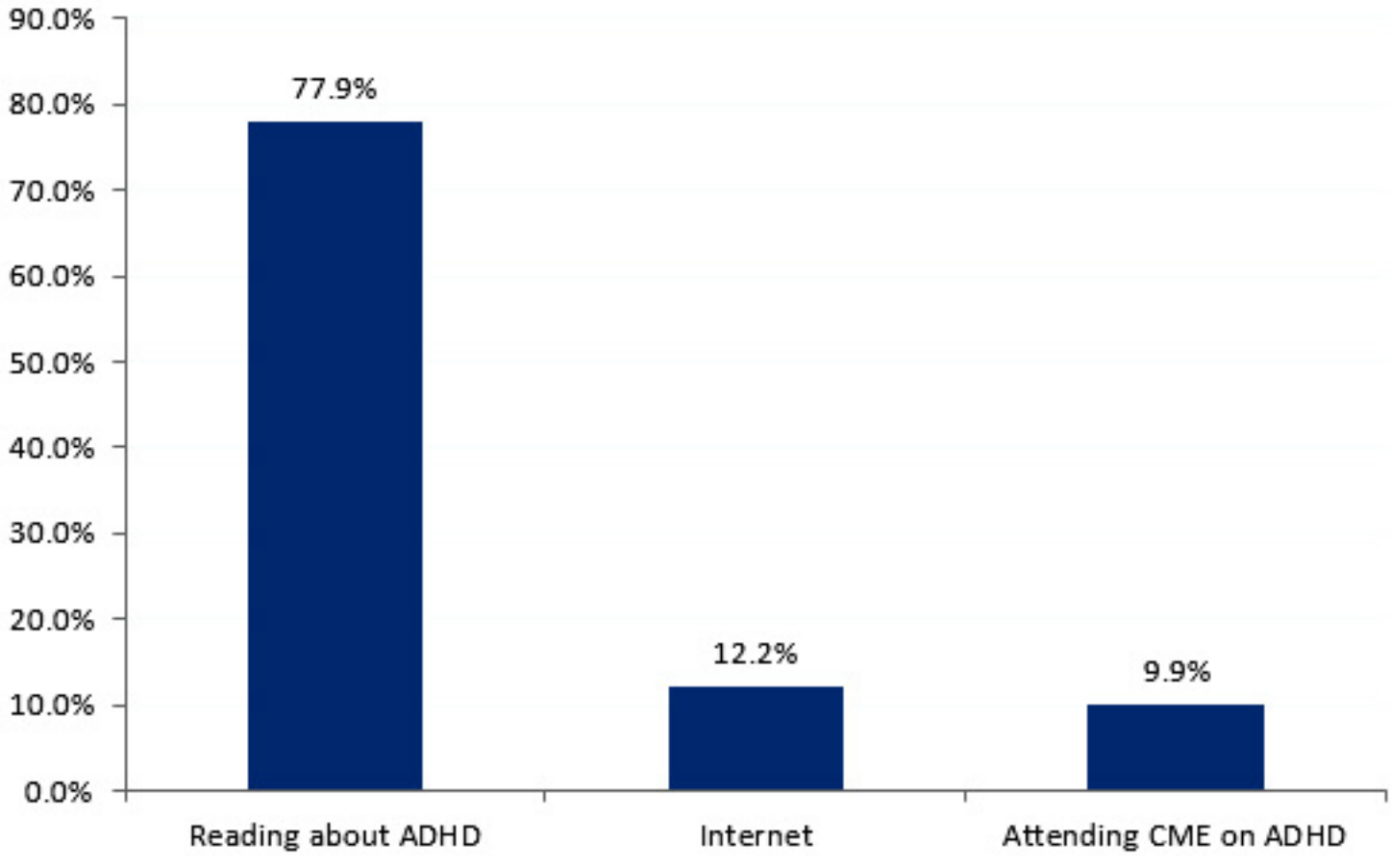

Table 3 presents the attitudes of primary healthcare (PHC) physicians toward ADHD diagnosis and management. A majority of physicians (119; 65.7%) agreed that ADHD is difýcult to diagnose or manage within the PHC setting. Despite this, 145 (80.1%) believed that PHC physicians can play an active role in 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 signiýcant 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 30ï40 (85.1%) (p = 0.049). Gender differences were also signiýcant (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), qualiýcation (p = 0.459), years of experience (p = 0.863), and perceived knowledge level (p = 0.859), showed no statistically signiýcant association with knowledge levels. Additionally, sources of knowledge, including attending CME (88.9%), internet (72.7%), and reading (83.0%), were not signiýcantly linked to knowledge level (p = 0.374). Similarly, whether physicians had diagnosed ADHD cases in the past year did not signiýcantly 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 (signiýcant)

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 qualiýcations, the vast majority held an MBBS degree, while a smaller percentage had a doctorate or higher qualiýcations. Years of experience were nearly evenly distributed between those with less than ýve years and those with more than ýve 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 deýciencies were identiýed, 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 ADHDîs 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 ýnding is consistent with studies from other regions, where primary care providers often report insufýcient ADHD training [37]. In Saudi Arabia, similar knowledge deýciencies 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 ýndings 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 conýdence 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 physiciansî knowledge about ADHD was suboptimal, but they had a positive attitude toward their role with regard to ADHD. Also, these ýndings have been reported in studies in several countries. In Pakistan, Jawaid et al. [34] reported that the knowledge of general practitioners on ADHD was deýcient. 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) physiciansî 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 difýculties, possibly reþecting 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 insufýcient training, lack of conýdence, 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 speciýc 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 signiýcant 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 ýndings also indicate that knowledge levels were signiýcantly 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 clariýcation of the role of PHC physicians in ADHD care through guidelines and structured training to empower their involvement.

References

1. Shaýullah S, Dhaneshwar S. Current perspectives on attention-deýcit hyperactivity disorder. Current Molecular Medicine. 2025;25(3):289-304.
2. Frank-Briggs AI. Attention deýcit hyperactivity disorder (ADHD). Journal of Pediatric Neurology. 2011 Sep;9(03):291-8.
3. Popit S, Serod K, Locatelli I, Stuhec M. Prevalence of attention-deýcit hyperactivity disorder (ADHD): systematic review and meta-analysis. European Psychiatry. 2024 Jan; 67(1):e68.
4. Al-Habeeb AA, Qureshi NA, Al-Maliki TA. Pattern of child and adolescent psychiatric disorders among patients consulting publicly-funded child psychiatric clinics in Saudi Arabia. East Mediterr Health J Rev Sante Mediterr Orient Al-Majallah Al-Sihhiyah Li-Sharq Al-Mutawassit. 2012 Feb; 18(2):112ï9.
5. Al-Haidar FA. Co-morbidity and treatment of attention deýcit hyperactivity disorder in Saudi Arabia. East Mediterr Health J Rev Sante Mediterr Orient Al-Majallah Al-Sihhiyah Li-Sharq Al-Mutawassit. 2003; 9(5ï6):988ï95.
6. ABDUR-RAHIM FEA, AL-HAMAD AR, CHALEBY K, AL-SUBAIE A. A survey of a child psychiatry clinic in a teaching hospital in Saudi Arabia: Clinical proýle and cross-cultural comparison. Surv Child Psychiatry Clin Teach Hosp Saudi Arab Clin Proýle Cross-Cult Comp. 1996; 17(1):36ï41.
7. Al Hamed JH, Taha AZ, Sabra AA, Bella H. Attention Deýcit Hyperactivity Disorder (ADHD) among Male Primary School Children in Dammam, Saudi Arabia: Prevalence and Associated Factors. J Egypt Public Health Assoc. 2008; 83(3ï4):165ï82.
8. Alsafar FA, Alsaad AJ, Albukhaytan WA. Prevalence of adult attention deýcit hyperactivity disorder (ADHD) among medical students in the Eastern Province of Saudi Arabia. Saudi Medical Journal. 2024 Apr;45(4):397.
9. Barkley RA. Child behavior rating scales and checklists. In: Assessment and diagnosis in child psychopathology. New York, NY, US: The Guilford Press; 1988. p. 113ï55.
10. Tistarelli N, Fagnani C, Troianiello M, Stazi MA, Adriani W. The nature and nurture of ADHD and its comorbidities: A narrative review on twin studies. Neuroscience & Biobehavioral Reviews. 2020 Feb 1; 109:63-77.
11. Chou IC, Lin CC, Kao CH. Enterovirus Encephalitis Increases the Risk of Attention Deýcit Hyperactivity Disorder: A Taiwanese Population-based Case-control Study. Medicine (Baltimore). 2015 Apr; 94(16):e707.
12. Donzelli G, Carducci A, Llopis-Gonzalez A, Verani M, Llopis-Morales A, Cioni L, et al. The Association between Lead and Attention-Deýcit/Hyperactivity Disorder: A Systematic Review. Int J Environ Res Public Health. 2019 Jan 29; 16(3):382.
13. Luo Y, Weibman D, Halperin JM, Li X. A Review of Heterogeneity in Attention Deýcit/Hyperactivity Disorder (ADHD). Front Hum Neurosci. 2019; 13:42.
14. Sauver JL, Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ. Early life risk factors for attention-deýcit/hyperactivity disorder: a population-based cohort study. InMayo Clinic Proceedings 2004 Sep 1 (Vol. 79, No. 9, pp. 1124-1131). Elsevier.
15. Alhraiwil NJ, Ali A, Househ MS, Al-Shehri AM, El-Metwally AA. Systematic review of the epidemiology of attention deýcit hyperactivity disorder in Arab countries. Neurosci Riyadh Saudi Arab. 2015 Apr; 20(2):137-44.
16. Alqahtani MMJ. Attention-deýcit hyperactive disorder in school-aged children in Saudi Arabia. Eur J Pediatr. 2010 Sep; 169(9):1113-.
17. Wolraich ML, Hagan JF, Allan C, Chan E, Davison D, Earls M, et al. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deýcit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019 Oct; 144(4):e20192528.
18. Bussing R, Zima BT, Gary FA, Garvan CW. Barriers to detection, help-seeking, and service use for children with ADHD symptoms. J Behav Health Serv Res. 2003; 30(2):176-89.
19. Excellence NI for C. Guidance on the use of methylphenidate (Ritalin, Equasym) for attention-deýcit/hyperactivity disorder (ADHD) in childhood (2000) Technology appraisal, Guidance No. 13. 2006.
20. Deýcit A. Hyperkinetic Disorders in Children and Young People. Sign Publ Number 52 2001 Scott Intercoll Guidel Netw. 2001;
21. Hill P, Taylor E. An auditable protocol for treating attention deýcit/hyperactivity disorder. Arch Dis Child. 2001 May; 84(5):404ï9.
22. Greenhill LL, Pliszka S, Dulcan MK, Bernet W, Arnold V, Beitchman J, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry. 2002 Feb; 41(2):26S-49S.
23. Kuhn D. What is scientiýc thinking and how does it develop?. The Wiley-Blackwell handbook of childhood cognitive development. 2010 Aug 16:497-523.
24. Biederman J, Faraone SV. The effects of attention-deýcit/hyperactivity disorder on employment and household income. MedGenMed Medscape Gen Med. 2006 Jul 18; 8(3):12.
25. Zwaanswijk M, van Dijk CE, Verheij RA. Child and adolescent mental health care in Dutch general practice: time trend analyses. BMC Fam Pract. 2011 Dec 1; 12:133.
26. Zwaanswijk M, Verhaak PFM, van der Ende J, Bensing JM, Verhulst FC. Consultation for and identiýcation of child and adolescent psychological problems in Dutch general practice. Fam Pract. 2005 Oct; 22(5):498ï506.
27. Meltzer H, Gatward R, Goodman R, Ford T. Mental health of children and adolescents in Great Britain. Int Rev Psychiatry Abingdon Engl. 2003; 15(1ï2):185ï7.

28. Guevara J, Lozano P, Wickizer T, Mell L, Gephart H. Utilization and cost of health care services for children with attention-deýcit/hyperactivity disorder. Pediatrics. 2001 Jul; 108(1):71ï8.
29. Leibson CL, Katusic SK, Barbaresi WJ, Ransom J, Oîbrien PC. Use and costs of medical care for children and adolescents with and without attention-deýcit/hyperactivity disorder. JAMA. 2001 Jan 3; 285(1):60ï6.
30. Chan E, Zhan C, Homer CJ. Health care use and costs for children with attention-deýcit/hyperactivity disorder: national estimates from the medical expenditure panel survey. Arch Pediatr Adolesc Med. 2002 May; 156(5):504ï11.
31. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. International journal of epidemiology. 2014 Apr 1; 43(2):434-42.
32. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deýcit hyperactivity disorder: a meta-analysis of follow-up studies. Psychological medicine. 2006 Feb;36(2):159-65.
33. Kieling C, Kieling RR, Rohde LA, Frick PJ, Mofýtt T, Nigg JT, Tannock R, Castellanos FX. The age at onset of attention deýcit hyperactivity disorder. American Journal of Psychiatry. 2010 Jan 1; 167(1):14-6.
34. Quinn PO, Madhoo M. A review of attention-deýcit/hyperactivity disorder in women and girls: uncovering this hidden diagnosis. Prim Care Companion CNS Disord. 2014 Jun 15; 16(3): PCC-13r01596.
35. Larson K, Russ SA, Kahn RS, Halfon N. Patterns of comorbidity, functioning, and service use for US children with ADHD, 2007. Pediatrics. 2011 Mar 1; 127(3):462-70.
36. DuPaul GJ, Weyandt LL. School-based Intervention for Children with Attention Deýcit Hyperactivity Disorder: Effects on academic, social, and behavioural functioning. International journal of disability, development and education. 2006 Jun 1; 53(2):161-76.
37. Shaw K, Wagner I, Eastwood H, Mitchell G. A qualitative study of Australian GPsî attitudes and practices in the diagnosis and management of attention-deýcit/hyperactivity disorder (ADHD). Family Practice. 2003 Apr 1; 20(2):129-34.
38. AlZaben FN, Sehlo MG, Alghamdi WA, Tayeb HO, Khalifa DA, Mira AT, Alshuaibi AM, Alguthmi MA, Derham AA, Koenig HG. Prevalence of attention deýcit hyperactivity disorder and comorbid psychiatric and behavioral problems among primary school students in western Saudi Arabia. Saudi medical journal. 2018 Jan; 39(1):52.
39. Alqahtani MM. Attention-deýcit hyperactive disorder in school-aged children in Saudi Arabia. European journal of pediatrics. 2010 Sep; 169:1113-7.
40. Adler LD, Nierenberg AA. Review of medication adherence in children and adults with ADHD. Postgraduate medicine. 2010 Jan 1; 122(1):184-91.
41. Sayal K, Taylor E, Beecham J, Byrne P. Pathways to care in children at risk of attention-deýcit hyperactivity disorder. The British Journal of Psychiatry. 2002 Jul; 181(1):43-8.
42. Al-Ahmari AA, Bharti RK, Al-Shahrani MS, Alharthi MH, Alqarni HM, Alshehri HM. Knowledge, attitude, and performance of primary healthcare physicians in Aseer Region, Saudi Arabia about attention deýcit hyperactivity disorder. Journal of Family and Community Medicine. 2018 Sep 1; 25(3):194-8.
43. Jawaid A, Zafar AM, Naveed A, Sheikh S, Waheed S, Zafar MA, et al Knowledge of primary paediatric care providers regarding attention deýcit hyperactivity disorder and learning disorder: A study from Pakistan Singapore Med J. 2008; 49:985-93
44. Thapar A, Thapar A. Is primary care ready to take on attention deýcit hyperactivity disorder? BMC Fam Pract. 2002; 3:7
45. Ghanizadeh A. Educating and counseling of parents of children with attention-deýcit hyperactivity disorder Patient Educ Couns. 2007; 68:23ï8
46. Goodman DW, Surman CB, Scherer PB, Salinas GD, Brown JJ. Assessment of physician practices in adult attention-deýcit/hyperactivity disorder Prim Care Companion CNS Disord. 2012; 14:pii: PCC.11m01312

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

Nagham Alkrissi [1], Ahmed Raja Albalawi [2], Wejdan Mohammad Alshehri [1], Wejdan Abdullah Alshehri [1], Arub Albalawi [1], Asmaa Alharbi [3]

[1] Family Medicine Resident, Tabuk
[2] FM consultant, Diabetologist, Director of Family Medicine Academy, Tabuk Health Cluster
[3] FM senior registrar

Corresponding author
Nagham Alkrissi
Family Medicine Resident, Tabuk
Saudi Arabia
Phone: 0556676643
Email: naghamalkhrissi@gmail.com

Received: June 2025. Accepted: July 2025; Published:July 20, 2025.
Citation: Nagham Alkrissi et al. Prevalence of limitations and barriers of receiving herpes-zoster vaccine among patients attending PHC in Tabuk city, 2023, cross-sectional study. World Family Medicine. July-August 2025; 23(5): 17-29. DOI: 10.5742/MEWFM.2025.805257861

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 signiýcantly 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, signiýcant 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, signiýcantly impair quality of life and daily functioning [3].

Vaccination is currently the most effective preventive measure, with recombinant zoster vaccine (RZV) representing high efýcacy 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 efýcacy, 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% conýdence 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 reýne ambiguous questions and reduce medical jargon to ensure participant understanding. Data from the pilot were excluded from the ýnal analysis. Additionally, a biostatistician reviewed the questionnaire to conýrm 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 classiýed 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 signiýcance 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 participantsû 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 identiýed 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 participantsû 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 unspeciýed 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

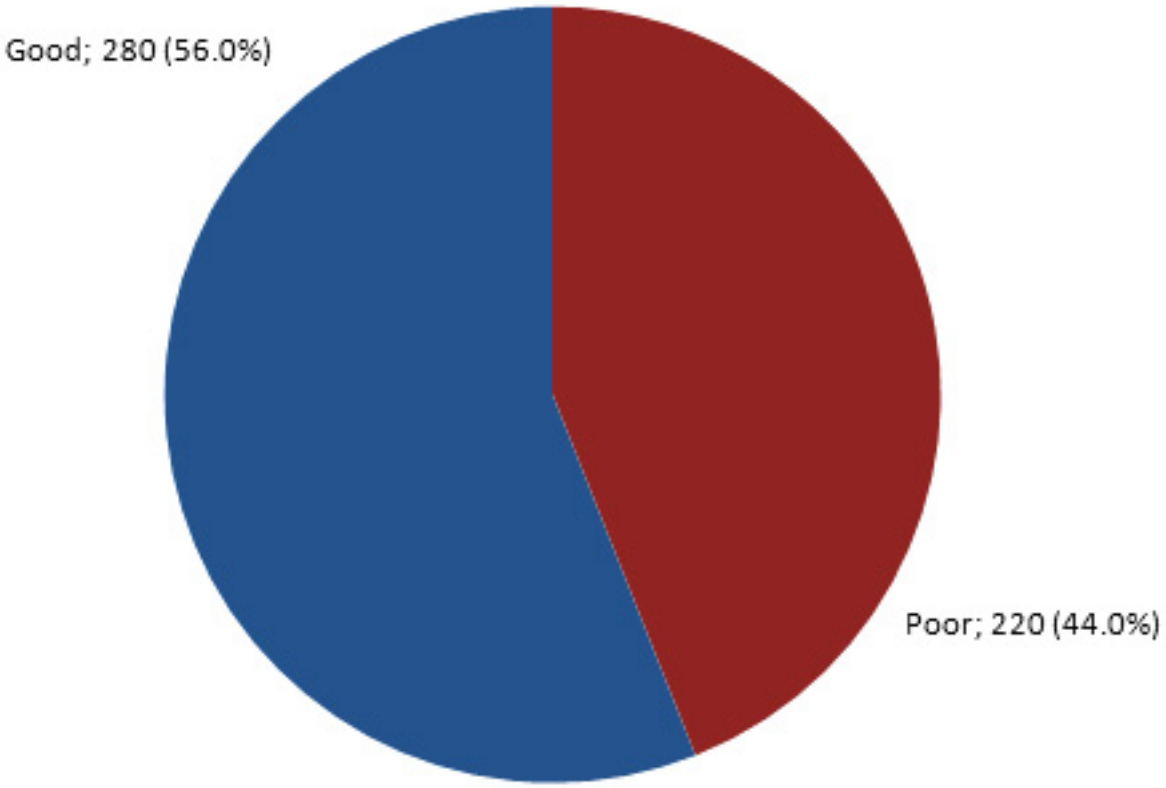

Figure 2. Source of Participants' Information about Varicella (Chickenpox), Shingles (Herpes Zoster), and Its Associated Symptoms and Vaccine

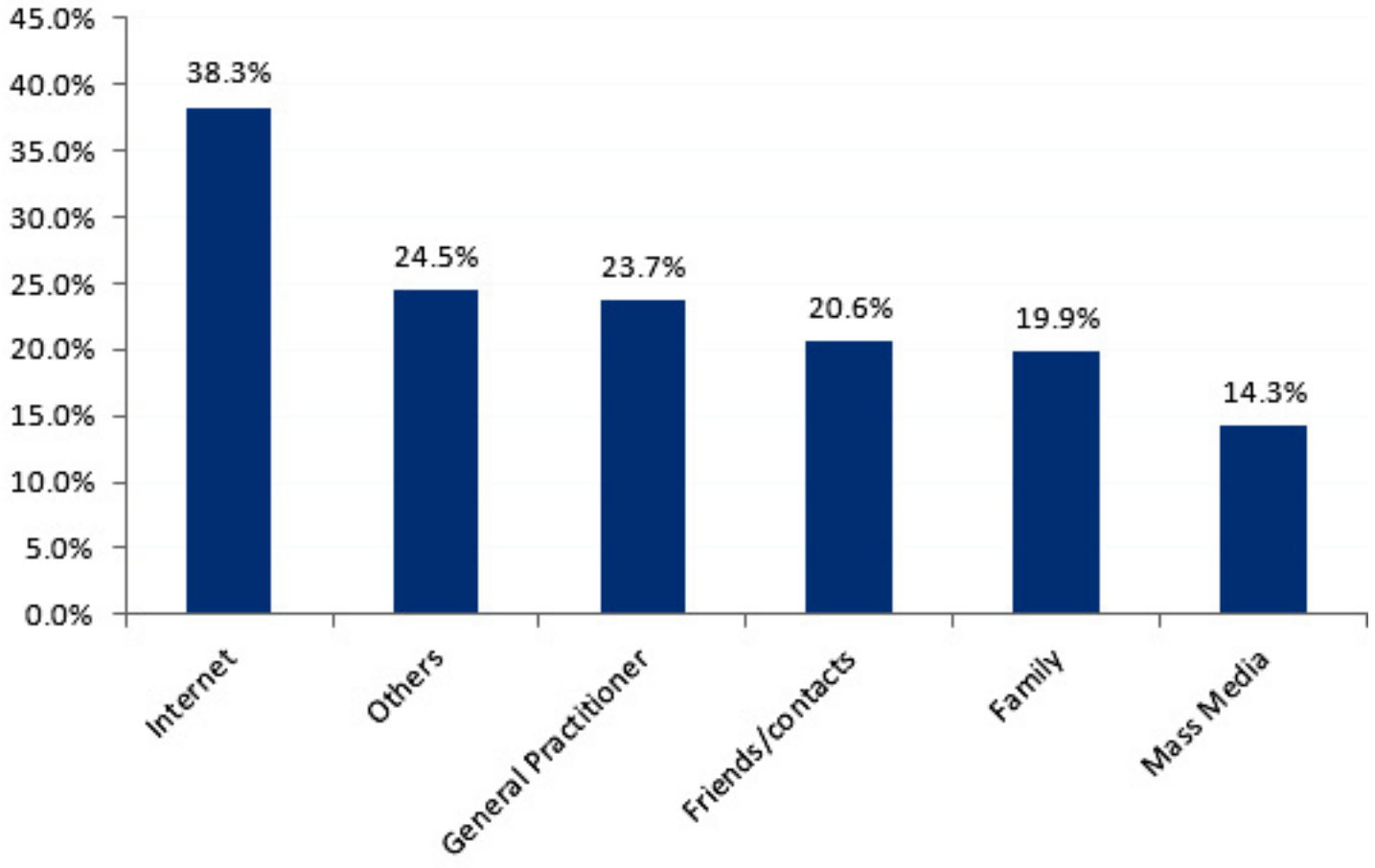

Table 3 presents the participants attitudes and perceptions toward vaccination in general and the shingles vaccine in particular. A strong majority (88.0%, n=440) believed that vaccines are an effective tool for prevention. When asked about their willingness to receive the shingles vaccine, 62.0% (n=310) 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%

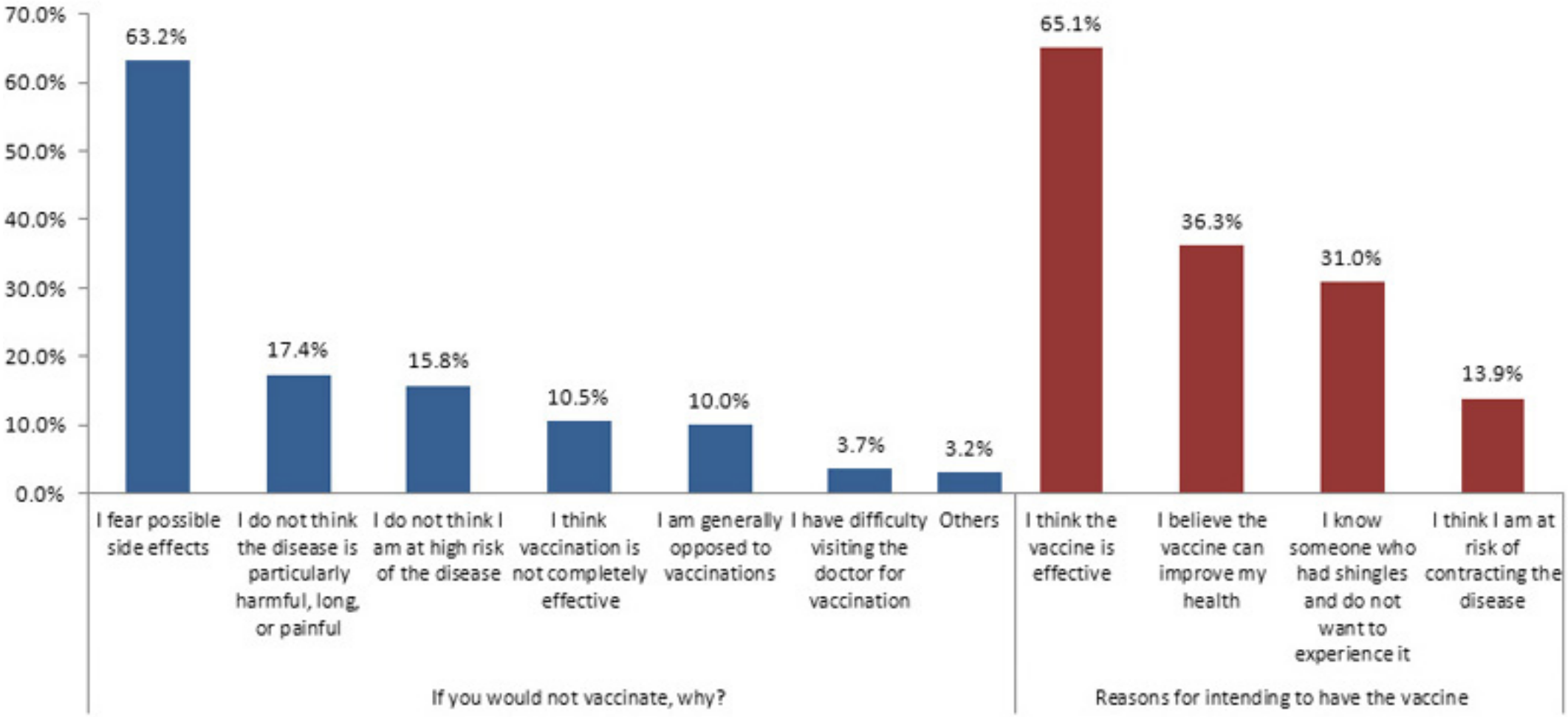

Figure 3. Reasons for Participants' Willingness or Unwillingness to Receive the Shingles Vaccine among Patients attending PHC in Tabuk city

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 difýculty 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 signiýcant difference, with females demonstrating higher knowledge levels than males (59.6% vs. 47.2%, p = .012). Nationality was also signiýcant (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 signiýcant 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 signiýcantly 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 signiýcantly higher knowledge levels (p = .001), compared to those relying on ñotherò sources (46.5%). On the other hand, age did not show a statistically signiýcant 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%	
Below secondary	37	69.8%	16	30.2%	.001*
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%	
Family	20	24.4%	62	75.6%	
Friends/contacts	28	32.9%	57	67.1%	.001*
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 signiýcant difference, with females demonstrating higher knowledge levels than males (59.6% vs. 47.2%, p = .012). Nationality was also signiýcant (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 signiýcant 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 signiýcantly 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 signiýcantly higher knowledge levels (p = .001), compared to those relying on ñotherò sources (46.5%). On the other hand, age did not show a statistically signiýcant association with knowledge level (p = .546).

Discussion

In this study, the bio-demographic proýle 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 signiýcant 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, reþecting deýciencies in personal health records and limited recall. This is consistent with ýndings 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 identiýed 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 reþect underdiagnosis, misreporting, or a lack of awareness among patientsû 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 signiýcantly 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 insufýcient 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, signiýcant 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-ýfth 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, reþecting gaps in public awareness of the diseaseîs 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 ýndings that conýdence in vaccines drives uptake [33]. Personal exposure to shingles and perceived health beneýts also played key roles, suggesting that direct experience with the disease may enhance vaccine willingness. However, the low inþuence 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 signiýcant 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 signiýcantly 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 inþuence vaccine acceptance. Public health campaigns to deliver accurate, culturally tailored messages, countering misinformation were commonly found online.

References

1. Schmader K. Herpes zoster in older adults. Clinical infectious diseases. 2001 May 15:1481-6.
2. Johnson RW, Alvarez-Pasquin MJ, Bijl M, Franco E, Gaillat J, Clara JG, Labetoulle M, Michel JP, Naldi L, Sanmarti LS, Weinke T. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. Therapeutic advances in vaccines. 2015 Jul;3(4):109-20.
3. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ open. 2014 Jun 1;4(6): e004833.
4. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, Levin MJ, McElhaney JE, Poder A, Puig-Barber¨ J, Vesikari T. Efýcacy of an adjuvanted herpes zoster subunit vaccine in older adults. New England Journal of Medicine. 2015 May 28;372(22):2087-96.
5. Moustafa NM, Alsaif N, Alsaeed E, Alanezi A, Algarni A, Alkathery L, Mohamed R, Alsaif NF, Alkathery LS. Assessing the Knowledge, Attitude, and Practice of Healthcare Workers on the Herpes Zoster Vaccine in Saudi Arabia: A Cross-Sectional Study. Cureus. 2025 Jan 11;17(1).
6. Duque S, Marinho A, Almeida P, Marques Pereira R, Buzaco R. Expanding the coverage of herpes zoster vaccination recommendations in European countries: the example of Portugal. Drugs & Therapy Perspectives. 2025 Jan 15:1-0.
7. Gagliardi AM, Andriolo BN, Torloni MR, Soares BG. Vaccines for preventing herpes zoster in older adults. Cochrane Database of Systematic Reviews. 2016(3).
8. Gabutti G, Bolognesi N, Sandri F, Florescu C, Stefanati A. Varicella zoster virus vaccines: an update. ImmunoTargets and therapy. 2019 Aug 6:15-28.
9. Tseng HF, Smith N, Harpaz R, Bialek SR, Sy LS, Jacobsen SJ. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. Jama. 2011 Jan 12; 305(2):160-6.
10. Galagali PM, Kinikar AA, Kumar VS. Vaccine hesitancy: obstacles and challenges. Current pediatrics reports. 2022 Dec; 10(4):241-8.
11. Singh P, Dhalaria P, Kashyap S, Soni GK, Nandi P, Ghosh S, Mohapatra MK, Rastogi A, Prakash D. Strategies to overcome vaccine hesitancy: a systematic review. Systematic reviews. 2022 Apr 26; 11(1):78.
12. World Health Organization (WHO). Varicella and herpes zoster vaccines: WHO position paper. Wkly Epidemiol Rec. 2014;89(25):265-88.
13. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report: Recommendations and Reports. 2008 Jun 6; 57(5):1-30.
14. Alsubaie SS, Gosadi IM, Alsaadi BM, Albacker NB, Bawazir MA, Bin-Daud N, Almanie WB, Alsaadi MM, Alzamil FA. Vaccine hesitancy among Saudi parents and its determinants: Result from the WHO SAGE working group on vaccine hesitancy survey tool. Saudi medical journal. 2019 Dec;40(12):1242.

15. Yawn BP, Gilden D. The global epidemiology of herpes zoster. Neurology. 2013 Sep 3; 81(10):928-30.
16. Albrecht MA, Levin MJ, Hirsch M, Mitty J. Epidemiology, clinical manifestations, and diagnosis of herpes zoster. UptoDate. 2022 [Internet]. 2023.
17. Al-Orini D, Alshoshan AA, Almutiri AO, Almreef AA, Alrashidi ES, Almutiq AM, Noman R, Al-Wutayd O. Acceptability of herpes zoster vaccination among patients with diabetes: a cross-sectional study in Saudi Arabia. Vaccines. 2023 Mar 14;11(3):651.
18. Alleft LA, Alhosaini LS, Almutlaq HM, Alshayea YM, Alshammari SH, Aldosari MA, Alateeq FA, Alhosaini L, Alshammari S, Aldosari M. Public knowledge, attitude, and practice toward herpes zoster vaccination in Saudi Arabia. Cureus. 2023 Nov 25;15(11).
19. Marin M, Marti M, Kambhampati A, Jeram SM, Seward JF. Global varicella vaccine effectiveness: a meta-analysis. Pediatrics. 2016 Mar 1; 137(3).
20. World Health Organization (WHO). Herpes zoster vaccine position paper. Wkly Epidemiol Rec. 2014; 89(25):265-88.
21. Lu PJ. Surveillance of vaccination coverage among adult populations ð United States, 2018. MMWR. Surveillance Summaries. 2021; 70.
22. Johnson RW, Alvarez-Pasquin MJ, Bijl M, Franco E, Gaillat J, Clara JG, Labetoulle M, Michel JP, Naldi L, Sanmarti LS, Weinke T. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. Therapeutic advances in vaccines. 2015 Jul; 3(4):109-20.
23. Patil A, Goldust M, Wollina U. Herpes zoster: a review of clinical manifestations and management. Viruses. 2022 Jan 19; 14(2):192.
24. Patel NJ, Chauhan D, Patel MR. Vaccination Hesitancy among Caregivers of Children under Five: A Mixed-Methods Study in Semi-Urban Areas. European Journal of Cardiovascular Medicine. 2025 Apr 9; 15:243-5.
25. Bunker D. Who do you trust? The digital destruction of shared situational awareness and the COVID-19 infodemic. International Journal of Information Management. 2020 Dec 1; 55:102201.
26. Marar SD, Al-Madaney MM, Almousawi FH. Health information on social media. Perceptions, attitudes, and practices of patients and their companions. Saudi medical journal. 2019 Dec;40(12):1294.
27. Alduraywish SA, Altamimi LA, Aldhuwayhi RA, AlZamil LR, Alzeghayer LY, Alsaleh FS, Aldakheel FM, Tharkar S. Sources of health information and their impacts on medical knowledge perception among the Saudi Arabian population: cross-sectional study. Journal of Medical Internet Research. 2020 Mar 19;22(3):e14414.
28. Alshakhs F, Alanzi T. The evolving role of social media in health-care delivery: measuring the perception of health-care professionals in Eastern Saudi Arabia. Journal of multidisciplinary healthcare. 2018 Sep 21:473-9.
29. MacDonald NE. Vaccine hesitancy: Deýnition, scope and determinants. Vaccine. 2015 Aug 14; 33(34):4161-4.
30. Newman AM, Jhaveri R. Myths and misconceptions: varicella-zoster virus exposure, infection risks, complications, and treatments. Clinical therapeutics. 2019 Sep 1; 41(9):1816-22.
31. Wang Q, Yang L, Li L, Liu C, Jin H, Lin L. Willingness to vaccinate against herpes zoster and its associated factors across WHO regions: global systematic review and meta-analysis. JMIR public health and surveillance. 2023 Mar 9; 9:e43893.
32. AlMuammar S, Albogmi A, Alzahrani M, Alsharef F, Aljohani R, Aljilani T. Herpes zoster vaccine awareness and acceptance among adults in Saudi Arabia: a survey-based cross-sectional study. Tropical Diseases, Travel Medicine and Vaccines. 2023 Oct 21; 9(1):17.
33. Hoffmann M, Baggio M, Krawczyk M. Vaccination demand and acceptance.

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

Mehmet Rami Helvaci[1], Hulya Halici[2], Kevser Erdogan[3], Murat Albayrak[1], Alper Sevinc[1], Celaletdin Camci[1], Abdulrazak Abyad[4], Lesley Pocock[5]

1 Specialist of Internal Medicine, MD, Turkey
2 Manager of Writing and Statistics, Turkey
3 Specialist of Public Health, MD, Turkey
4 Dar Alshifa Hospital Kuwait; Kuwait. Middle-East Academy for Medicine of Aging, Lebanon, MD
5 Medi-WORLD International, Australia

Corresponding author:
Prof Dr Mehmet Rami Helvaci
07400, ALANYA,
Turkey
Phone: 00-90-506-4708759
Email: mramihelvaci@hotmail.com

Received: June 2025. Accepted: July 2025; Published:July 20, 2025.
Citation: Helvaci MR et al. Chronic idiopathic thrombocytopenic purpura may even prolong survival in human beings in general. World Family Medicine. July-August 2025; 23(5): 30- 45. DOI: 10.5742/MEWFM.2025.805257862

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, signiýcantly.

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 inþammation, 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 chieþy affected in the process. Therefore the term of venosclerosis is not as famous as atherosclerosis in the literature. Due to the chronic endothelial damage, inþammation, edema, and ýbrosis, 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 inþammatory process are physical inactivity, sedentary lifestyle, emotional stress, animal-rich diet, smoking, alcohol, overweight, chronic inþammations, 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 insufýciencies and aging, the endothelial changes cannot be reversed, completely due to their ýbrotic 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 inþammatory and highly destructive processes on vascular endothelium, initiated at birth and terminated with an accelerated atherosclerosis-induced multiorgan insufýciencies 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 inþammations, infections, and additional stresses of the body. The hardened RBC-induced chronic endothelial damage, inþammation, edema, and ýbrosis 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 insufýciencies are the ýnal 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 inþammatory event were treated at ýrst, 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 ýlm, 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 patientsû 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 ýndings, 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 inýltrates on chest x-ray ýlm, fever, cough, sputum production, dyspnea, or hypoxia (16). An x-ray ýlm 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 Schamrothûs 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 ýndings as movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic ýndings, 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 ÀNonsigniýcant (p>0.05) ÿThalassemia 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 ÀNonsigniýcant (p>0.05) ÿRed blood cells ÄCoronary heart disease ÆChronic 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 ÀChronic obstructive pulmonary disease ÿPulmonary hypertension ÄCoronary heart disease ÆDeep 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 beneýt either to improve excess weight or to prevent its complications. Excess fat tissue may lead to a chronic and low-grade inþammation 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 inþammation 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 ýbrinolytic abnormalities suggesting that it causes a prothrombotic and proinþammatory state (21). The chronic inþammatory 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 inþammation on vascular endothelium terminating with an accelerated atherosclerosis-induced multiorgan insufýciencies in whole body (32). Its atherosclerotic effect is the most obvious in the COPD and Buergerîs disease (33). Buergerîs disease is an obliterative vasculitis characterized by inþammatory changes in the small and medium-sized arteries and veins, and it has never been documented in the absence of smoking. Its characteristic ýndings are acute inþammation, 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 Buergerîs disease. It is an intense pain caused by insufýcient blood þow 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. Raynaudîs phenomenon may also be seen in which ýngers or toes turn a white color upon exposure to cold. Skin ulcerations and gangrene of ýngers or toes are the ýnal consequences. Gangrene of ýngertips may even need amputation. Unlike many other forms of vasculitis, Buergerîs 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 Buergerîs disease, particularly in the lower extremities. Angiograms of upper and lower extremities are diagnostic for Buergerîs 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 Buergerîs 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 Buergerîs 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 Buergerîs 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 inþammation in this disorder, anti-inþammatory dose of aspirin plus low-dose warfarin may probably be effective to prevent microvascular infarctions in ýngers 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 inþammatory 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 inþammatory effects on vascular endothelium (35). In another deýnition, smoking causes a chronic inþammation 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 ýrst 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 inþammation 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 inþammation 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 inþammation 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, ýbrous 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 ýbrillation 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 inþammations, 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 Ó 40 kg/m2), and 81 kg between the lower borders of normal weight and super obesity (BMI Ó 45 kg/m2) in adults. In fact, there is a signiýcant 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 inþammation 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 þow-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 inþammatory process of the capillary endothelium in liver, since the systemic inþammatory effects of smoking on endothelial cells is well-known with Buergerûs disease and COPD (39). Increased oxidative stress, inactivation of antiproteases, and release of proinþammatory 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 inþammatory 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, inþammation, edema, tissue hypoxia, and multiorgan insuýciencies. So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with the following crises by leaving signiýcant 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 ýnal 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 difýcult 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 signiýcant efýcacy 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 inþammation 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 inþammatory 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 inþammatory 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 inþammatory 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 patientsî 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, ýnal 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 insufýciencies. 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 difýcult.

Aspirin is a member of nonsteroidal anti-inþammatory drugs (NSAID) used to reduce pain, fever, inþammation, and acute thromboembolic events. Although aspirin has similar anti-inþammatory 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 inþammation in the body. TX are responsible for the aggregation of PLT to form blood clots. In another deýnition, 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 ýrst 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 signiýcant 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 inþuenza 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-inþammatory dose in childhood in the SCD (76).

Warfarin is an anticoagulant, and ýrst 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 artiýcial 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 ýbrillation (AF), valvular heart disease, or artiýcial 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 ýve 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 sufýcient 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 ýve 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 signiýcant 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 signiýcant 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-beneýt proýle with signiýcant 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-inþammatory dose plus low-dose warfarin may be a life-saving treatment regimen even at childhood both to decrease severity of capillary endothelial inþammation 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 inþammations, prolonged infections, and cancers may be the major underlying causes. Atherosclerotic effects of smoking may be the most obvious in the COPD and Buergerîs 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 signiýcant 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 inþammatory process of vascular endothelium is enhanced by release of various chemicals by inþammatory cells, and it terminates with an advanced ýbrosis, 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 inþammation 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 Buergerûs disease, the leg ulcers occur in the distal segments of the body with a lesser collateral blood þow (101). The hardened RBC-induced chronic endothelial damage, inþammation, edema, and ýbrosis 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 insufýciencies 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, Buergerûs 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 ýrst 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 patientsû 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 inþammation and edema instead of the terminal ýbrosis alone.

Digital clubbing is characterized by the increased normal angle of 165Á between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal ýnger (105). Although the exact cause and signiýcance is unknown, the chronic tissue hypoxia is highly suspected (106). In the previous study, only 40% of clubbing cases turned out to have signiýcant 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, inþammation, edema, and ýbrosis 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, inþammatory or infectious processes, and cancers may be the major causes of the renal endothelial inþammation. The inþammatory 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 inþammation 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 signiýcant 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 hyperýltration 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 inþammatory 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 inþammatory 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 deýnition, 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 inþammations, 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 inþammation, edema, and ýbrosis (119). Probably, stroke may not have a macrovascular origin in the SCD, and diffuse capillary endothelial inþammation, edema, and ýbrosis may be much more important. Infections, inþammations, medical or surgical emergencies, and emotional stresses may precipitate stroke by increasing basal metabolic rate and sickling. A signiýcant reduction of stroke with hydroxyurea may also suggest that a signiýcant proportion of cases is developed due to the increased WBC and PLT counts-induced exaggerated capillary inþammation 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 ýndings suggest that these T cells can be inþuenced 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 efýcacy of splenectomy, ýndings on its long-term efýcacy 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.

References

1. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol 2003; 42(7): 1149-60.
2. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365(9468): 1415-28.
3. Franklin SS, Barboza MG, Pio JR, Wong ND. Blood pressure categories, hypertensive subtypes, and the metabolic syndrome. J Hypertens 2006; 24(10): 2009-16.
4. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) ýnal report. Circulation 2002; 106(25): 3143-421.
5. Helvaci MR, Aydin LY, Aydin Y. Digital clubbing may be an indicator of systemic atherosclerosis even at microvascular level. HealthMED 2012; 6(12): 3977-81.
6. Anderson RN, Smith BL. Deaths: leading causes for 2001. Natl Vital Stat Rep 2003; 52(9): 1-85.
7. Helvaci MR, Gokce C, Davran R, Akkucuk S, Ugur M, Oruc C. Mortal quintet of sickle cell diseases. Int J Clin Exp Med 2015; 8(7): 11442-8.
8. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994; 330(23): 1639-44.
9. Helvaci MR, Yaprak M, Abyad A, Pocock L. Atherosclerotic background of hepatosteatosis in sickle cell diseases. World Family Med 2018; 16(3): 12-8.
10. Helvaci MR, Kaya H. Effect of sickle cell diseases on height and weight. Pak J Med Sci 2011; 27(2): 361-4.
11. Helvaci MR, Aydin Y, Ayyildiz O. Hydroxyurea may prolong survival of sickle cell patients by decreasing frequency of painful crises. HealthMED 2013; 7(8): 2327-32.
12. Mankad VN, Williams JP, Harpen MD, Manci E, Longenecker G, Moore RB, et al. Magnetic resonance imaging of bone marrow in sickle cell disease: clinical, hematologic, and pathologic correlations. Blood 1990; 75(1): 274-83.
13. Helvaci MR, Aydin Y, Ayyildiz O. Clinical severity of sickle cell anemia alone and sickle cell diseases with thalassemias. HealthMED 2013; 7(7): 2028-33.
14. Fisher MR, Forýa PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009; 179(7): 615-21.
15. Vestbo J, Hurd SS, Agust² AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013; 187(4): 347-65.
16. Davies SC, Luce PJ, Win AA, Riordan JF, Brozovic M. Acute chest syndrome in sickle-cell disease. Lancet 1984; 1(8367): 36-8.
17. Vandemergel X, Renneboog B. Prevalence, aetiologies and signiýcance of clubbing in a department of general internal medicine. Eur J Intern Med 2008; 19(5): 325-9.
18. Schamroth L. Personal experience. S Afr Med J 1976; 50(9): 297-300.
19. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999; 341(15): 1097-105.
20. Helvaci MR, Aydin Y, Gundogdu M. Smoking induced atherosclerosis in cancers. HealthMED 2012; 6(11): 3744-9.
21. De Pergola G, Pannacciulli N. Coagulation and ýbrinolysis abnormalities in obesity. J Endocrinol Invest 2002; 25(10): 899-904.
22. Ross R. Atherosclerosis--an inþammatory disease. N Engl J Med 1999; 340(2): 115-26.
23. Ridker PM. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001; 103(13): 1813-8.
24. Ridker PM. High-sensitivity C-reactive protein and cardiovascular risk: rationale for screening and primary prevention. Am J Cardiol 2003; 92(4B): 17-22.
25. Danesh J, Collins R, Appleby P, Peto R. Association of ýbrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998; 279(18): 1477-82.
26. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999; 282(22): 2131-5.
27. Funahashi T, Nakamura T, Shimomura I, Maeda K, Kuriyama H, Takahashi M, et al. Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. Intern Med 1999; 38(2): 202-6.
28. Zhou B, Wu Y, Yang J, Li Y, Zhang H, Zhao L. Overweight is an independent risk factor for cardiovascular disease in Chinese populations. Obes Rev 2002; 3(3): 147-56.
29. Zhou BF. Effect of body mass index on all-cause mortality and incidence of cardiovascular diseases--report for meta-analysis of prospective studies open optimal cut-off points of body mass index in Chinese adults. Biomed Environ Sci 2002; 15(3): 245-52.
30. Helvaci MR, Kaya H, Yalcin A, Kuvandik G. Prevalence of white coat hypertension in underweight and overweight subjects. Int Heart J 2007; 48(5): 605-13.
31. Heilbronn LK, Ravussin E. Calorie restriction and aging: review of the literature and implications for studies in humans. Am J Clin Nutr 2003; 78(3): 361-9.
32. Fodor JG, Tzerovska R, Dorner T, Rieder A. Do we diagnose and treat coronary heart disease differently in men and women? Wien Med Wochenschr 2004; 154(17-18): 423-5.
33. Helvaci MR, Aydin LY, Aydin Y. Chronic obstructive pulmonary disease may be one of the terminal end points of metabolic syndrome. Pak J Med Sci 2012; 28(3): 376-9.
34. Helvaci MR, Kayabasi Y, Celik O, Sencan H, Abyad A, Pocock L. Smoking causes a moderate or severe inþammatory process in human body. Am J Biomed Sci & Res 2023; 7(6): 694-702.
35. Grunberg NE, Greenwood MR, Collins F, Epstein LH, Hatsukami D, Niaura R, et al. National working

conference on smoking and body weight. Task Force 1: Mechanisms relevant to the relations between cigarette smoking and body weight. Health Psychol 1992; 11: 4-9.
36. Helvaci MR, Camci C, Nisa EK, Ersahin T, Atabay A, Alrawii I, Ture Y, Abyad A, Pocock L. Severity of sickle cell diseases restricts smoking. Ann Med Medical Res 2024; 7: 1074.
37. Walker JF, Collins LC, Rowell PP, Goldsmith LJ, Moffatt RJ, Stamford BA. The effect of smoking on energy expenditure and plasma catecholamine and nicotine levels during light physical activity. Nicotine Tob Res 1999; 1(4): 365-70.
38. Hughes JR, Hatsukami DK. Effects of three doses of transdermal nicotine on post-cessation eating, hunger and weight. J Subst Abuse 1997; 9: 151-9.
39. Miyata G, Meguid MM, Varma M, Fetissov SO, Kim HJ. Nicotine alters the usual reciprocity between meal size and meal number in female rat. Physiol Behav 2001; 74(1-2): 169-76.
40. Froom P, Melamed S, Benbassat J. Smoking cessation and weight gain. J Fam Pract 1998; 46(6): 460-4.
41. Helvaci MR, Kaya H, Gundogdu M. Gender differences in coronary heart disease in Turkey. Pak J Med Sci 2012; 28(1): 40-4.
42. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ 1998; 316(7137): 1043-7.
43. Helvaci MR, Kabay S, Gulcan E. A physiologic eventsû cascade, irritable bowel syndrome, may even terminate with urolithiasis. J Health Sci 2006; 52(4): 478-81.
44. Helvaci MR, Dede G, Yildirim Y, Salaz S, Abyad A, Pocock L. Smoking may even cause irritable bowel syndrome. World Family Med 2019; 17(3): 28-33.
45. Helvaci MR, Algin MC, Kaya H. Irritable bowel syndrome and chronic gastritis, hemorrhoid, urolithiasis. Eurasian J Med 2009; 41(3): 158-61.
46. Kamimura D, Loprinzi PD, Wang W, Suzuki T, Butler KR, Mosley TH, et al. Physical activity is associated with reduced left ventricular mass in obese and hypertensive African Americans. Am J Hypertens 2017; 30(6): 617-23.
47. Bhatia LS, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? Eur Heart J 2012; 33(10): 1190-1200.
48. Paciýco L, Nobili V, Anania C, Verdecchia P, Chiesa C. Pediatric nonalcoholic fatty liver disease, metabolic syndrome and cardiovascular risk. World J Gastroenterol 2011; 17(26): 3082-91.
49. Mawatari S, Uto H, Tsubouchi H. Chronic liver disease and arteriosclerosis. Nihon Rinsho 2011; 69(1): 153-7.
50. Bugianesi E, Moscatiello S, Ciaravella MF, Marchesini G. Insulin resistance in nonalcoholic fatty liver disease. Curr Pharm Des 2010; 16(17): 1941-51.
51. Mostafa A, Mohamed MK, Saeed M, Hasan A, Fontanet A, Godsland I, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors. Gut 2010; 59(8): 1135-40.
52. Helvaci MR, Ayyildiz O, Gundogdu M, Aydin Y, Abyad A, Pocock L. Hyperlipoproteinemias may actually be acute phase reactants in the plasma. World Family Med 2018; 16(1): 7-10.
53. Parfrey NA, Moore W, Hutchins GM. Is pain crisis a cause of death in sickle cell disease? Am J Clin Pathol 1985; 84: 209-12.
54. Helvaci MR, Ayyildiz O, Gundogdu M. Hydroxyurea therapy and parameters of health in sickle cell patients. HealthMED 2014; 8(4): 451-6.
55. Helvaci MR, Tonyali O, Yaprak M, Abyad A, Pocock L. Increased sexual performance of sickle cell patients with hydroxyurea. World Family Med 2019; 17(4): 28-33.
56. Helvaci MR, Atci N, Ayyildiz O, Muftuoglu OE, Pocock L. Red blood cell supports in severe clinical conditions in sickle cell diseases. World Family Med 2016; 14(5): 11-8.
57. Helvaci MR, Ayyildiz O, Gundogdu M. Red blood cell transfusions and survival of sickle cell patients. HealthMED 2013; 7(11): 2907-12.
58. Helvaci MR, Cayir S, Halici H, Sevinc A, Camci C, Abyad A, Pocock L. Red blood cell transfusions may have the strongest analgesic effect during acute painful crises in sickle cell diseases. Ann Clin Med Case Rep 2024; V13(12): 1-12.
59. Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ, et al. Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med 2000; 342: 83-9.
60. Balkaran B, Char G, Morris JS, Thomas PW, Serjeant BE, Serjeant GR. Stroke in a cohort of patients with homozygous sickle cell disease. J Pediatr 1992; 120: 360-6.
61. Cole TB, Sprinkle RH, Smith SJ, Buchanan GR. Intravenous narcotic therapy for children with severe sickle cell pain crisis. Am J Dis Child 1986; 140: 1255-9.
62. Miller BA, Platt O, Hope S, Dover G, Nathan DG. Inþuence of hydroxyurea on fetal hemoglobin production in vitro. Blood 1987; 70(6): 1824-9.
63. Platt OS. Is there treatment for sickle cell anemia? N Engl J Med 1988; 319(22): 1479-80.
64. Helvaci MR, Aydogan F, Sevinc A, Camci C, Dilek I. Platelet and white blood cell counts in severity of sickle cell diseases. Pren Med Argent 2014; 100(1): 49-56.
65. Charache S. Mechanism of action of hydroxyurea in the management of sickle cell anemia in adults. Semin Hematol 1997; 34(3): 15-21.
66. Charache S, Barton FB, Moore RD, Terrin ML, Steinberg MH, Dover GJ, et al. Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive ñswitchingò agent. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Medicine (Baltimore) 1996; 75(6): 300-26.
67. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and beneýts up to 9 years of treatment. JAMA 2003; 289(13): 1645-51.
68. Lebensburger JD, Miller ST, Howard TH, Casella JF, Brown RC, Lu M, et al; BABY HUG Investigators. Inþuence of severity of anemia on clinical ýndings in infants with sickle cell anemia: analyses from the BABY HUG study. Pediatr Blood Cancer 2012; 59(4): 675-8.

69. Toghi H, Konno S, Tamura K, Kimura B, Kawano K. Effects of low-to-high doses of aspirin on platelet aggregability and metabolites of thromboxane A2 and prostacyclin. Stroke 1992; 23(10): 1400-3.
70. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 373(9678): 1849-60.
71. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol 2012; 13(5): 518-27.
72. Macdonald S. Aspirin use to be banned in under 16 year olds. BMJ 2002; 325(7371): 988.
73. Schr°r K. Aspirin and Reye syndrome: a review of the evidence. Paediatr Drugs 2007; 9(3): 195-204.
74. Pugliese A, Beltramo T, Torre D. Reyeîs and Reyeîs-like syndromes. Cell Biochem Funct 2008; 26(7): 741-6.
75. Hurwitz ES. Reyeîs syndrome. Epidemiol Rev 1989; 11: 249-53.
76. Meremikwu MM, Okomo U. Sickle cell disease. BMJ Clin Evid 2011; 2011: 2402.
77. Mohamed S, Fong CM, Ming YJ, Kori AN, Wahab SA, Ali ZM. Evaluation of an initiation regimen of warfarin for international normalized ratio target 2.0 to 3.0. J Pharm Technol 2021; 37(6): 286-92.
78. Chu MWA, Ruel M, Graeve A, Gerdisch MW, Ralph J, Damiano Jr RJ, Smith RL. Low-dose vs standard warfarin after mechanical mitral valve replacement: A randomized trial. Ann Thorac Surg 2023; 115(4): 929-38.
79. Crowther MA, Douketis JD, Schnurr T, Steidl L, Mera V, Ultori C, et al. Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneously vitamin K in the treatment of warfarin-associated coagulopathy. A randomized, controlled trial. Ann Intern Med 2002; 137(4): 251-4.
80. Brown DG, Wilkerson EC, Love WE. A review of traditional and novel oral anticoagulant and antiplatelet therapy for dermatologists and dermatologic surgeons. J Am Acad Dermatol 2015; 72(3): 524-34.
81. Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. CMAJ 2007; 177(4): 347-51.
82. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, major bleeding, and mortality outcomes in warfarin users with atrial ýbrillation and chronic kidney disease: a meta-analysis of observational studies. Chest 2016; 149(4): 951-9.
83. Chai-Adisaksopha C, Lorio A, Hillis C, Siegal D, Witt DM, Schulman S, et al. Warfarin resumption following anticoagulant-associated intracranial hemorrhage: A systematic review and meta-analysis. Thromb Res 2017; 160: 97-104.
84. Ferro JM, Coutinho JM, Dentali F, Kobayashi A, Alasheev A, Canhao P, et al. Safety and efýcacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: A randomized clinical trial. JAMA Neurol 2019; 76(12): 1457-65.
85. Meade TW. Low-dose warfarin and low-dose aspirin in the primary prevention of ischemic heart disease. Am J Cardiol 1990; 65(6): 7C-11C.
86. Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, Maraventano SW, et al. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial ýbrillation. N Engl J Med 1990; 323(22): 1505-11.
87. Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanya A, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. Lancet 1994; 343(8902): 886-9.
88. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efýcacy and safety of new oral anticoagulants with warfarin in patients with atrial ýbrillation: a meta-analysis of randomised trials. Lancet 2014; 383(9921): 955-62.
89. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and beneýts of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. BMJ 2018; 362: k2505.
90. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial ýbrillation. N Engl J Med 2009; 361(12): 1139-51.
91. Helvaci MR, Cayir S, Halici H, Sevinc A, Camci C, Abyad A, Pocock L. Terminal endpoints of systemic atherosclerotic processes in sickle cell diseases. World Family Med 2024; 22(5): 13-23.
92. Helvaci MR, Daglioglu MC, Halici H, Sevinc A, Camci C, Abyad A, Pocock L. Low-dose aspirin plus low-dose warfarin may be the standard treatment regimen in Buergerîs disease. World Family Med 2024; 22(6): 22-35.
93. Helvaci MR, Erden ES, Aydin LY. Atherosclerotic background of chronic obstructive pulmonary disease in sickle cell patients. HealthMED 2013; 7(2): 484-8.
94. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: deýnition, assessment, and prevention. Lancet 2015; 385(9979): 1778-88.
95. Schoepf D, Heun R. Alcohol dependence and physical comorbidity: Increased prevalence but reduced relevance of individual comorbidities for hospital-based mortality during a 12.5-year observation period in general hospital admissions in urban North-West England. Eur Psychiatry 2015; 30(4): 459-68.
96. Singh G, Zhang W, Kuo YF, Sharma G. Association of Psychological Disorders With 30-Day Readmission Rates in Patients With COPD. Chest 2016; 149(4): 905-15.
97. Mannino DM, Watt G, Hole D, Gillis C, Hart C, McConnachie A, et al. The natural history of chronic obstructive pulmonary disease. Eur Respir J 2006; 27(3): 627-43.
98. Mapel DW, Hurley JS, Frost FJ, Petersen HV, Picchi MA, Coultas DB. Health care utilization in chronic obstructive pulmonary disease. A case-control study in a health maintenance organization. Arch Intern Med 2000; 160(17): 2653-58.
99. Anthonisen NR, Connett JE, Enright PL, Manfreda J; Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002; 166(3): 333-9.

100. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA; TORCH Clinical Endpoint Committee. Ascertainment of cause-speciýc mortality in COPD: operations of the TORCH Clinical Endpoint Committee. Thorax 2007; 62(5): 411-5.
101. Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. Adv Skin Wound Care 2004: 17(8); 410-6.
102. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg ulcers in sickle cell disease. Am J Hematol 2010; 85(10): 831-3.
103. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 2014; 312(10): 1033-48.
104. Helvaci MR, Aydogan F, Sevinc A, Camci C, Dilek I. Platelet and white blood cell counts in severity of sickle cell diseases. HealthMED 2014; 8(4): 477-82.
105. Myers KA, Farquhar DR. The rational clinical examination. Does this patient have clubbing? JAMA 2001; 286(3): 341-7.
106. Toovey OT, Eisenhauer HJ. A new hypothesis on the mechanism of digital clubbing secondary to pulmonary pathologies. Med Hypotheses 2010; 75(6): 511-3.
107. Nassiri AA, Hakemi MS, Asadzadeh R, Faizei AM, Alatab S, Miri R, et al. Differences in cardiovascular disease risk factors associated with maximum and mean carotid intima-media thickness among hemodialysis patients. Iran J Kidney Dis 2012; 6(3): 203-8.
108. Helvaci MR, Gokce C, Sahan M, Hakimoglu S, Coskun M, Gozukara KH. Venous involvement in sickle cell diseases. Int J Clin Exp Med 2016; 9(6): 11950-7.
109. Xia M, Guerra N, Sukhova GK, Yang K, Miller CK, Shi GP, et al. Immune activation resulting from NKG2D/ligand interaction promotes atherosclerosis. Circulation 2011; 124(25): 2933-43.
110. Hall JE, Henegar JR, Dwyer TM, Liu J, da Silva AA, Kuo JJ, et al. Is obesity a major cause of chronic kidney disease? Adv Ren Replace Ther 2004; 11(1): 41-54.
111. Nerpin E, Ingelsson E, Ris®rus U, Helmersson-Karlqvist J, Sundstr°m J, Jobs E, et al. Association between glomerular ýltration rate and endothelial function in an elderly community cohort. Atherosclerosis 2012; 224(1): 242-6.
112. Stengel B, Tarver-Carr ME, Powe NR, Eberhardt MS, Brancati FL. Lifestyle factors, obesity and the risk of chronic kidney disease. Epidemiology 2003; 14(4): 479-87.
113. Bonora E, Targher G. Increased risk of cardiovascular disease and chronic kidney disease in NAFLD. Nat Rev Gastroenterol Hepatol 2012; 9(7): 372-81.
114. Helvaci MR, Cayir S, Halici H, Sevinc A, Camci C, Sencan H, Davran R, Abyad A, Pocock L. Acute chest syndrome and coronavirus disease may actually be genetically determined exaggerated immune response syndromes particularly in pulmonary capillaries. World Family Med 2024; 22(3): 6-16.
115. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006; 17(7): 2034-47.
116. Helvaci MR, Aydin Y, Aydin LY. Atherosclerotic background of chronic kidney disease in sickle cell patients. HealthMED 2013; 7(9): 2532-7.
117. DeBaun MR, Gordon M, McKinstry RC, Noetzel MJ, White DA, Sarnaik SA, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med 2014; 371(8): 699-710.
118. Majumdar S, Miller M, Khan M, Gordon C, Forsythe A, Smith MG, et al. Outcome of overt stroke in sickle cell anaemia, a single institutionîs experience. Br J Haematol 2014; 165(5): 707-13.
119. Kossorotoff M, Grevent D, de Montalembert M. Cerebral vasculopathy in pediatric sickle-cell anemia. Arch Pediatr 2014; 21(4): 404-14.
120. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med 1995; 332(20): 1317-22.
121. Stasi R, Stipa E, Masi M, Cecconi M, Scim¸ MT, Oliva F, et al. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. Am J Med 1995; 98(5): 436-42.
122. McMillan R, Durette C. Long-term outcomes in adults with chronic ITP after splenectomy failure. Blood 2004; 104(4): 956-60.
123. Vianelli N, Galli M, de Vivo A, Intermesoli T, Giannini B, Mazzucconi MG, et al. Efýcacy and safety of splenectomy in immune thrombocytopenic purpura: long-term results of 402 cases. Haematologica 2005; 90(1): 72-7.
124. Chaturvedi S, Arnold DM, McCrae KR. Splenectomy for immune thrombocytopenia: down but not out. Blood 2018; 131(11): 1172-82.
125. Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). Blood 2005; 106(7): 2244-51.
126. Schoonen WM, Kucera G, Coalson J, Li L, Rutstein M, Mowat F, et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. Br J Haematol 2009; 145(2): 235-44.

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

Hamad Ibrahim Albalawi [1], Majed Akram AlGhassab [1], Nawaf Almalki [1], Nada Awad Dabi AlSuhaimi [2], Rasha Hassan [3], Ahmad Raja Saeed Albalawi [4]

[1] Family Medicine Resident, MOH Tabuk Program, Saudi Arabia
[2] Senior Registrar, Family Medicine, King Salman Armed Forces Hospital, Tabuk, Saudi Arabia
[3] Consultant Family Medicine, Ministry of Health Tabuk, Saudi Arabia
[4] Family Medicine & Diabetes Management Consultant, Director Family Medicine Academy, Tabuk Health Cluster

Corresponding author:
Hamad Ibrahim Albalawi
Family Medicine Resident, Tabuk Health Cluster, Saudi Arabia
Mobile Number: +966580504300
Email: hhamad143@gmail.com

Received: June 2025. Accepted: July 2025; Published:July 20, 2025.
Citation: Hamad Ibrahim Albalawi et al. 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 World Family Medicine. July-August 2025; 23(5): 46-54.
DOI: 10.5742/MEWFM.2025.805257863

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 identiýcation 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 Fisherûs Exact Test, t-tests, and ANOVA. A p-value < 0.05 was considered statistically signiýcant.

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 signiýcant association was found between CD and being underweight (p = 0.049). Other variables such as age, gender, insulin dosage, and DKA frequency showed no signiýcant correlation with CD. However, males and patients diagnosed with T1DM at an older age were found to have a signiýcantly 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 speciýc 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 conýrmation 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 deýciencies, 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 deýciency due to autoimmune destruction of pancreatic ß-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 identiýed, and the minimum required sample size was calculated to be 373 patients, using a 95% conýdence level, 5% margin of error, and assuming a prevalence of 50%. The ýnite population formula was applied for this calculation. All patients with a conýrmed 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 ýrst 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 signiýcant 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 15ï30 years [n=189], and 49.3% aged 0ï14 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 10ï12 years [42.9%, n=160], with a mean age of diagnosis of 12.6 Ñ 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 Ñ 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 ýve [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)

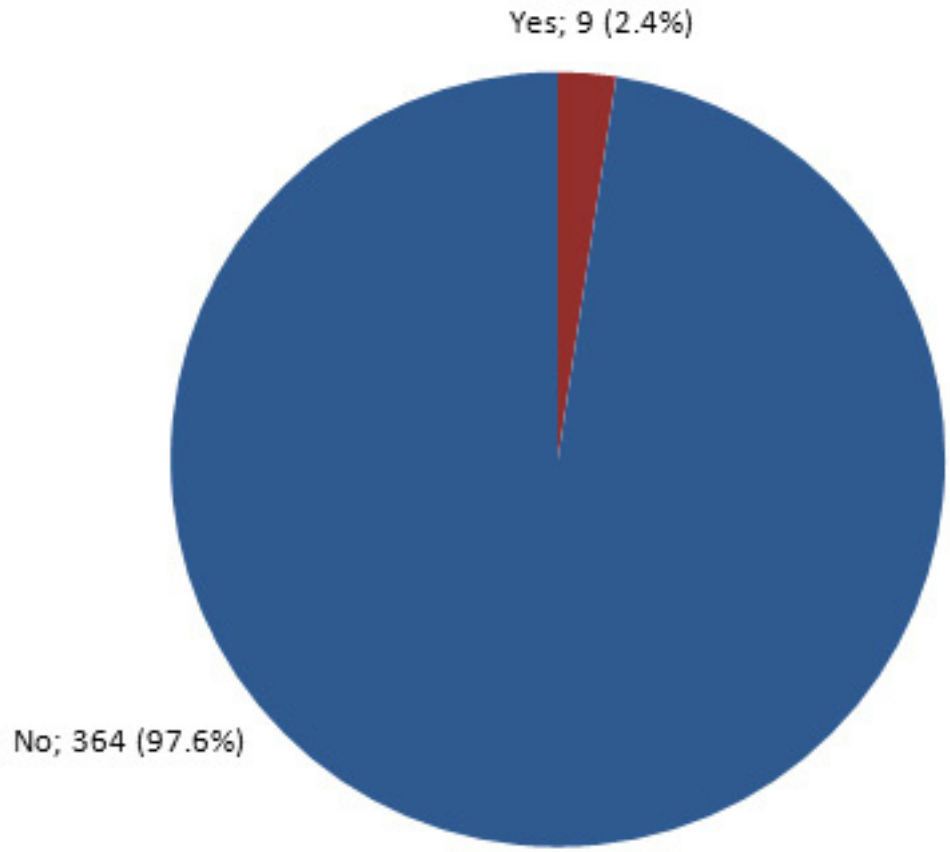

Table 1. Bio-Demographic Characteristics of Type 1 Diabetic Patients in Diabetic center of Tabuk City, Saudi Arabia 2024 (N=373)

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 ñwellò physical condition at the time of diagnosis [100%]. Glycemic control, as reþected 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 signiýcant associations with celiac disease, except for body mass index [BMI], which demonstrated a signiýcant 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 signiýcant associations. For example, 2.7% of children aged 0ï14 years and 2.1% of those aged 15ï30 years had celiac disease. Males and females had similar prevalence rates [2.3% vs. 2.5%, respectively]. Likewise, no signiýcant 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%].