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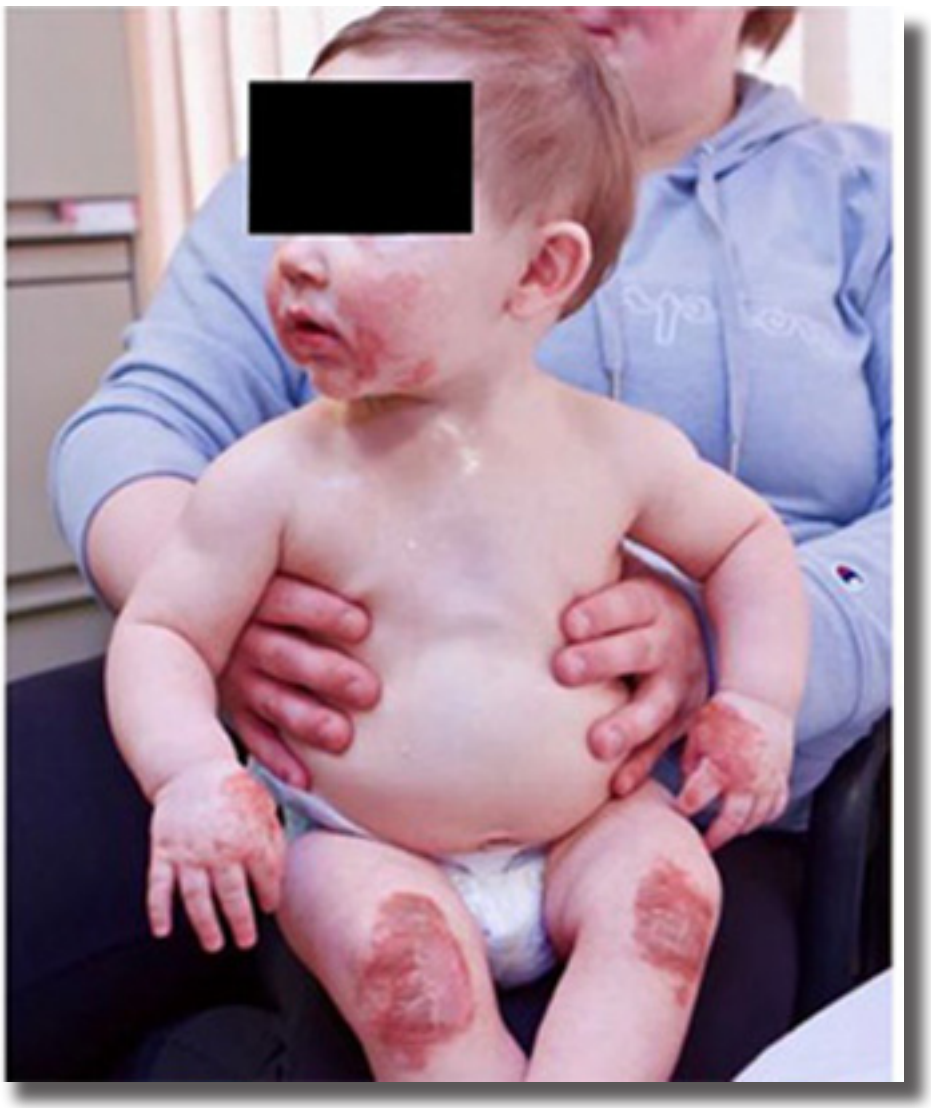

The Prescribing of Zinc in Family Medicine ... page 6

Editorial

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Editorial: Advancing Community-Oriented Primary Care through Evidence and Awareness

As we welcome the May issue of the Middle East Journal of Family Medicine, we are reminded of the essential role family physicians play in bridging primary care with public health priorities. This month's issue presents a diverse set of research contributions that not only highlight diagnostic and therapeutic challenges in clinical practice, but also point to the urgent need for health education and community-level interventions in the Middle East.

The feature article on zinc prescribing in family medicine underscores the importance of recognizing micronutrient deficiencies that often remain undiagnosed in everyday practice. Despite the availability of testing, zinc deficiency continues to be overlooked, resulting in non-specific presentations that delay diagnosis and treatment. The authors emphasize the diagnostic overlap with conditions like hypothyroidism and vitamin deficiencies and advocate for a more structured approach to supplementation and monitoring. As we push toward holistic patient care, such insights reinforce the value of integrative, nutrition-aware primary care.

Another standout paper explores the use of acarbose in patients with chronic obstructive pulmonary disease (COPD)—a condition deeply linked to systemic inflammation and metabolic disturbances. Through a nuanced discussion on endothelial dysfunction and the broader implications of atherosclerosis in COPD, the authors propose acarbose as a low-cost, oral agent with potential to modulate both glycemic control and systemic inflammation. This novel approach opens avenues for rethinking metabolic interventions in non-diabetic populations, especially in the context of excess fat tissue and vascular risk in the Middle East.

This month's issue features a critical contribution from Nepal examining the local adverse reactions associated with inhaled corticosteroid (ICS) use among patients with asthma and COPD. In this cross-sectional study of 138 patients, over half (58.7%) reported at least one local side effect—including tooth decay, throat irritation, and oral candidiasis—with a higher incidence among females, illiterate individuals, and those using higher ICS doses (200 mcg or BID regimens).

Importantly, the study found that self-management strategies such as saltwater gargling, mouthwash use, and antifungal creams were commonly used to mitigate symptoms. However, many patients lacked proper education on inhaler use, underscoring a persistent gap in patient counseling and device technique training.

The findings emphasize the need for patient-centered respiratory care that goes beyond prescribing medication—highlighting the importance of education, follow-up, and the use of spacers to reduce side effects. As the burden of COPD and asthma grows across South Asia and the Middle East, such studies offer practical insights for improving medication adherence and long-term outcomes.

The second maternal health contribution addresses the epidemiology and management of ectopic pregnancy at a tertiary center in Saudi Arabia. Through retrospective analysis, the study identifies common risk factors such as prior abortions and cesarean deliveries while noting the relatively low rates of hemodynamic instability at presentation—a testament to improved diagnostic capabilities. Nonetheless, the findings call for enhanced screening, awareness, and timely intervention to reduce complications.

Together, these contributions shed light on clinical practices, diagnostic reasoning, and preventive strategies vital for family physicians. Whether it is optimizing micronutrient management, rethinking pharmacologic options in chronic disease, or closing the gap in maternal health literacy, the common thread is clear: evidence-based, community-oriented care is not a luxury—it is a necessity.

At MEJFM, we remain committed to disseminating research that informs practice, policy, and patient empowerment. We encourage our readers to reflect on the lessons offered in this issue and to apply them in ways that enhance care across all levels of the health system.

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

Letter to the Editor: Fear not the path of righteousness for the lack of people walking on it

Dr Safaa T. Bahjat MD

On behalf of the Gaza people and the cognoscenti of global health I would like to express gratitude to Lesley Pocock for her contributions.

Lesley, you are touching more souls through your writings than you realize.

These poignant, meaningful and thought provoking articles throw knives right into the heart of truth. Courageously she has decided to take a stand for the innocent people and our planet. Most of us feel that we can't stand up and say much lest we become marked as trouble makers and outsiders, after all we need our paychecks to survive in the dreary grind of daily living and the evaporated future and squandered life. Some are too busy paying mortgages; others try to make sure the kids get to school on time and try to get them to eat some breakfast before they go. In the last two articles published in the Middle East Journal of Family Medicine she shatters the silence surrounding crucial issues by choosing to travel through the inner recesses of Tyrone's psyche. Rather than pontification from a distance about the war crimes in Gaza, she pulls the trigger and shoots the targets. She reminds me of the tree stump in Shel Silverstein's children's story by giving a sip of humanity to the world when it is most parched!

No wonder she lives in a place that used to be the home of lions with a body trained to endure severe tropical cyclone Savannah. I envision the strength of her hands and her tool (pen) like claws that could hold down any threat until it surrendered!. Her recent two articles are an eloquent appeal to a world on the edge of civilization Suicide.!!!

This J'accuse she hurls in the face of tyranny and tyrants who sway public opinions and change behavior. She believes that Gods/Universe desire to keep the stuff of life hidden from us. There is no instruction book for human progress and despite the accumulation of human knowledge the application of our talent never results in linear advance. She calls it mortal predicament. Her world revolves around it. She understands the cruelty of men as an evil that metastasized in the planet.

It is so easy to get overwhelmed and have decision paralysis by living in a world where capitalist democracies have become mere facade democracies and populism as the symptom of democratic failure.

I am someone who is unusually prone to despair. Maybe I have been fighting this for a long time. Part of the reason we feel despair is because we do not see long term change when we are looking at crisis after crisis after crisis. She continues to grapple with these questions. Would life on earth be just fine without us? What is the biggest blind spot we have that the future generations will look back on and think "What were they doing?"

When I ponder my life and the world I feel optimistic because I see more people like her with unexpected acts of generosity that restore one's faith in humanity. People like her that provide us at least a glimmer of light at the end of the tunnel. Yet others disappoint us terribly. Both of these things are true at the same time and holding these competing concepts together is really exhausting but it is also essential. Finally I quote: *The most beautiful people we have known are those who have known defeat, known suffering, known struggle, known loss, and have found their way out of the depths. These persons have an appreciation, a sensitivity, and an understanding of life that fills them with compassion, gentleness, and a deep loving concern. Beautiful people do not just happen*. Elisabeth Kübler-Ross.

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Special Editorial: Peace, Reconstruction and Justice for Palestinians - in Gaza, the West Bank and beyond
http://www.mejfm.com/JanFeb%202025/Special%20Editorial.pdf
Lesley Pocock
DOI: 10.5742/MEWFM.2025.95257876

Opinion: War and planetary viability are the biggest family medicine issues globally
http://www.mejfm.com/November%202024/War%20and%20peace.pdf
Lesley Pocock
DOI: 10.5742/MEWFM.2024.95257861

The Prescribing of Zinc in Family Medicine

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Abstract

Zinc is a trace mineral that is required by the human body. Despite testing being readily available in the Middle East, zinc deficiency and its management is poorly understood within the family medicine model. Diagnosis can be difficult because manifestations can vary from mild to severe symptoms. We must exercise caution due to co-existing alternative mineral deficiencies. Understanding the difference between acquired and genetic deficiencies can guide treatment. This paper will focus on diagnosing and treating symptoms of zinc deficiency within the community setting.

Keywords:zinc, zinc deficiency,severe symptoms, treatment

Background

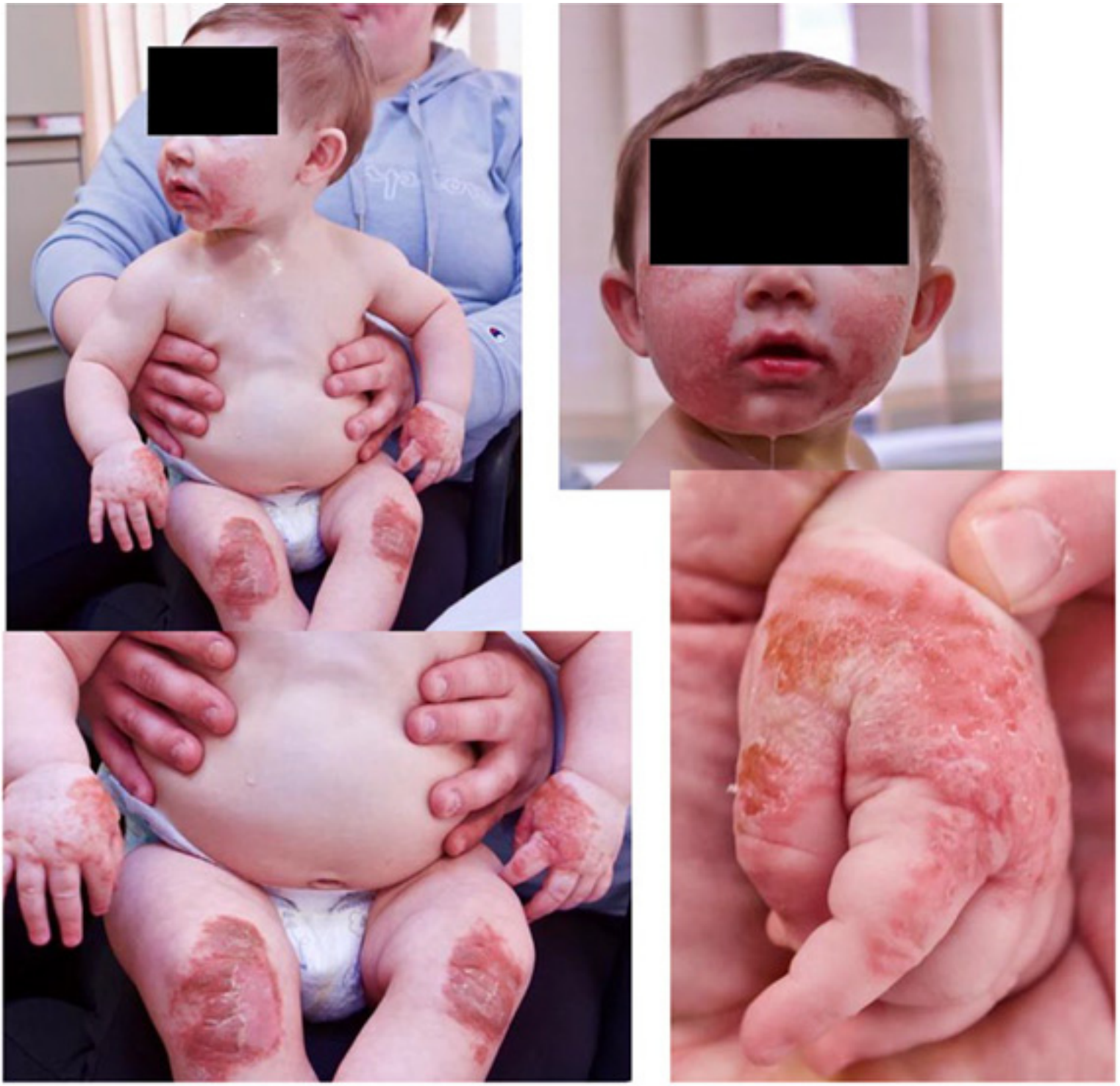
Zinc is a fundamental antioxidant in the function of enzymes and transcription factors. The micronutrient plays an important role in development, immunity, protein synthesis, taste, smell, skin and hair health. The link between zinc deficiency and the myriad signs and symptoms is currently not well understood and we suggest that is why zinc deficiency is often overlooked, especially in primary care [1].

Zinc deficiency can be delineated into two aetiologies: congenital and acquired.

Acrodermatitis enteropathica is the rare autosomal-recessive genetic disorder that causes severe zinc deficiency and affects fewer than 1 in 500,000 people globally. It typically presents in infancy with vesicular dermatitis, malabsorptive diarrhoea, chronic infections and failure to thrive [2].

Acquired zinc deficiency can be further dichotomised into nutritional and metabolic causes. Nutritional deficiency is prevalent in least developed countries where diets may have reduced quantities of zinc, as well as foodstuffs that inhibit zinc absorption: phytates, oxalates and clay. More developed countries tend to consume more meat which is rich in zinc, as well as having zinc fortification in common staple foods. Notwithstanding, metabolic conditions such as end-organ disease and HIV may reduce the level of zinc found in plasma and serum, as well as frailty and iatrogenic factors such as thiazide diuretics. Another factor to consider is that significant alcohol consumption impacts nutritional zinc levels, which is more prevalent in the developed world [3] [4].

Figure 1: Acrodermatitis enteropathica [5]



Epidemiology

It is estimated approximately 17% of the global population are at risk from zinc deficiency. This further increases to 30% in South Asia, with a similar number in the Arab World. It is estimated that there is degree of zinc deficiency in approximately 2 billion people in developing areas; those most at risk are children and the elderly [6].

There is limited data on zinc deficiency in the Middle East. Studies on school children revealed low dietary intake of zinc. In a further study it showed that it may be common in type 2 diabetic patients because of their hyperglycaemia and polyurea [7] [8].

Symptoms

Diagnosis of zinc deficiency tends to be delayed due to the gross overlap of non-specific symptoms, especially within the time-pressured environment of family medicine. Suspicion should remain high in high-risk groups, such as: end-organ damage; haemoglobinopathy; iatrogenic risk (hydrochlorothiazide, penicillamine, ethambutol, among others); elderly >65 years; alcohol excess; vegan diet. Symptoms vary depending on severity of the deficiency, with multiple organ systems affected:

Table 1: Signs and Symptoms of Zinc Deficiency [9]

Mild	Moderate	Severe
Stomatitis	Chronic kidney disease	Bullous or pustular dermatitis
Weight-loss	Chronic liver disease	Diarrhoea
Altered testosterone and sperm count	Growth retardation including osteopenia/osteoporosis	Hair-loss
Altered sense of taste	Delayed gonadal development	Recurrent infections
	Skin reactions	Immunodeficiency
	Anorexia	Mood changes
	Delayed wound healing	Neurological symptoms

Differential Diagnosis

- Hypothyroidism – Can be difficult to differentiate clinically with zinc deficiency due to overlapping symptoms. Thyroid function testing is integral [10].
- Haematinic deficiency – Can co-exist with reduced zinc; full blood count and haematinic testing can be used to differentiate [10].
- Vitamin A & D deficiency – Can also co-exist with reduced zinc; vitamin testing can be used to differentiate [10].
- Depression – Many overlapping symptoms including low mood and anhedonia. This is a clinical diagnosis and zinc levels are normal [10].
- Atopic Dermatitis – Can be differentiated clinically from zinc deficiency as this does not cause hair loss. In addition, zinc deficiency typically presents with a cutaneous rash in an acral and peri-orifical distribution [11].
- Seborrhoeic Dermatitis – Can be differentiated clinically from zinc deficiency as this typically presents in the flexural distribution [11].
- Langerhans Cell Histiocytes – Can be differentiated clinically from zinc deficiency as this presents with a papulopustular rash in the napkin area [12].
- Bullous Disorders – Can be differentiated clinically from zinc deficiency as this can leave slow-healing wounds when the blisters burst [13].
- Human Immunodeficiency Virus – Can present with recurrent infections and skin rashes. Virology testing prudent.
- Malabsorption Symptoms (including Gluten Enteropathy) – Can present with abdominal pain/distension, bloating, vomiting and diarrhoea [11] [12].

Treatment

Dietary sources of zinc can be obtained from meat, dairy and seafood such as oysters and shellfish. Plant-based sources include whole grains, nuts and beans [14]. Prior to any zinc treatment, the underlying causes must also be addressed.

The National Institute of Health stipulate the daily intake of elemental zinc is as follows (measuring the minimum quantity of absorption to match the total excretion of endogenous zinc): [15]

Table 2: Daily Intake of Zinc [15]

Age	Male	Female
Birth to 6 months	2mg	2mg
7-12 months	3mg	3mg
1-3 years	3mg	3mg
4-8 years	5mg	5mg
9-13 years	8mg	8mg
4-18 years	11mg	9mg
Adults >18 years	11mg	8mg

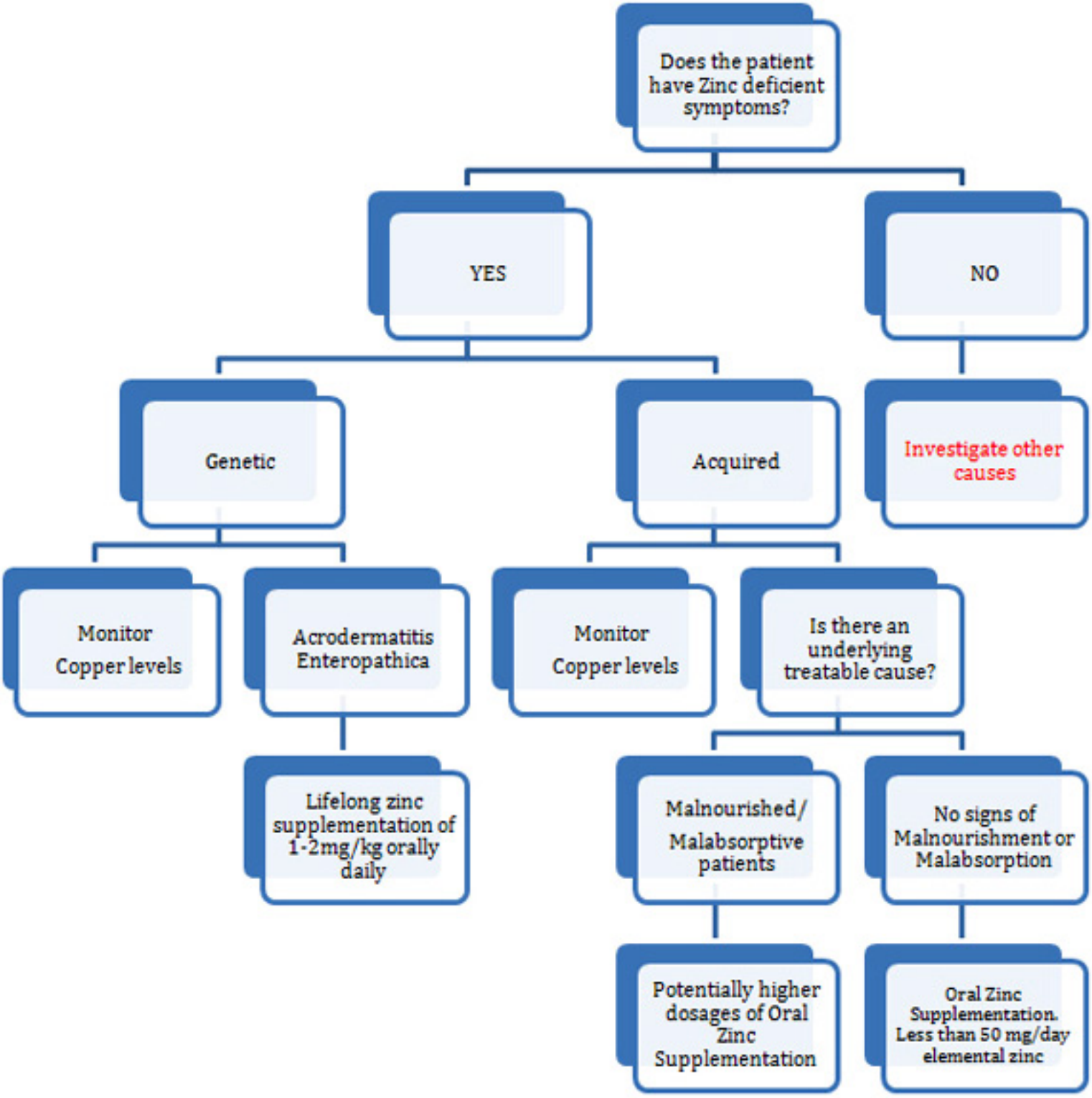
Higher doses may be required for malnourished/malabsorptive patients, pregnant or breastfeeding patients [15].

The supplemental doses of elemental zinc vary due to the degree of variability between subjects and their degree of absorption. When one looks at understanding how much zinc is required in deficiency, one should utilise the 'no observed adverse effect level' (NOAEL).

It is the consensus from several studies that high doses of zinc supplementation can cause displacement of metal ions and therefore cause potential harm. A particular element that is relevant is copper. A measure of copper status or balance can determine the safe NOAEL. This has been determined for a healthy adult to be a value of 50mg/day of elemental zinc [16] [17].

Considerations of the route of supplementation include intestinal absorption and the mode of their nutritional intake. Parenteral zinc is rarely necessary, therefore oral zinc treatment is commonly used. Oral treatment dosage should be less than this NOAEL. Some common forms of supplementation including zinc sulphate, zinc acetate and zinc gluconate. Their bioavailability may vary significantly. Actual dosages of these supplements vary, but their elemental amounts usually are generally less than 50mg [18].

Figure 2: Treating Zinc Deficiency



Monitoring

Patients should be regularly monitored for their response to treatment and alleviation of symptoms. It is widely accepted that whilst on treatment most minerals should tested up-to every 3 months. Thereafter at least yearly monitoring is required. With Acrodermatitis Enteropathica treatment can be tailored individually by monitoring.

Zinc toxicity can be classified as acute and chronic. Acute toxicity (>200mg/day) can cause neurological and gastrointestinal symptoms, whereas chronic raised levels (50-150mg/day) may affect absorption, or the metabolism of copper and iron. It can also lead to atherosclerosis, genitourinary, cardiac and pancreatic complications. Rarely can excess dietary intake cause toxic zinc levels. [10] [15] [18].

Summary

Zinc is an essential component in the human body and deficiencies can produce a varying degree of symptoms. Many other conditions share similar signs which is why the diagnosis may prove challenging to clinicians. Although there is limited data on its prevalence in the Middle East, this will change with time. More awareness is required to allow for quicker diagnosis and more rapid treatment. There may be other associated mineral deficiencies alongside zinc. Treatment can be tailored and is usually safe, but monitoring is required.

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Evaluation of Inhaled Corticosteroids use and Associated Local Adverse Reactions in Respiratory Disease Patients at a Tertiary Care Teaching Hospital in Nepal

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Abstract

Background: Bronchial asthma and Chronic Obstructive Pulmonary Disease (COPD) are major respiratory diseases in Nepal, with an increasing prevalence. Inhaled corticosteroids (ICS) are the cornerstone of treatment, reducing exacerbations and mortality. However, local adverse reactions such as oropharyngeal candidiasis, dysphonia, and throat irritation can impact medication adherence and patient quality of life.

Materials and Methods: This cross-sectional descriptive study was conducted at a tertiary care teaching hospital in Nepal over a period of six months. Patients diagnosed with asthma or COPD and prescribed inhaled corticosteroids were included. Data on demographic characteristics, ICS usage, their dosage duration and severity of adverse drug reactions were collected through structured questionnaires. Those adverse drug reactions were observed and preventive measures taken by patients to counteract adverse drug reactions were included. Statistical analysis was performed using SPSS version 22, with chi-square tests applied to assess associations between variables.

Results: Among 138 patients, 81 (58.7%) reported at least one ICS-related adverse reaction, with a higher prevalence in females ($p<0.001$) and illiterate patients ($p<0.001$). The most commonly used Inhaled Corticosteroids was fluticasone (33.3%), and frequently reported adverse effects included tooth decay (35.8%), throat irritation (20.99%), and tongue abrasion (19.75%). Higher Inhaled corticosteroids dosages (200 mcg) and twice-daily regimens were significantly associated with increased adverse reactions ($p<0.001$). Self- management strategies included salt and water gargling (30.9%), use of antifungal cream (22.2%), and mouthwash use (21%).

Conclusion: ICS-related local adverse effects are common and influenced by demographic and drug related factors. Proper inhaler techniques, patient education, and preventive measures can help mitigate those effects and enhance treatment adherence.

Key words: Inhaled corticosteroids, adverse drug reactions, oral candidiasis, dysphonia

Introduction

Bronchial asthma is a chronic inflammatory disease that typically begins in childhood characterized by dyspnea, chest tightness, cough and recurrent episodes of wheezing. Chronic obstructive pulmonary disease (COPD) is marked by an enhanced chronic inflammatory response that distorts lung architecture, causing progressive irreversible airflow limitation. Both are major respiratory diseases with significant health concerns in Nepal (1). Diagnosis relies on clinical history, physical examination, chest x-ray and spirometry, the gold standard for confirmation (2).In Nepal the prevalence of respiratory diseases is increasing day by day in which the prevalence of asthma ranges from 4.2%to 8.9% and that of COPD varies between 1.67% to 14.3% (3).

Current guidelines recommend inhaled medications as the first line of treatment, including bronchodilators and inhaled corticosteroids. Bronchodilators help in dilation of constricted bronchioles for the flow of air in the obstructed airways: inhaled corticosteroids reduce exacerbations, inflammatory reaction and decrease mortality rates (4). Systemic adverse reactions of ICSs have been extensively studied, which are more common compared to infrequent local adverse reactions. Oro-pharyngeal candidiasis, dysphonia, pharyngitis, tongue abrasion, choking, tongue burning and cough are generally considered as common local adverse reactions which are more clinically significant and affect patient's quality of life by hampering daily food intake, compliance with medication and also mask symptoms of more serious diseases (5,6).

Local adverse reaction also depends on the drug formulation, dose, duration of use, regimen, characteristics of the inhaler device, intrinsic inflammation of the upper airways in respiratory disease patients, mechanical irritation caused by cough and concomitant inflammatory environmental factors (air pollution) and occupational exposure to chemical irritants. Similarly patients' related factors like physical disability, ageing, dementia, and difficulties in cognition leading to incorrect use of devices are major factors so careful attention to proper use of metered dose inhaler (MDI), and usage of spacer device are important factors to reduce local adverse reactions (7).
This study aims to find out various local adverse reactions on patients using inhaled corticosteroids on respiratory diseases and their management in order to prevent the further serious complications. Selection of better inhaled corticosteroids with appropriate doses for required duration are utmost important steps to prevent adverse drug reactions. It also helps in identifying proper use of inhaler device, spacers to prevent local adverse reactions and also helps in identification of various methods to manage the local adverse reactions.

Methods

This cross sectional descriptive study was designed to assess the prevalence, types and management of local adverse reactions associated with inhaled corticosteroids (ICS) among patients with respiratory diseases at a tertiary care teaching hospital. The study was conducted from August 2024 to 2025 for a period of six months after obtaining ethical approval from Institutional Review Committee (IRC) of Kathmandu Medical College (Ref:05082024/06).The study included patients diagnosed with respiratory diseases (e.g. Asthma, COPD) who are under treatment with inhaled corticosteroids (ICS) after taking informed verbal/written consent in the department of Internal Medicine.

Inclusion Criteria:
• Patients aged 18 years or older.
• Diagnosed with respiratory diseases such as asthma or COPD.
• Currently using ICS therapy.
• Capable of understanding study objectives and providing informed consent.
Exclusion Criteria:
• Pregnant or lactating women.
• Patients with mental health issues, cancers, or other terminal illnesses.
• Patients who are unable to provide informed consent.
• Uncooperative or unwilling participants

Data were collected using structured questionnaires in which demographic characteristics like (age, sex, occupation, education, and associated disease were included along with types of ICS used and their dose, and duration;) similarly types and frequency of local adverse effects were recorded along with measures taken to manage local adverse effects. A systematic random sampling method was used to calculate the sample size.

Sample size:

$n = z^2pq/e^2$

. Z = 1.96 (for 95% confidence level),

p = 0.10

(expected local adverse reactions)

e = 0.05 (desired precision),

N = 5000 (population size).

$$n = \frac{(1.96)^2 . 0.10 . (1-0.10) . 5000}{(0.05)^2} \quad \frac{}{5000+1}$$

$$n = \frac{3.8416 . 0.10 . 0.90 . 0.9998}{0.0025}$$

n = 138.29. 0.9998

n = 138

Descriptive statistics (mean, standard deviation, frequency and percentage) were used to summarize patient characteristics and prevalence of adverse reactions. Chi square test was used to identify the effect of demographic and drug related factors with adverse reactions and their management. Data were analyzed using SPSS program, version 22.The study aimed to provide insights into optimizing ICS therapy and improving patient outcomes by enhancing understanding and management of local adverse reactions in this population.

Results

Out of 150 enrolled patients 138 patients participated in the study. The socio-demographic characteristics of patients are given in Table 1.There were 59(42.8%) from the age group below 60 years and 79(57.2%) were from age group more than 60 years. The number of male patients were 66(47.8%) and female 72(52.2%) respectively. On the basis of residence 58(42%) were residing in a village whereas 80(58%) were residing in the city. The Majority 52(37.7%) had obtained school level of education whereas 38(27.5%) were illiterate. On the basis of occupation 58(42%) were house builders, 31(22.5%) were office workers and 15(10.9%) were drivers. More than 70(50.7%) were suffering from respiratory diseases for more than 5 years and 68(49.3%) had been suffering from respiratory diseases less than 5 years duration. On the basis of associated diseases 88(63.8%) had respiratory disease along with other systemic diseases whereas 50(36.2%) were suffering from only respiratory disease. Chronic kidney disease followed by heart disease, diabetes mellitus and skin lesion disease are the other associated diseases.

Table 1: Socio-demographic characteristics of patients (n=138)

	Frequency	Percent
1.1 Age		
≤ 60 years	59	42.8
>60 years	79	57.2
Total	138	100.0
1.2 Sex		
Male	66	47.8
Female	72	52.2
Total	138	100.0
1.3 Residence		
Village	58	42.0
City	80	58.0
Total	138	100.0
1.4 Education		
Illiterate	38	27.5
School level	52	37.7
College level	39	28.3
University level	9	6.5
Total	138	100.0
1.5 Occupation		
Farmer	16	11.6
House builder	58	42.0
Office worker	31	22.5
Driving	15	10.9
Other	18	13.0
Total	138	100.0
1.6 Duration of disease		
≤5 years	68	49.3
> 5 years	70	50.7
Total	138	100.0
1.7 Associated other diseases		
Heart disease	23	26.1
Diabetes mellitus	20	22.7
Chronic kidney disease	27	30.7
Skin diseases	16	18.2
Other diseases	2	2.3
Total	138	100.0

On the basis of used of inhaled corticosteroids for the treatment of respiratory diseases (33.33%) had used Fluticasone followed by combination Salmeterol+Fluticasone (23.91%), Budesonide(22.46%) and Beclomethasone (20.29%).

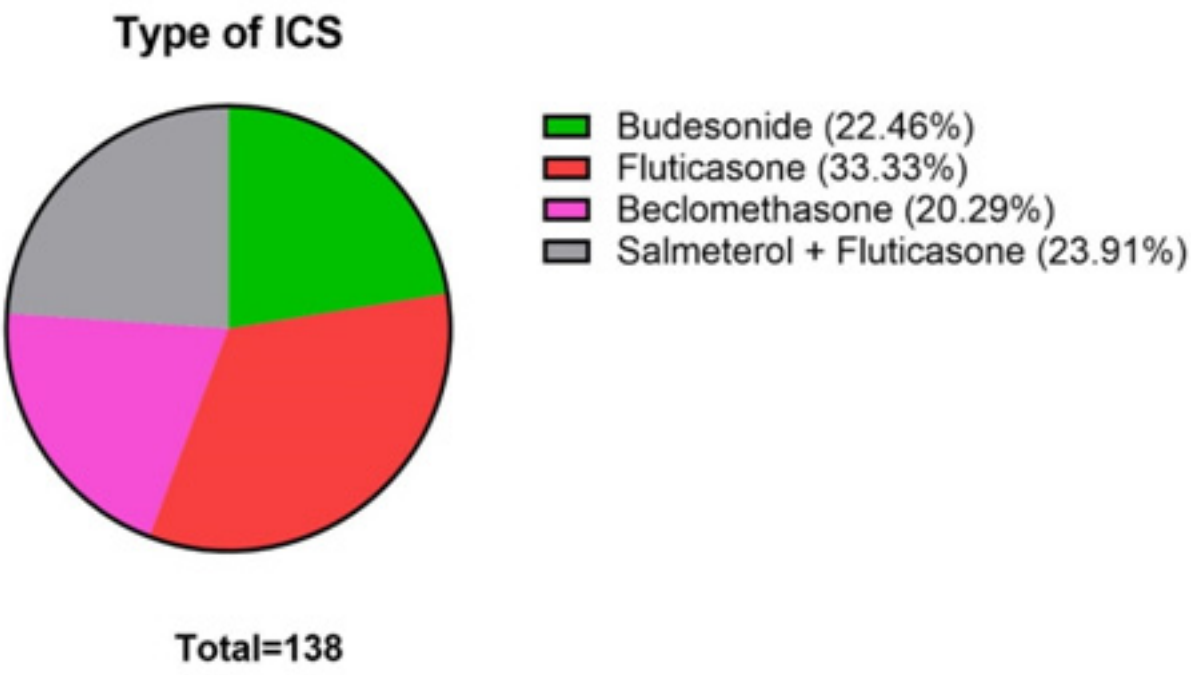

Figure 1: Types of inhaled corticosteroids used by the patients

Among 138 patients using inhaled corticosteroids for respiratory disease like asthma, chronic obstructive pulmonary disease 81 (58.7%) were found/ reported to have one or more signs of adverse drug reactions whereas 57(41.3) had not reported any adverse drug reaction.

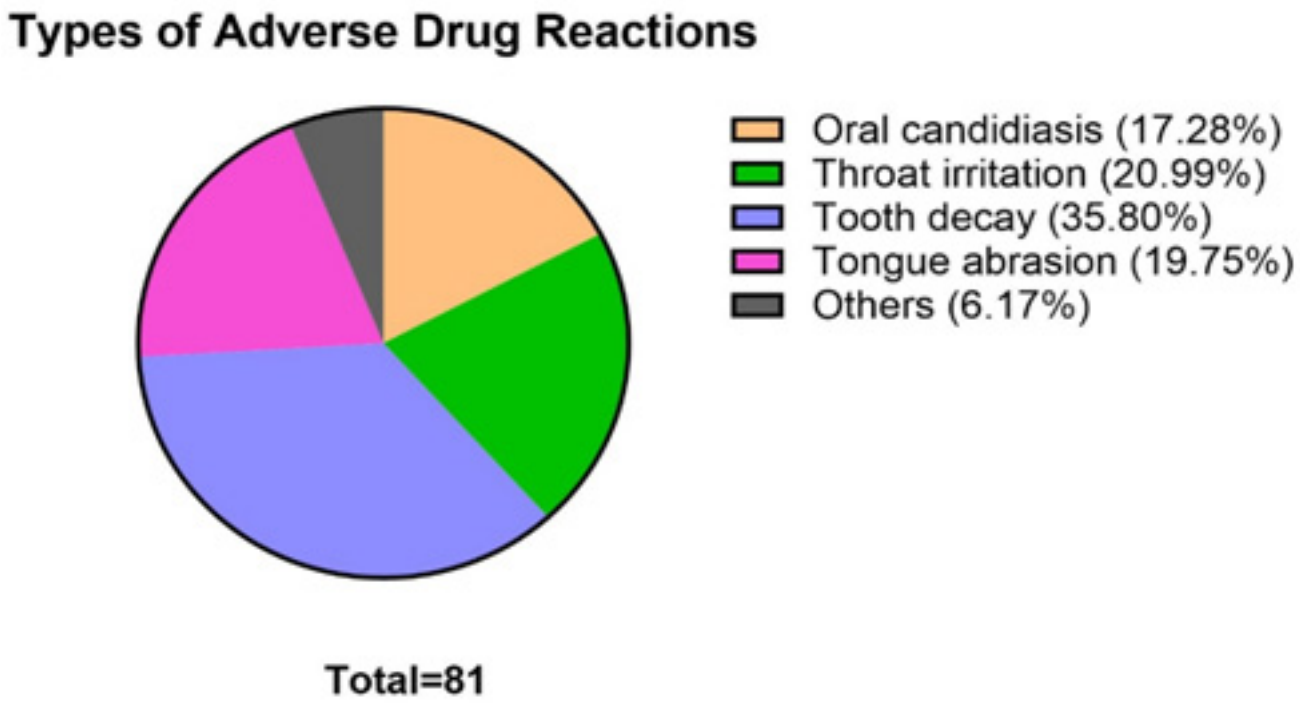

Figure 2: Types of adverse drug reactions from objective assessment

There was no significant difference in adverse reaction occurrence observed between age groups (p=0.37).On the basis of gender higher incidence was found in the female population which was significant (p<0.001).Similarly on the basis of education illiterate patients experienced more adverse drug reaction compared to educated (p<0.001).House builder reported more adverse effects compared to farmer and office worker in the context of occupation (p<0.001).

Table 2: Effect of demographic characteristics on adverse drug reactions (n=81)

Demographic feature	Frequency	Percent	Chi-square value (df)	p-value
Age			0.80 (1)	0.37
≤ 60 years	36	44.4		
>60 years	45	55.6		
Sex			10.86 (1)	<0.001
Male	39	48.1		
Female	42	51.8		
Education			27.17 (3)	<0.001
Illiterate	27	33.3		
School level	27	33.3		
College level	18	22.2		
University level	9	11.2		
Occupation			23.57 (4)	<0.001
Farmer	22	27.1		
House builder	35	43.2		
Office worker	9	11.1		
Driving	10	12.3		
Other	5	6.1		

Patients with disease duration ≤5 years reported more adverse effects compare to >5years (p=0.005).Similarly based on co-morbidities patients with diabetes mellitus were found with more adverse effects significantly (p=0.01).On the basis of dosage and its relation with adverse effects patients with 200mcg dosage had more adverse effects (p<0.001). Those patient who took twice daily dose (BID) were associated with higher incidence of adverse effects compare to single dose taking patients (p<0.001).

Table 3: Effect of asthma, other diseases and corticosteroid dosage on adverse drug reactions (n=81)

Variable	Frequency	Percent	Chi-square value (df)	p-value
Duration of disease			7.82 (1)	0.005
≤5 years	42	51.8		
>5 years	39	48.1		
Co-occurrence of other disease			10.59 (3)	0.01
Heart disease	21	25.9		
Diabetes mellitus	27	33.3		
Kidney disease	17	20.9		
Skin disease	16	19.7		
Type of ICS drug			3.85 (3)	0.28
Budesonide	17	20.9		
Fluticasone	23	28.3		
Beclomethasone	23	28.3		
Salmeterol+ Fluticasone	18	22.2		
Dosage of ICS drug			22.13 (2)	<0.001
100 mcg	12	14.8		
200 mcg	44	54.3		
250 mcg	25	30.8		
ICS dosage frequency			14.28 (1)	<0.001
OD	26	32.0		
BID	55	68.0		

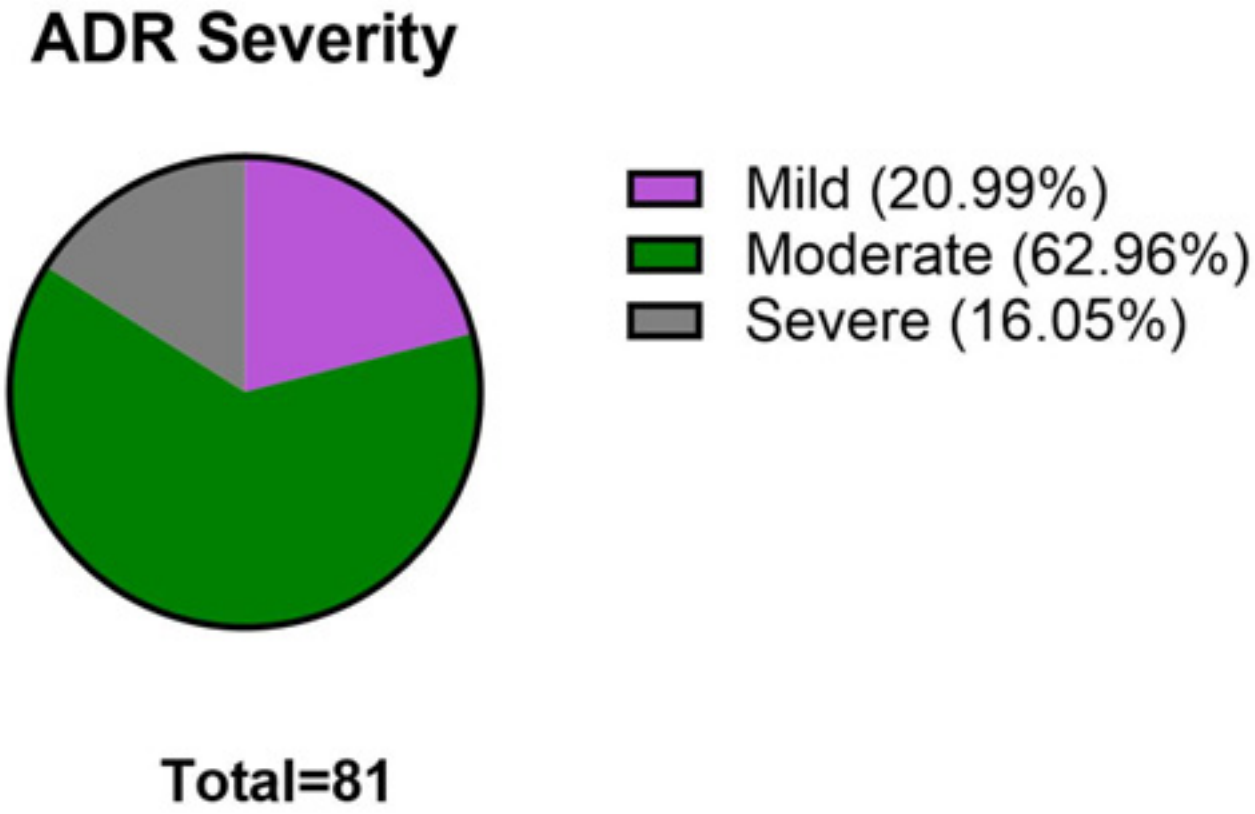

Figure 3: Severity of adverse drug reactions in the patients

Among 81 patients with adverse drug reactions, 16.0%had an episode almost every day, 56.8% at least once a week and 27.2% had it at least once a month. About 68 % of the patients had an adverse drug reaction onset after a month while 32% developed within a week of use of inhaled corticosteroids.

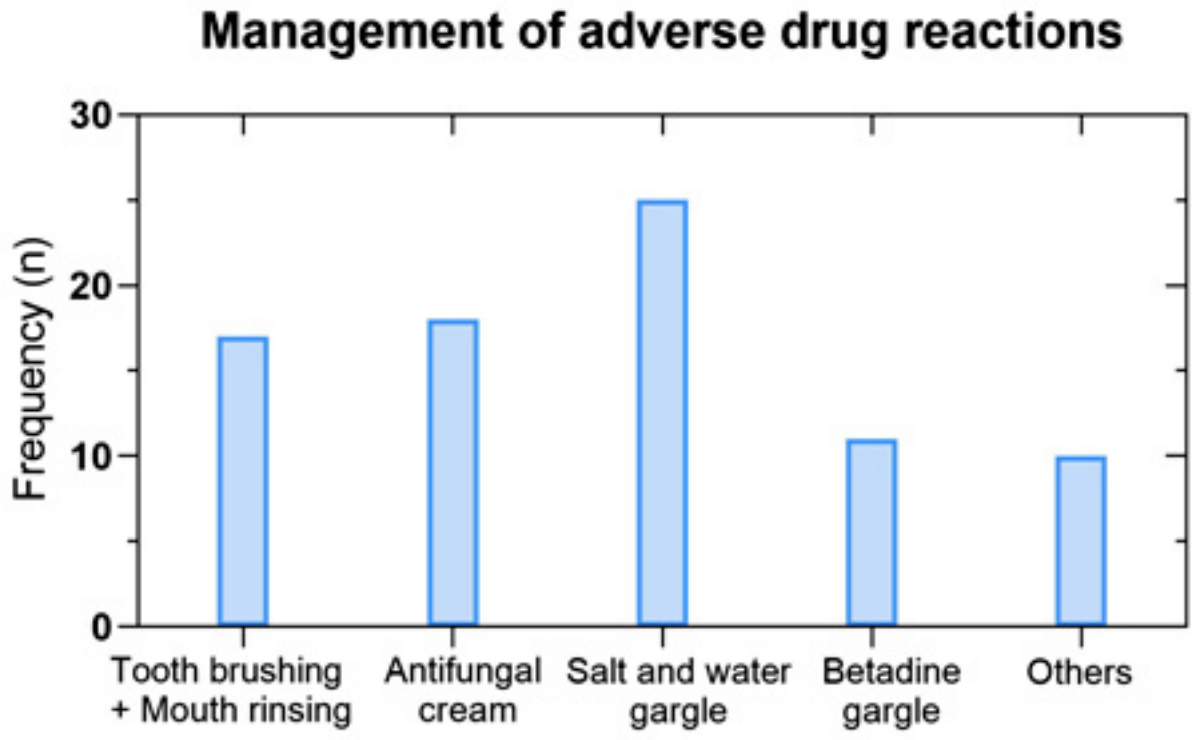

Figure 4: Management of adverse drug reactions adopted by the patients

For the management of adverse drug reaction 25(30.9%) had used salt and water gargle. Similarly 18(22.2%) had used antifungal cream for the treatment of oral candidiasis, 17(21%) had used mouthwash for rinsing and regular tooth brushing, 11(13.6%) had used Betadine gargle for the management whereas 10(7.2%) had used other methods like using oral ointments for the management of adverse reaction.

Discussion

This study provides a comprehensive analysis of the socio-demographic characteristics and adverse drug reactions associated with inhaled corticosteroids (ICS) therapy in patients with respiratory diseases and their management at tertiary care teaching hospital. Among 138 diagnosed respiratory disease patient using inhaled corticosteroids the majority of them 79 (57.2%) were over 60 years of age which is similar with the study conducted by Cooper et al which might be due to age related changes in drug metabolism (8).Another similar study found that asthma was more prevalent in children and COPD was more prevalent in older patients (9).Sex-based differences were also notable, with 66 (47.8%) male and 72 (52.2%) female participants which is similar with the study conducted in Nepal by Adhikari et al in which 54% of the patients were female and also Cooper had similar findings which might be due to variations in hormone levels and differences in immune system (1).

Regarding residence, 58 (42%) of the patients were from rural areas, while 80 (58%) resided in urban settings which is similar with the findings of a study done in Nepal which could be linked to increased environmental pollution, lifestyle factors, and greater healthcare access leading to more frequent prescriptions (10).Education level significantly influenced ADR occurrence. Among participants, 38 (27.5%) were illiterate, 52 (37.7%) had attained school-level education, 39 (28.3%) held a bachelor's degree, and 9 (6.5%) had a university-level education. Lower educational attainment has been associated with improper medication use and poor adherence, thereby increasing the risk of ADRs (11). Occupational based analysis showed that 58(42%) were house builders,31(22.5%)were office workers,15(10.9%) were drivers,16(11.6%)were farmers and 18(13%) were involved in other professions which is similar with the study conducted on a brick kiln in Nepal which clarify occupational factors contributing to respiratory disease, particularly in construction workers exposed to dust, chemicals and other irritants (12).Comorbid conditions were present in 88 (63.8%) patients, with chronic kidney disease (30.7%), heart disease (26.1%), diabetes mellitus (22.7%), and skin diseases (18.2%) being the most prevalent which is similar with the findings of Augusti et al which might lead to alteration in drug metabolism and enhanced susceptibility to adverse drug reaction requiring careful monitoring for the patient (13, 14).

Among the use of types of Inhaled corticosteroids in respiratory diseases fluticasone was more commonly prescribed followed by salmetorol+Fluticasone, budesonide and Beclomethasone which is similar with the study conducted in Finland where patients were prescribed with long acting bronchodilator followed by inhaled corticosteroids which is effective in reducing inflammatory reaction and bronchodilatation (15).

On the basis of reported local adverse drug reaction 81 (58.7%) reported experiencing one or more adverse drug reaction which is similar with the study in which 58% of the patient had complained of local adverse effects (16).The significant association of ADRs with gender ($p < 0.001$), education level ($p < 0.001$), and occupation ($p < 0.001$) suggests that these demographic factors influence the likelihood of experiencing Inhaled corticosteroid related adverse effects. Female patients and illiterate individuals reported a higher incidence of ADRs which is similar with the finding of Liu et al which may be due to biological differences in drug metabolism and a lack of awareness regarding proper Inhaled corticosteroids use, respectively. Additionally, house builders were found to be more affected than farmers and office workers, which could be attributed to occupational exposures that may exacerbate respiratory conditions (11, 17).

The study also examined the effect of disease duration and co-morbidities on adverse drug reaction occurrence. Patients with disease duration of ≤5 years had a significantly higher prevalence. Additionally, individuals with diabetes mellitus reported more ADRs ($p = 0.01$), which is similar with the study done by See KC and Suissa et al which has found the rise in 34% of diabetes incidence in patients using inhaled corticosteroids in a large group of COPD and asthma patients which can be linked to corticosteroid-induced hyperglycemia and immune system alterations (18, 19).Inhaled Corticosteroids dosage and frequency were critical factors influencing adverse drug reaction occurrence. Patients using 200 mcg dosages had significantly more adverse drug reaction compared to other doses. Moreover, those on a twice-daily regimen experienced more adverse drug reactions compared to those on a once-daily regimen, indicating a possible dose-dependent relationship between ICS use and adverse effects. This finding aligns with previous studies suggesting that higher cumulative exposure to ICS increases the risk of local and systemic side effects (5).

In terms of ADR severity and onset, 16% of patients experienced daily ADR episodes, 56.8% at least once a week, and 27.2% at least once a month. Notably, 68% of the patients developed ADRs after a month of ICS use, while 32% experienced ADRs within the first week. A similar study (81.5%) reported at least one adverse effect, and 131 (65.5%) had a daily perception of at least one symptom. Likewise 28.5% had vocal symptoms and 77% had pharyngeal symptoms respectively. The most commonly reported adverse effects were dry throat, throat clearing, sensation of thirst, and hoarseness which suggest that prolonged ICS exposure may increase the risk of ADRs, necessitating regular patient monitoring (20). In our study the most common local adverse drug reaction was tooth decay(35.80%) followed by throat irritation (20.99%)tongue abrasion(19.75%),oral candidiasis (17.28%) and others taste disturbances, dry mouth, hoarseness of voice which could be due to reduced salivary flow leading to increased risk of dental caries, local deposition of inhaled corticosteroids in the Oro-pharyngeal mucosa and improper use of inhaler (20.21).A similar study had shown rise of incidence of oral candidiasis from 3.3% to 16.3% after the initiation of use of inhaled corticosteroids (5).

Management strategies for ADRs varied among patients. The most common methods included salt and water gargle (30.9%), which is similar to the study done by Kajiwara et al in which gargling with water after use of ICs was effective in reducing local adverse effects (22).Similarly,was the use of antifungal cream for oral candidiasis, mouthwash and regular tooth brushing, Betadine gargle and other methods such as oral ointments. These strategies highlight the importance of patient education in minimizing ICS-related ADRs and maintaining medication adherence. Similar studies suggest that digital measurement of use of medicaments inhaler along with spacers are effective in reducing local adverse effects (23).The study was conducted in a single setting tertiary care hospital with limited number of patients but still it can help to know the prevalence of adverse effects and methods like proper use of inhalers with appropriate doses and duration of therapy which will be effective in preventing adverse drug reactions and it can help to manage the adverse effects through various methods like use of salt and water gargling, using mouthwashes and proper maintenance of oral hygiene in respiratory disease patients.

Conclusion

Inhaled corticosteroids are essential for managing asthma and COPD which are the most common respiratory diseases but they are associated with significant local adverse effects, which can impact patient adherence and treatment outcomes. This study concluded that ICS-related local adverse reactions, such as tooth decay, throat irritation, and tongue abrasion, were prevalent, particularly among females and illiterate patients. Higher ICS doses and frequent usage increased the risk of adverse drug reaction. Preventive measures, including proper inhaler techniques, salt and water gargling, and mouthwash use, can help mitigate these effects. Educating patients on ICS side effects and management strategies is crucial in improving adherence and ensuring prevention of long term complications of respiratory disease.

Author Contribution

Concept design: BR,SK,SP,SG; Literature search: BR,SK,SP,SG; Data collection: BR,SK,SP; Data analysis: BR, SG, SK; Draft manuscript: BR,SP,SK,SG; Final manuscript and accountability: BR,SK,SP,SG

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Conflict of interest
None

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Epidemiology, Risk Factors, and Management Strategies of Ectopic Pregnancy: A Retrospective Study

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Abstract

Background: Ectopic pregnancy remains a significant cause of maternal morbidity and mortality worldwide. This study examines the incidence, risk factors, clinical presentation, and management of ectopic pregnancy at a tertiary care hospital in Saudi Arabia.

Methods: A retrospective analysis was conducted on 154 women diagnosed with ectopic pregnancy at Khamis Mushayet Obstetrics and Gynecology Hospital between 2020 and March 2025. Data on demographic characteristics, clinical presentation, risk factors, diagnostic methods, and pregnancy outcomes were collected from medical records.

Results: The annual incidence of ectopic pregnancy ranged from 0.75 to 1.52 per 100 live births, peaking in 2022. Most cases (42.9%) occurred in women aged 31–40 years, with high proportions of overweight (27.9%) and obese (25.3%) patients. The majority (82.5%) were tubal pregnancies, while 9.7% were ovarian and 7.8% occurred at other sites. Common risk factors included spontaneous pregnancy(41.6%),priorabortion(47.4%),andcesarean section (13.6%). Vaginal bleeding (74.0%) and abdominal pain (66.9%) were the most frequent symptoms. Diagnosis primarily relied on β-hCG testing (92.2%) and transvaginal ultrasound (63.0%). Rupture occurred in 20.1% of cases, but only 0.6% presented with hemodynamic instability.

Conclusion: This study highlights the demographic and clinical profile of ectopic pregnancy in a Saudi population, emphasizing the need for early diagnosis and risk factor awareness. The findings support improved prenatal care and targeted health education to reduce complications. Further multicenter studies are recommended to validate these results nationally.

Keywords:
Ectopic pregnancy, Saudi Arabia, risk factors, clinical presentation, maternal health.

Introduction

Ectopic pregnancy is a potentially life-threatening condition in which a fertilized egg implants and grows outside the uterine cavity, most commonly in the fallopian tube (tubal pregnancy) [1]. Rarely, implantation may occur in other sites such as the ovary, cervix, or abdominal cavity [2]. Since these locations cannot support a growing embryo, ectopic pregnancies are non-viable and pose serious risks to the mother, including rupture, severe hemorrhage, and even death if untreated [3].

The abnormal implantation is mainly attributed to factors that disrupt the normal transport of the egg towards the uterus. Tubal damage, often resulting from pelvic inflammatory disease (PID) caused by sexually transmitted infections [4], prior tubal surgeries [5], or endometriosis [6], creates physical obstructions or alters tubal function. These obstructions impair the egg's movement, leading to implantation within the tube itself. Additionally, abnormal tubal motility, influenced by hormonal imbalances or previous infections, can impede the egg's progression. While intrauterine devices (IUDs) generally prevent pregnancy, those that do occur in their presence are more likely to be ectopic [7]. Assisted reproductive technologies (ART), smoking, a history of ectopic pregnancy, and congenital tubal abnormalities also contribute to the risk [8, 9]. As the ectopic pregnancy progresses, the fallopian tube, ill-equipped for embryonic development, can rupture, resulting in severe internal haemorrhage [10].

Early diagnosis through clinical evaluation, ultrasound, and beta-human chorionic gonadotropin (β-hCG) monitoring is crucial to prevent complications [11, 12]. Treatment options include medical management with methotrexate or surgical intervention, depending on the patient's condition [13, 14]. Recognizing symptoms such as abdominal pain, vaginal bleeding, and signs of shock is essential for prompt medical care [15]. Ectopic pregnancy remains a leading cause of maternal morbidity and mortality in the first trimester, highlighting the need for delicate awareness and appropriate intervention [16]. This study aims to evaluate the incidence, identify the risk factors, and assess the management strategies and outcomes of ectopic pregnancy among women at Khamis Mushayet Obstetrics and Gynaecology Hospital from 2020 to 2025.

Methodology

This study was a retrospective, record-based analysis conducted at Khamis Mushayet Obstetrics and Gynaecology Hospital, aimed at examining the risk factors, clinical presentation, management, and outcomes of ectopic pregnancy. The study reviewed all cases of ectopic pregnancy from 2020 to March 2025, utilizing data extracted from patient records. The data were extracted from the hospital's electronic medical records system. Relevant patient information was accessed by reviewing case files that included demographic data, clinical presentation, diagnostic tests, risk factors, management methods, and outcomes of ectopic pregnancies. A standardized data extraction form was used to ensure consistency across all records reviewed. All women diagnosed with ectopic pregnancy at Khamis Mushayet Obstetrics and Gynaecology Hospital between 2020 and March 2025 were included in the study. The inclusion criteria included cases where the diagnosis of ectopic pregnancy was confirmed through clinical findings, ultrasound imaging, and/or surgical intervention. Only cases where the full medical records were available for review were included. Cases were excluded from the study if the diagnosis of ectopic pregnancy was uncertain, or if patient records were incomplete or inaccessible. To ensure the accuracy and reliability of the data extracted from patient files, several measures were implemented. First, a pilot data extraction was conducted on a small sample of records to refine the data extraction form and ensure clarity in the variables being recorded. The data extraction process was performed by two independent researchers who followed a standardized protocol, and any discrepancies between the two were resolved through discussion and consultation with a senior researcher.

Data analysis

Data analysis was performed using SPSS version 27 (IBM Corp, 2019). Descriptive statistics were used to summarize the demographic characteristics, clinical profiles, risk factors, and management strategies of the women with ectopic pregnancy. Continuous variables were described using means and standard deviations, while categorical variables were presented as frequencies and percentages. To assess relationships between categorical variables, cross-tabulation was used. This method allowed for the assessment of the distribution of risk factors, complications, and other clinical characteristics across various groups, such as age, type of ectopic pregnancy, and management methods. The chi-square test was used to determine the statistical significance of these relationships, with p-values set at <0.05 for significance. Exact probability tests were applied where appropriate to account for small sample sizes in some categories.

Results

A total of 154 women with ectopic pregnancy were included during the period from 2020 to March 2025. Regarding the annual incidence % of ectopic pregnancy in the study setting (Figure 1), it ranged from 0.75 / 100 live births in 2020 to 1.52 / 100 live births in 2022, 1.28 / 100 live births in 2024, and dropped to 1 / 100 live births in 2025.

The table presents the bio-demographic characteristics and clinical profile of pregnant women diagnosed with ectopic pregnancy at Khamis Mushayet Obstetrics and Gynaecology Hospital. Among the participants, the majority (42.9%) were aged between 31-40 years, with 66 women (No = 66, 42.9%) in this age group. The least represented group was those over 40 years, accounting for 10.4% (No = 16). In terms of body mass index, overweight women made up 27.9% (No = 43), and morbid obesity was seen in 25.3% (No = 39) of the women.

Regarding the number of pregnancies, the largest group was those with 2-4 pregnancies, comprising 46.8% (No = 72). Nulliparous women, with no previous live births, represented 33.1% (No = 51) of the sample, while 47.4% (No = 73) of the participants had a history of abortion, with the majority (83.6%, No = 61) having experienced 1-2 abortions. Additionally, the intake of folic acid was reported by only 5.8% (No = 9) of the women, indicating a potential gap in prenatal care practices.

Figure 2 illustrates the risk factors associated with ectopic pregnancy among cases at Khamis Mushayet Obstetrics and Gynaecology Hospital. The most prevalent risk factor was spontaneous pregnancy, accounting for 41.6% (N = 64) of the cases. Other factors included a history of spontaneous abortion (14.9%, N = 23) and a history of caesarean section (13.6%, N = 21). Additionally, 18.8% (N = 29) of the cases were categorized as idiopathic, meaning no identifiable risk factor was present. Smaller proportions of women had a history of previous ectopic pregnancy (7.8%, N = 12), pelvic surgery (7.1%, N = 11), or tubal surgery (0.6%, N = 1). The table also highlights that the use of intrauterine contraceptive devices (IUCD) was linked to 3.2% (N = 5) of cases. Other risk factors, including in vitro fertilization (IVF), congenital uterine defects, and appendicitis complicated by peritonitis, were present in lower percentages.

Table 2 clarifies the distribution of ectopic pregnancies according to the location of implantation, clinical presentation, and diagnostic tests at Khamis Mushayet Obstetrics and Gynaecology Hospital. The majority of ectopic pregnancies (82.5%, N = 127) were located in the fallopian tube, followed by ovarian ectopic pregnancies (9.7%, N = 15), and other locations (isthmus, cervical, and at scar site) (7.8%, N = 12). Ruptured ectopic pregnancies were observed in 20.1% (N = 31) of cases. Regarding clinical symptoms, vaginal bleeding was the most common symptom at presentation, reported in 74.0% (N = 114) of cases, while abdominal pain was noted in 66.9% (N = 103). Amenorrhea was present in 7.1% (N = 11), and a small number of cases (3.2%, N = 5) reported no symptoms. Hemodynamic instability, indicating a more severe presentation, was seen in only 0.6% (N = 1) of the cases. For diagnosis, the most frequently used test was the B-human chorionic gonadotropin (b-hCG) level, which was conducted in 92.2% (N = 142) of cases, followed by transvaginal ultrasonography (TVU) in 63.0% (N = 97), and transabdominal ultrasound in 55.8% (N = 86). Laparoscopy, a more invasive diagnostic method, was used in only 2.6% (N = 4) of cases.

Table 3 outlines the various management strategies and outcomes for ectopic pregnancy cases at Khamis Mushayet Obstetrics and Gynaecology Hospital. The most common approach to management was methotrexate treatment, used in 40.9% (N = 63) of cases, followed by surgical intervention in 35.1% (N = 54). Observation alone was used in 18.2% (N = 28) of cases. Regarding medical management, single-dose methotrexate was the most commonly used, in 39.6% (N = 61), with double-dose methotrexate used in 7.1% (N = 11). For surgical management, 26.0% (N = 40) underwent laparotomy and 14.3% (N = 22) had laparoscopy. Only 0.6% (N = 1) had an evacuation and curettage (E&C) procedure. The preferred surgical method was salpingectomy, performed in 95.2% (N = 60) of surgeries, with segmental resection conducted in 4.8% (N = 3). As for complications, the majority of cases (93.5%, N = 144) had no complications. However, 5.8% (N = 9) experienced bleeding, and a small number (0.6%, N = 1) reported abdominal pain.

Table 4 shows the distribution of ectopic pregnancy risk factors by women's age. For women aged 18-25, the highest risk factors were spontaneous pregnancy (44.1%, N = 15) and idiopathic (26.5%, N = 9). Among women aged 26-30, spontaneous pregnancy remained the most common risk factor (52.6%, N = 20), followed by history of spontaneous abortion (15.8%, N = 6). In the 31-40 age group, the two highest risk factors were spontaneous pregnancy (34.8%, N = 23) and history of spontaneous abortion (15.2%, N = 10). For women over 40 years, the most prominent risk factor was previous ectopic pregnancy (31.3%, N = 5), followed by history of spontaneous abortion (25.0%, N = 4). These differences were not statistically significant (p-value of 0.119).

Table 5 reveals the distribution of ectopic pregnancy risk factors by type of ectopic pregnancy. For fallopian tube ectopic pregnancies, spontaneous pregnancy was the most common risk factor, accounting for 44.1% (N = 56), followed by idiopathic causes at 17.3% (N = 22). Among ovarian ectopic pregnancies, history of spontaneous abortion (20.0%, N = 3) was the most common risk factor, followed by history of caesarean section at 13.3% (N = 2). For other ectopic pregnancy locations, spontaneous pregnancy was also a prominent factor, accounting for 33.3% (N = 4), while idiopathic causes were observed in 16.7% (N = 2).

Table 6 presents the complications associated with ectopic pregnancy by the type of implantation location. For fallopian tube ectopic pregnancies, a small percentage of cases experienced complications: abdominal pain was reported in 0.8% (N = 1) of cases, and bleeding occurred in 7.1% (N = 9). No complications were observed in cases of ovarian or other ectopic pregnancy types, as all cases in these categories (100%, N = 15 for ovarian and N = 12 for others) did not report complications (P=.686).

Figure 1. The annual incidence % of ectopic pregnancy during the period from 2020 to 2025 in Khamis Mushayet Obstetrics and Gynaecology Hospital

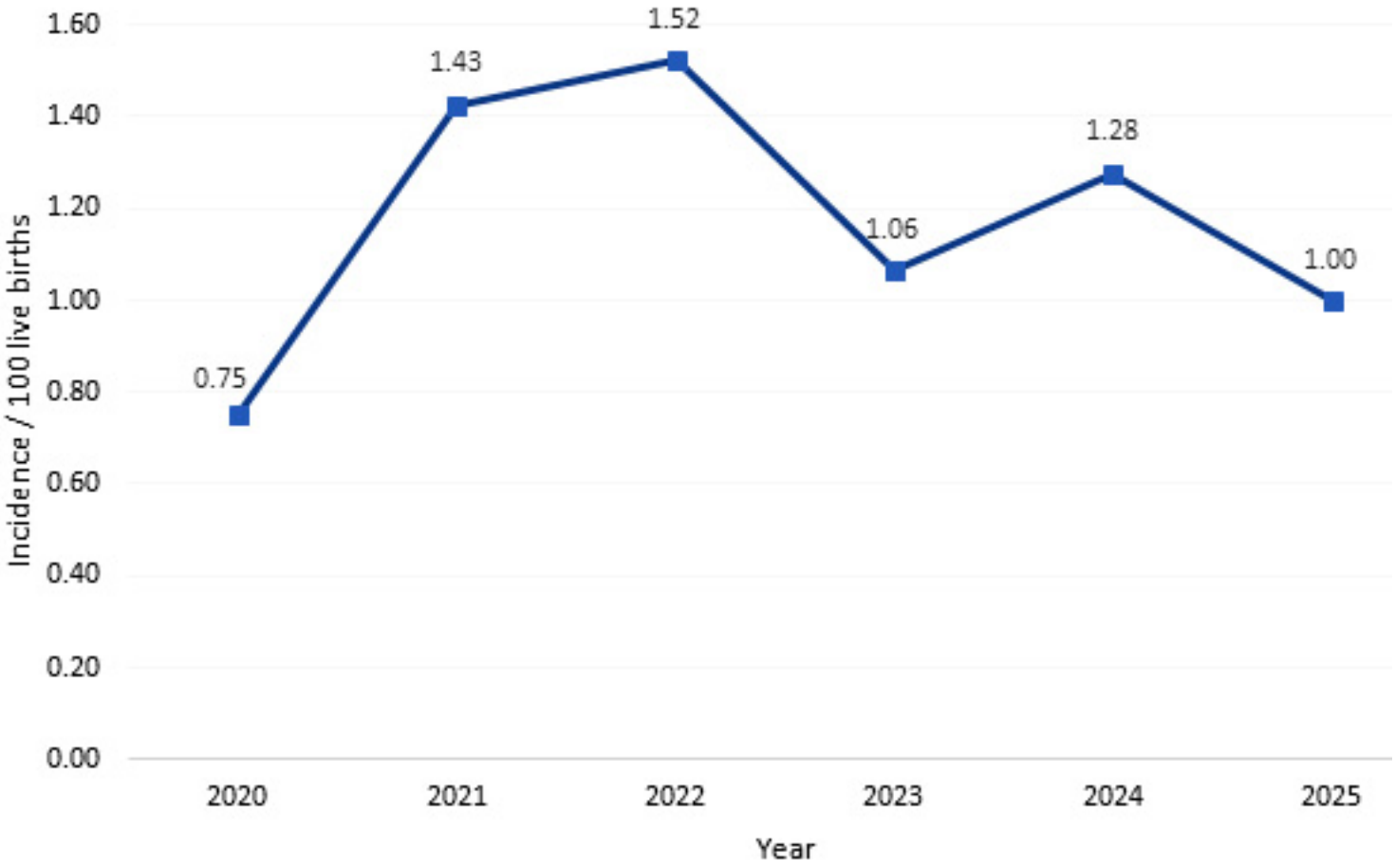

Table 1: Bio-demographic Characteristics of Pregnant Women with Ectopic Pregnancy at Khamis Mushayet Obstetrics and Gynaecology Hospital, Saudi Arabia (N=154)

Data	No	%
Age in years		
18-25	34	22.1%
26-30	38	24.7%
31-40	66	42.9%
> 40	16	10.4%
Mean ± SD	30.4 ± 6.8	
Body mass index		
Normal	42	27.3%
Overweight	43	27.9%
Obese	30	19.5%
Morbid obesity	39	25.3%
Number of Pregnancies		
Primigravida	42	27.3%
2-4	72	46.8%
5+	40	26.0%
Mean ± SD	3.5 ± 2.6	
Number of Live births		
Nullipara	51	33.1%
Primipara	36	23.4%
2-3	42	27.3%
4+	25	16.2%
Mean ± SD	1.7 ± 1.3	
History of abortion		
Yes	73	47.4%
No	81	52.6%
Number of abortions (n=73)		
1-2	61	83.6%
3+	12	16.4%
Drug intake		
Folic acid	9	5.8%
No	145	94.2%

Figure 2: Risk Factors of Ectopic Pregnancy among Cases at Khamis Mushayet Obstetrics and Gynaecology Hospital, Saudi Arabia (N=154)

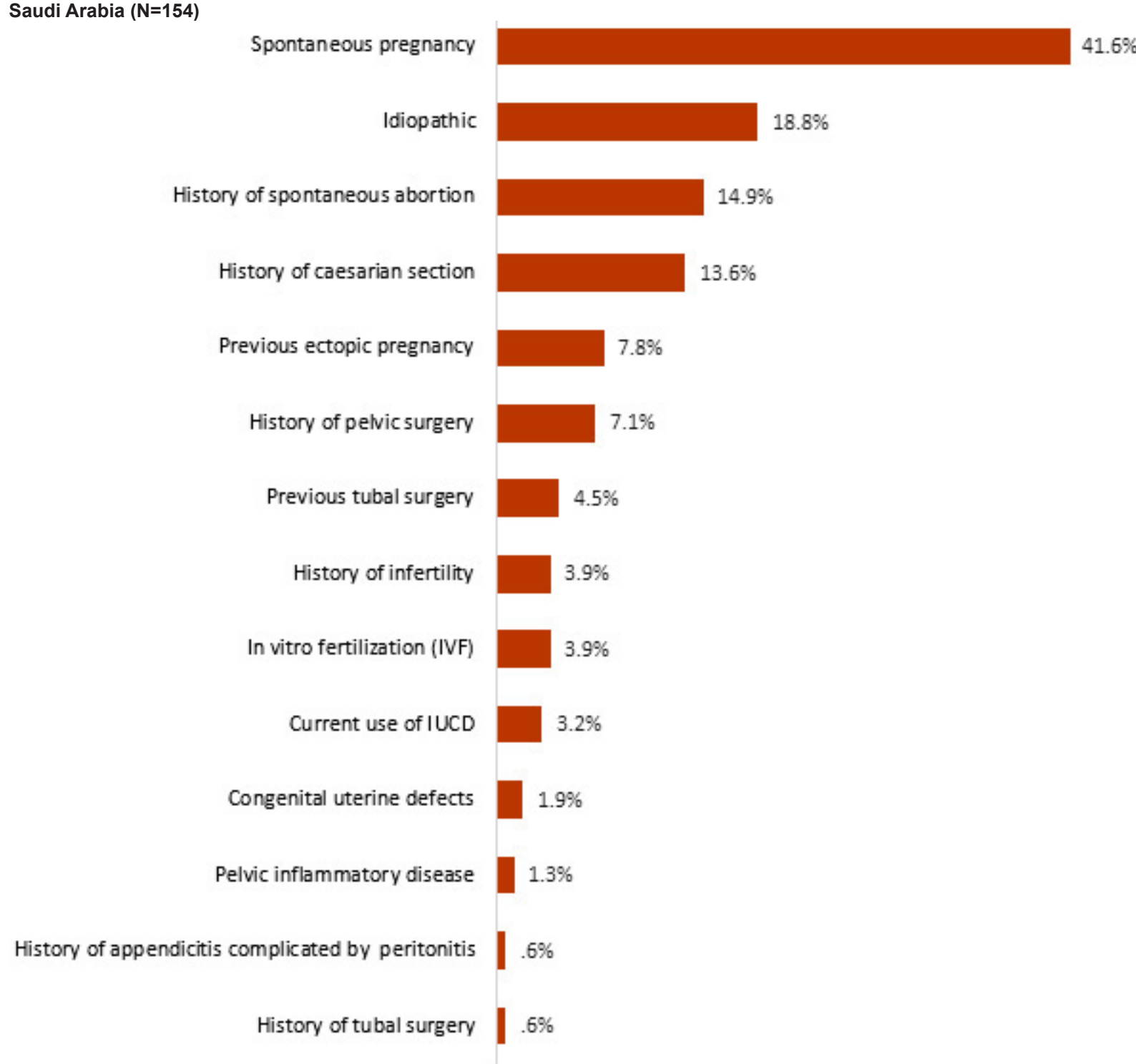

Table 2. Types, Symptoms, and Diagnostic Findings of Ectopic Pregnancy at Khamis Mushayet Obstetrics and Gynaecology Hospital, Saudi Arabia

Data	No	%
Types according to the location of implantation		
Fallopian tube	127	82.5%
Ovarian	15	9.7%
Others	12	7.8%
Rupture ectopic		
Yes	31	20.1%
No	123	79.9%
Symptoms at presentation		
Bleeding per vagina	114	74.0%
Pain abdomen	103	66.9%
Amenorrhea	11	7.1%
None	5	3.2%
Hemodynamics unstable	1	.6%
Diagnostic tests		
B-human chorionic gonadotropin (b-hCG) level	142	92.2%
Transvaginal ultrasonography (TVU)	97	63.0%
Trans abdominal US	86	55.8%
Laparoscopic	4	2.6%

Table 3. Management Approaches and Outcomes for Ectopic Pregnancy at Khamis Mushayet Obstetrics and

Management	No	%
Method of management		
Methotrexate	63	40.9%
Surgery	54	35.1%
Observation	28	18.2%
Combined	9	5.8%
Medical management		
None	82	53.2%
Single dose methotrexate	61	39.6%
Double dose methotrexate	11	7.1%
Surgical management		
None	91	59.1%
Laparotomy	40	26.0%
Laparoscopy	22	14.3%
E and C	1	.6%
Type of Surgery		
Salpingectomy	60	95.2%
Segmental resection	3	4.8%
Complications		
No	144	93.5%
Bleeding	9	5.8%
Abdominal pain	1	.6%

Table 4. Distribution of ectopic pregnancy risk factors by women's age, Khamis Mushayet Obstetrics and Gynaecology Hospital

Risk factors	Age in years								p-value
	18-25		26-30		31-40		> 40		
	No	%	No	%	No	%	No	%	
Pelvic inflammatory disease	0	0.0%	1	2.6%	1	1.5%	0	0.0%	.119
History of tubal surgery	0	0.0%	0	0.0%	1	1.5%	0	0.0%	
History of pelvic surgery	2	5.9%	2	5.3%	7	10.6%	0	0.0%	
In vitro fertilization (IVF)	0	0.0%	1	2.6%	5	7.6%	0	0.0%	
History of spontaneous abortion	3	8.8%	6	15.8%	10	15.2%	4	25.0%	
Congenital uterine defects	0	0.0%	0	0.0%	3	4.5%	0	0.0%	
History of infertility	1	2.9%	0	0.0%	5	7.6%	0	0.0%	
Current use of IUCD	0	0.0%	0	0.0%	5	7.6%	0	0.0%	
History of Cesarean Section	4	11.8%	4	10.5%	11	16.7%	2	12.5%	
Spontaneous pregnancy	15	44.1%	20	52.6%	23	34.8%	6	37.5%	
The history of appendicitis complicated by peritonitis	0	0.0%	0	0.0%	1	1.5%	0	0.0%	
Previous ectopic pregnancy	0	0.0%	3	7.9%	4	6.1%	5	31.3%	
Idiopathic	9	26.5%	6	15.8%	12	18.2%	2	12.5%	
Previous tubal surgery	3	8.8%	1	2.6%	2	3.0%	1	6.3%	

P: exact probability test

Table 5. Distribution of ectopic pregnancy risk factors by type of ectopic pregnancy, Khamis Mushayet Obstetrics and Gynaecology Hospital

Risk factors	Types according to the location of implantation						p-value
	Fallopian tube		Ovarian		Others		
	No	%	No	%	No	%	
Pelvic inflammatory disease	1	.8%	0	0.0%	1	8.3%	
History of tubal surgery	1	.8%	0	0.0%	0	0.0%	
History of pelvic surgery	9	7.1%	1	6.7%	1	8.3%	
In vitro fertilization (IVF)	4	3.1%	1	6.7%	1	8.3%	
History of spontaneous abortion	18	14.2%	3	20.0%	2	16.7%	
Congenital uterine defects	2	1.6%	0	0.0%	1	8.3%	
History of infertility	6	4.7%	0	0.0%	0	0.0%	.730
Current use of IUCD	5	3.9%	0	0.0%	0	0.0%	
History of Cesarean Section	18	14.2%	2	13.3%	1	8.3%	
Spontaneous pregnancy	56	44.1%	4	26.7%	4	33.3%	
The history of appendicitis complicated by peritonitis	1	.8%	0	0.0%	0	0.0%	
Previous ectopic pregnancy	11	8.7%	1	6.7%	0	0.0%	
Idiopathic	22	17.3%	5	33.3%	2	16.7%	
Previous tubal surgery	4	3.1%	1	6.7%	2	16.7%	

P: exact probability test

Table 6. Complications Associated with Ectopic Pregnancy by Type of Implantation Location at Khamis Mushayet Obstetrics and Gynaecology Hospital, Saudi Arabia

Types according to the location of implantation	Complications						p-value
	Abdominal pain		Bleeding		No		
	No	%	No	%	No	%	
Fallopian tube	1	.8%	9	7.1%	117	92.1%	.686
Ovarian	0	0.0%	0	0.0%	15	100.0%	
Others	0	0.0%	0	0.0%	12	100.0%	

P: exact probability test

Discussion

The study included 154 women diagnosed with ectopic pregnancy between 2020 and March 2025, revealing fluctuations in annual incidence rates. The rate increased from 0.75 per 100 live births in 2020 to a peak of 1.52 in 2022, then declined to 1.28 in 2024 and further to 1.0 in 2025. This pattern matches global trends showing variability in ectopic pregnancy rates, possibly influenced by changes in risk factors such as pelvic inflammatory disease (PID), previous tubal surgery, or assisted reproductive technologies (ART) [17]. The rise in incidence up to 2022 may reflect improved diagnostic techniques, such as transvaginal ultrasound and serial beta-hCG monitoring, leading to earlier detection [18]. However, the subsequent decline could be attributed to better preventive measures, including increased screening and treatment for sexually transmitted infections (STIs), which are major contributors to tubal damage [19]. The findings are consistent with studies reporting ectopic pregnancy rates between 1% and 2% of live births in different populations [20]. The drop in 2025, though is based on partial-year data.

The incidence of ectopic pregnancy in Saudi Arabia appears to be lower than in many Western countries but is increasing, possibly due to changing risk factors. Studies from Saudi Arabia report an incidence ranging from 0.8 to 1.2 per 100 live births [21, 22], which is slightly lower than rates in the United States (1.5–2.0 per 100 live births) and Europe (1.0–1.5 per 100 live births) [8, 23]. In Abha, Archibong et al. [24] reported the incidence of ectopic pregnancy was 0.74 per 100 live births, which is similar to our study findings on average. However, regional variations exist within Saudi Arabia, with higher rates observed in urban areas, possibly due to better diagnostic capabilities and increased risk factors such as pelvic inflammatory disease (PID) and caesarean section rates [22, 25]. The rising trend in Saudi Arabia could be linked to increased use of assisted reproductive technologies (ART) and delayed childbearing, similar to patterns seen in developed nations [26].

Our study also revealed that the majority of cases were aged 31–40 years, consistent with global studies linking advanced maternal age to higher ectopic pregnancy risk due to age-related tubal dysfunction and increased use of assisted reproductive technologies (ART) [23]. Only a few cases were over 40, possibly reflecting lower pregnancy rates in this age group. A significant proportion of women were overweight or morbidly obese, consistent with research suggesting obesity as a risk factor for ectopic pregnancy, possibly due to hormonal imbalances or chronic inflammation [27]. The high percentage of women with 2–4 previous pregnancies and a history of abortion supports evidence that multiparity and prior abortions (particularly surgical) increase tubal damage and ectopic risk [19]. The considerable number of nulliparous women highlights that ectopic pregnancy can occur even without prior live births, often associated with infertility, PID, or undiagnosed tubal pathology [28]. Worryingly, only 5.8% reported folic acid intake, suggesting inadequate preconception care, though folic acid's direct role in ectopic prevention remains unclear [29].

Regarding risk factors, the current study found that spontaneous pregnancies were the most frequently associated factor with ectopic pregnancies, consistent with global observations, but a substantial number of cases also involved prior spontaneous abortions and caesarean sections, suggesting possible connections to tubal damage or altered uterine anatomy [23, 30, 31]. A significant portion of ectopic pregnancies occurred without identifiable risk factors. The occurrence of prior ectopic pregnancies was lower compared to Western studies, potentially reflecting regional differences. Tubal ligation was infrequently associated, despite its known role as a risk factor [8]. Intrauterine device use was less frequent than some international reports [32], and assisted reproductive technology, uterine anomalies, and appendicitis with peritonitis were rarely observed.

Additionally, the study confirmed that tubal implantation is the most frequent site of ectopic pregnancy, though a higher-than-expected rate of ovarian ectopic pregnancies was also observed. Non-tubal ectopic pregnancies, including cervical, isthmic, and scar pregnancies, were also noted, consistent with increasing reports of atypical implantations, particularly in women with prior uterine surgery or caesarean sections [33]. The reported rupture rate suggested some diagnostic delays, although severe hemodynamic instability was rare. Vaginal bleeding and abdominal pain were the most common presenting symptoms, but a small proportion of cases lacked typical pregnancy symptoms or were asymptomatic, indicating the need for screening high-risk individuals. Beta-hCG testing was appropriately prioritized for diagnosis, and transvaginal ultrasound was favoured over transabdominal ultrasound due to its superior sensitivity [34, 35]. Laparoscopy was infrequently used, suggesting effective non-invasive diagnostic protocols, although it remains the gold standard for uncertain cases [36].

Strengths and limitations

This study provides important insights into the clinical and demographic characteristics of ectopic pregnancies at a major Saudi Arabian hospital, but several limitations must be acknowledged when interpreting the findings. As a single-centre study conducted at Khamis Mushayet Hospital, the results may not fully reflect the broader population across different regions of Saudi Arabia. The retrospective design introduces potential biases from incomplete medical records and inconsistent documentation of risk factors. The relatively short five-year study period (2020-2025) may be insufficient to identify long-term trends in ectopic pregnancy incidence and associated factors. Diagnostic challenges are another limitation, as some early ectopic pregnancies might have been missed if they resolved spontaneously before detection, while variations in ultrasound interpretation and β-hCG testing protocols could affect case classification accuracy.

Conclusions and Recommendations

In conclusion, the prominence of spontaneous pregnancy as a risk factor was reported, particularly among women aged 26-30, and the influence of previous spontaneous abortions and caesarean sections. Most ectopic pregnancies occurred in the fallopian tube, with abdominal pain and bleeding as common symptoms. Methotrexate was the primary management approach, followed by surgical options. While most cases were successfully managed without severe complications, a gap in prenatal care was identified due to low folic acid intake. Recommendations include enhancing prenatal education about folic acid benefits, improving screening for high-risk women, increasing follow-up for those with prior ectopic pregnancies, and conducting further research on obesity and BMI as potential risk factors.

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Acarbose in the treatment of chronic obstructive pulmonary disease

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Abstract

Background: Atherosclerosis may be the main cause of aging and death.

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

Results: We studied 222 males and 212 females with mean ages of 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 lifespans (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), chronic obstructive pulmonary disease (COPD) (25.2% vs 7.0%, p<0.001), coronary heart disease (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), clubbing (14.8% vs 6.6%, p<0.001), chronic renal disease (CRD) (9.9% vs 6.1%, p<0.05), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males.

Conclusion: As an accelerated atherosclerosis, hardened RBC-induced capillary endothelial damage initiating at birth terminates with multiorgan failures in early years of life in SCD. Excess fat tissue may be much more important than smoking and alcohol for atherosclerosis because excess weight-induced diabetes mellitus is the most common cause of CRD, and CHD and stroke are the main causes of deaths even in the COPD. The efficacy of acarbose to lower blood glucose by preventing breakdown of starch into sugar in the small intestine is obvious. Since acarbose is a safe, cheap, oral, and effective drug for excess weight, it should be advised in COPD because there are nearly 20 kg of excess fat even between upper and lower borders of normal weight in adults.

Key words: Acarbose, chronic obstructive pulmonary disease, sickle cell diseases, excess fat tissue, smoking, vascular endothelial inflammation, atherosclerosis

Introduction

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

Materal and Methods

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

electrocardiogram positive patients. Eventually, CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as movement abnormalities in the walls of heart. Rheumatic heart disease is detected with the echocardiographic findings, too. Stroke is diagnosed by the CT and MRI of the brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in cases 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 neither in males nor in females. Prevalences of associated TM were similar in males and females (72.5% vs 67.9%, p>0.05, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were both higher in males (p<0.001 for both) (Table 1). Transfused units of RBC in their lifespans (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), COPD (25.2% vs 7.0%, 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), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males, significantly. Although the mean age of mortality (30.2 vs 33.3 years) was lower in males, the difference was nonsignificant, probably due to the small sample size (Table 2). On the other hand, mean ages of the atherosclerotic consequences were shown in Table 3.

Table 1: Characteristic features of the study patients

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

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

Table 2: Associated pathologies of the study patients

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

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

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

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

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

Discussion

Excess weight may be the most common cause of vasculitis, and actually the term should be replaced with excess fat tissue in medicine. Probably, obesity is one of the endpoints of the metabolic syndrome, since after development of obesity, nonpharmaceutical approaches provide little benefit either to reverse obesity or to prevent its consequences. Excess fat leads to a chronic and low-grade inflammatory process on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess fat (19). The low-grade chronic inflammation may also cause genetic changes on the endothelial cells, and the systemic atherosclerosis may even decrease the clearance of malignant cells by natural killers (20). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (21, 22). Excess fat is considered as a strong factor for controlling of C-reactive protein (CRP) concentration in serum, since excess fat tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines (23, 24). On the other hand, individuals with excess fat will also have an increased cardiac output. The prolonged increase in blood volume may aggravate myocardial hypertrophy and decrease cardiac compliance further. Beside the systemic atherosclerosis and HT, fasting plasma glucose (FPG) and serum cholesterol increased and high density lipoproteins (HDL) decreased parallel to the increased body mass index (BMI) (25). Similarly, CHD and stroke increased parallel to the increased BMI (26). Eventually, the risk of death from all causes including atherosclerotic end-organ failures and cancers increased parallel to the severity of excess fat in all age groups, and the cases with underweight may even have lower biological ages and longer survival (27). Similarly, calorie restriction prolongs survival and retards age-related chronic diseases (28).

Smoking may be the second most common cause of vasculitis in human being. Probably, it causes a systemic inflammation on vascular endothelial cells terminating with an accelerated atherosclerosis-induced multiorgan failures in early years of life (29). Its atherosclerotic effect is obvious in the COPD and Buerger's disease (30). Buerger's disease is an obliterative vasculitis characterized by inflammatory changes in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking. Its characteristic findings are acute inflammation, fibrosis, and narrowing and occlusions of arteries and veins, particularly in the hands and feet. Probably, claudication is the most common symptom in Buerger's disease. It is an intense pain caused by insufficient blood supply during exercise in feet and hands but it may even develop at rest in severe cases. It typically begins in extremities but it may also radiate to more central areas in advanced cases. Numbness or tingling of the limbs is also common. Raynaud's phenomenon may also be seen in which fingers or toes turn a white color upon exposure to cold. Skin ulcerations and gangrene of fingers or toes are the final consequences. Gangrene of fingertips may even need amputation. Similar to the venous ulcers, diabetic ulcers, leg ulcers of the SCD, digital clubbing, onychomycosis, and delayed wound and fracture healings of the lower extremities, pooling of blood due to the gravity may be important in the development of Buerger's disease, particularly in the lower extremities. Angiograms of upper and lower extremities are diagnostic. In angiogram, multiple narrowings and occlusions in the arms and legs are seen. In order to rule out some other forms of vasculitis, it is sometimes necessary to perform angiograms of other body areas. Skin biopsies are rarely required since a biopsy site near a poorly perfused area will not heal, completely. Association of Buerger's disease with tobacco use, particularly cigarette smoking is clear. Although most patients are heavy smokers, some cases with limited smoking history have also been reported. The disease can also be seen in users of smokeless tobacco. The limited smoking history of some patients may support the hypothesis that Buerger's disease may be an autoimmune reaction triggered by some constituent of tobacco. Although the only treatment way is complete cessation of smoking, the already developed narrowings and occlusions are irreversible. Due to the obvious role of inflammation, anti-inflammatory dose of aspirin plus low-dose warfarin may be effective to prevent microvascular infarctions in fingers and toes. On the other hand, FPG and HDL may be negative whereas triglycerides, low density lipoproteins (LDL), erythrocyte sedimentation rate, and CRP may be positive acute phase reactants indicating such inflammatory effects of smoking on vascular endothelial cells (31). Similarly, smoking was associated with the lower BMI values due to the systemic inflammatory effects (32). In another definition, smoking causes a chronic inflammation in human body (33). Additionally, an increased heart rate was detected just after smoking even at rest (34). On the other hand, nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (35). According to an animal study, nicotine may lengthen intermeal time, and decrease amount of meal eaten (36). Smoking may be associated with a postcessation weight gain, but the risk is the highest during the first year, and decreases with the following years (37). 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 (38). 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 (39). In another definition, smoking may be more dangerous for women about the atherosclerotic consequences probably due to the higher BMI. Several toxic substances found in the cigarette smoke-induced vascular endothelial inflammation can affect various organ systems. For example, smoking is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis (40). There may be several underlying mechanisms to explain these associations (41). First of all, smoking may have some antidepressant properties with several side effects. Secondly, smoking-induced vascular endothelial inflammation may disturb

epithelial functions for absorption and excretion in the gastrointestinal and genitourinary tracts which may terminate with urolithiasis, loose stool, diarrhea, and constipation. Thirdly, diarrheal losses-induced urinary changes may cause urolithiasis (42). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the gastrointestinal and genitourinary tracts terminating with the IBS and urolithiasis. Eventually, immunosuppression secondary to smoking-induced vascular endothelial inflammation may 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 by 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 the IBS ($p<0.01$) (40).

Beside the stroke, CHD is the other terminal cause of death in human being. The most common triggering event is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade. The plaque is a gradual and unstable collection of lipids, fibrous tissue, and white blood cells (WBC), particularly the macrophages in arterial walls 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 takes its place which may also cause life threatening arrhythmias since the scar tissue conducts electrical impulses more slowly. The difference in conduction velocity between the injured and uninjured tissue can trigger re-entry or a feedback loop that is believed to be the cause of lethal arrhythmias. Ventricular fibrillation is the most serious arrhythmia that is the leading cause of sudden cardiac death. It is an extremely fast and chaotic heart rhythm. Ventricular tachycardia may also cause sudden cardiac death that usually results in rapid heart rates preventing effective cardiac pumping. Cardiac output and BP may fall to dangerous levels which can lead to further coronary ischemia and extension of the infarct. This scar tissue may even cause ventricular aneurysm, rupture, and sudden cardiac death. Aging, physical inactivity, sedentary lifestyle, animal-rich diet, excess fat tissue, emotional stresses, smoking, alcohol, prolonged infections, chronic inflammations, and cancers are important in atherosclerotic plaque formation. Moderate physical exercise is associated with a 50% reduced incidence of CHD (43). Probably, excess fat tissue may be the most important cause of CHD since there are nearly 20 kg of excess fat tissue between the lower and upper borders of normal weight, 35 kg between the obesity, 66 kg between the morbid obesity (BMI ≥ 40 kg/m2), and 81 kg between the super obesity (BMI ≥ 45 kg/m2) in adults. In fact, there is a significant percentage of adults with a heavier fat mass than their organ plus muscle masses in their bodies that brings a heavy stress both on the heart and brain.

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 (44). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (44). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases (45). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (46). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCD (47). Probably smoking also takes role in the inflammatory process of the capillary endothelium in liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (36). Increased oxidative stress, inactivation of antiproteases, and release of proinflammatory mediators may terminate with the systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious or inflammatory processes and cancers may also terminate with an accelerated atherosclerosis in whole body (48). 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 (48, 49). 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 (50). The increased basal metabolic rate during such stresses aggravates the sickling, capillary endothelial damage, inflammation, edema, tissue hypoxia, and multiorgan insufficiencies. So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with the following crises by leaving significant sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with sudden multiorgan failures and death during a final acute painful crisis that may even be silent, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCD. Unfortunately, most of the deaths develop just after the hospital admission, and majority of them are patients without hydroxyurea therapy (51, 52). Rapid RBC supports are usually life-saving for such patients, although preparation of RBC units for

transfusion usually takes time. Beside that RBC supports in emergencies become much more difficult in terminal cases due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBC complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBC transfusions should be kept just for acute events and emergencies in the SCD (51, 52). According to our experiences, simple and repeated transfusions are superior to RBC exchange in the SCD (53, 54). 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 (55). Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation all over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices. On the other hand, pain is the result of complex and poorly understood interactions between RBC, WBC, platelets (PLT), and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes is unknown. The adverse actions of WBC on endothelium are of particular interest with regard to the cerebrovascular diseases in the SCD. For example, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCD (56), and it was associated with the risk of stroke in a cohort of Jamaican patients (57). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Because of the severity of pain, narcotic analgesics are usually required to control them (58), but according to our practice, simple and repeated RBC transfusions may be highly effective both to relieve pain and to prevent sudden death that may develop secondary to multiorgan failures on the chronic inflammatory background of the SCD.

Hydroxyurea may be the only life-saving drug for the treatment of the SCD. It interferes with the cell division by blocking the formation of deoxyribonucleotides by means of inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the suppression of leukocytosis and thrombocytosis by blocking the DNA synthesis in the SCD (59, 60). By this way, the chronic inflammatory and destructive process of the SCD is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As in the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' own WBC and PLT. So suppression of proliferation of them may limit the endothelial damage-induced edema, ischemia, and infarctions in whole body (61). Similarly, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels (62). 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 (63). 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 (63). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (63). 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 (63). 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 (51). 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 (64). Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may also decrease severity of disease and prolong survival (64). 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 (65). Hydroxyurea therapy in early years of life may protect splenic function, improve growth, and prevent multiorgan insufficiencies. RBC transfusions can also reduce all of the complications, but with the risks of infections, iron overload, and development of allo-antibodies causing subsequent transfusions much more difficult.

Aspirin is a member of nonsteroidal anti-inflammatory drugs (NSAID) used to reduce pain, fever, inflammation, and acute thromboembolic events. Although aspirin has similar anti-inflammatory effects with the other NSAID, it also suppresses the normal functions of PLT, irreversibly. This property causes aspirin being different from other NSAID, which are reversible inhibitors. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin inactivates the COX enzyme, irreversibly, which is required for prostaglandins (PG) and thromboxanes (TX) synthesis. PG are the locally produced hormones with some diverse effects, including the transmission of pain into the brain

and modulation of the hypothalamic thermostat and inflammation in the body. TX are responsible for the aggregation of PLT to form blood clots. In another definition, low-dose aspirin use irreversibly blocks the formation of TXA2 in the PLT, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLT (8-9 days). Since PLT do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin has inhibited the enzyme. The antithrombotic property of aspirin is useful to reduce the incidences of myocardial infarction, transient ischemic attack, and stroke (66). 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 (67). According to the literature, aspirin may also be effective in prevention of colorectal cancers (68). 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 (69). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (70). Reye syndrome is a rapidly worsening brain disease (70). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (71). The syndrome mostly affects children, but it can only affect fewer than one in a million children a year (71). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (70). Although the liver toxicity typically occurs in the syndrome, jaundice is usually not seen with it, but the liver is enlarged in most cases (70). Although the death occurs in 20-40% of affected cases, about one third of survivors get a significant degree of brain damage (70). The cause of Reye syndrome is unknown (71). It usually starts just after recovery from a viral infection, such as influenza or chicken pox. About 90% of cases in children are associated with an aspirin use (71, 72). 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 (70). 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 (71). Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling (71). Due to the very low risk of Reye syndrome but much higher risk of death due to the SCD in children, aspirin should be added both into the acute and chronic phase treatments with an anti-inflammatory dose even in childhood in the SCD (73).

Warfarin is an anticoagulant, and first came into large-scale commercial use in 1948 as a rat poison. It was formally approved as a medication to treat blood clots in human being by the U.S. Food and Drug Administration in 1954. In 1955, warfarin's reputation as a safe and acceptable treatment was bolstred when President Dwight David Eisenhower was treated with warfarin following a massive and highly publicized heart attack. Eisenhower's treatment kickstarted a transformation in medicine whereby CHD, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. Warfarin is found in the List of Essential Medicines of WHO. In 2020, it was the 58th most commonly prescribed medication in the United States. It does not reduce blood viscosity but inhibits blood coagulation. Warfarin is used to decrease the tendency for thrombosis, and it can prevent formation of future blood clots and reduce the risk of embolism. Warfarin is the best suited for anticoagulation in areas of slowly running blood such as in veins and the pooled blood behind artificial and natural valves, and in blood pooled in dysfunctional cardiac atria. It is commonly used to prevent blood clots in the circulatory system such as DVT and pulmonary embolism, and to protect against stroke in people who have atrial fibrillation (AF), valvular heart disease, or artificial heart valves. Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery. The warfarin initiation regimens are simple, safe, and suitable to be used in ambulatory and in patient settings (74). 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 (75). When warfarin is used and INR is in therapeutic range, simple discontinuation of the drug for five days is usually enough to reverse the effect, and causes INR to drop below 1.5 (76). Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Blood products should not be routinely used to reverse warfarin overdose, when vitamin K1 could work alone. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticlotting protein C and protein S are also inhibited, but to a lesser degree. A few days are required for full effect to occur, and these effects can last for up to five days. The consensus agrees that patient self-testing and patient self-management are effective methods of monitoring oral anticoagulation therapy, providing outcomes at least as good as, and possibly better than, those achieved with an anticoagulation clinic. Currently available self-testing/self-management devices give INR results that are comparable with those obtained in laboratory testing. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is low with a yearly rate of 1-3% (77). All types of bleeding may occur, but the most severe ones are those involving the brain and spinal cord (76). The risk is particularly increased once the INR exceeds 4.5 (77). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (78). 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 (79). 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 ($p>0.05$) (79). Similarly, warfarin resumption is associated

with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (80). Death occured in 18.7% of patients who resumed warfarin and 32.3% who did not resume warfarin (p= 0.009) (80). Ischemic stroke occured in 3.5% of patients who resumed warfarin and 7.0% of patients who did not resume warfarin (p= 0.002) (80). Whereas recurrent ICH occured in 6.7% of patients who resumed warfarin and 7.7% of patients who did not resume warfarin without any significant difference in between (p>0.05) (80). 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 (81). 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 (82). 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 (83). 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) (83). The mortality was markedly lower in the warfarin group, too (p= 0.005) (83). 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) (83). Additionally, very-low-dose warfarin was a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer (84). The warfarin dose was 1 mg daily for 6 weeks, and was adjusted to maintain the INR value of 1.3 to 1.9 (84). The average daily dose was 2.6 mg, and the mean INR was 1.5 (84). On the other hand, new oral anticoagulants had a favourable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding (85). Interestingly, rivaroxaban and low-dose apixaban were associated with increased risks of all cause mortality compared with warfarin (86). 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 (87). 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 (88). So lifelong aspirin with an anti-inflammatory dose plus low-dose warfarin may be a life-saving treatment regimen even at childhood both to decrease severity of capillary endothelial inflammation and to prevent thromboembolic complications in the SCD (89).

COPD is the third leading cause of death in the world (90, 91). Aging, smoking, alcohol, male gender, excess fat tissue, chronic inflammations, prolonged infections, and cancers may be the major causes. Atherosclerotic effects of smoking may be the most obvious in the COPD and Buerger's disease, probably due to the higher concentrations of toxic substances in the lungs and pooling of blood in the extremities. After smoking, excess fat tissue may be the second common cause of COPD due to the excess fat tissue-induced atherosclerotic process in whole body. 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 (92). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (93). Probably an accelerated atherosclerotic process is the main structural background of functional changes that are characteristics of the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may actually be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD (94). For example, there may be close relationships between COPD, CHD, PAD, and stroke (95). 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 (96). When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again (96). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (97). On the other hand, COPD may be the pulmonary consequence of the systemic atherosclerotic process caused by the hardened RBC in the SCD (90).

Leg ulcers are seen in 10% to 20% of the SCD (98). Its prevalence increases with aging, male gender, and SCA (99). 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 (98). Similar to Buerger's disease, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow (98). The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes (99). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC-induced venous insufficiencies may also accelerate the process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also be important for the development of venous ulcers, diabetic ulcers, Buerger's disease, clubbing, and onychomycosis in

in the lower extremities. Furthermore, pooling of blood may be the cause of delayed wound and fracture healings in the lower extremities. Smoking and alcohol may also have some additional atherosclerotic effects on the leg ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCD (100). It is an oral, 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 (101). Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by immune systems. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of tissue damage and pain (62). Prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBC and PLT counts-induced exaggerated capillary endothelial inflammation and edema.

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (102). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (103). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, and hepatic diseases and smoking which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect their functions in a short period of time. On the other hand, digital clubbing is also common in the SCD, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, $p<0.001$) may also show some additional role of male gender in the systemic atherosclerotic process.

CRD is also increasing all over the world that can also be explained by aging of the human being, and increased prevalence of excess weight (104). Aging, animal-rich diet, excess fat tissue, smoking, alcohol, inflammatory or infectious processes, and cancers may be the major causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts (105). Excess fat tissue-induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause tissue inflammation and immune cell activation (106). For example, age ($p= 0.04$), high-sensitivity CRP ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT (104). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess weight (107). Excess fat tissue also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (107). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (108). 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, CRD progresses much more easily (107). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (109). Although some authors reported that alcohol was not related with the CRD (109), various metabolites of alcohol circulate in blood vessels of kidneys and give harm to the endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature (108). Because of the systemic nature of atherosclerosis, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (110, 111). For example, the most common causes of death were the CHD and stroke in the CRD again (112). The hardened RBC-induced capillary endothelial damage may be the main cause of CRD in the SCD. In another definition, CRD may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCD, again (113).

Beside the CHD, stroke is the other terminal cause of death in human being, and it develops as an acute thromboembolic event on the chronic atherosclerotic background in most of the cases. Aging, male gender, smoking, alcohol, and excess fat tissue may be the major underlying causes. Stroke is also a common complication of the SCD (114). Similar to the leg ulcers, stroke is particularly higher in the SCA and cases with higher WBC counts (115). Sickling-induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial inflammation, edema, and fibrosis (116). Probably, stroke may not have a macrovascular origin in the SCD, and diffuse capillary endothelial inflammation, edema, and fibrosis may be much more important. Infections, inflammations, medical or surgical emergencies, and emotional stress may precipitate stroke by increasing basal metabolic rate and sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed due to the increased WBC and PLT counts-induced exaggerated capillary inflammation and edema (117).

Acarbose, a pseudotetrasaccharide, is a natural microbial product derived from culture broths of Actinoplanes strain SE 50. It is an alpha-glucosidase inhibitor. It binds reversibly and competitively, and in a dose-dependent manner to oligosaccharide binding site of alpha-glucosidase enzymes in the brush border of the small intestinal mucosa. It inhibits glycoamylase, sucrase, maltase, dextranase, and pancreatic alpha-amylase. It has little affinity for isomaltase but does not have any effect on beta-glucosidases such as lactase. As a result, it delays the intestinal hydrolysis of oligo- and disaccharides by alpha-glucosidases mainly in the upper half of the small intestine. By this way, the absorption of monosaccharides after a meal is delayed, and transport through the mucosal surfaces into the circulation is interrupted. On the other hand, it does not have any direct effect on absorption of glucose. Although the acute effect is seen with in a few minutes, its effects may prolong up to 5 hours. Acarbose should be taken with the first bite of the meal. The suppression of alpha-glucosidases is reversible, although pharmacological activity is reliable and persistent with long-term use. Effects with continued use can be maintained over years. Up to now, acarbose failure has not been reported in the literature. Initial therapy with an alpha-glucosidase inhibitor often results with carbohydrates appearing in the colon, where bacterial fermentation occurs, accounting for the frequency and severity of gastrointestinal adverse effects such as flatulence, loose stool, and abdominal discomfort (118). If started with a lower dose and titrated slowly, it tends to cause occasional gastrointestinal side effects that are generally tolerable (119). Long-term use of acarbose increases colonic bacterial mass that of lactobacteria in particular. The finally impaired carbohydrate absorption, increased bacterial carbohydrate fermentation, and fecal acidification mimic effects of lactulose in patients with liver cirrhosis and portosystemic encephalopathy. So acarbose has a favourable therapeutic profile for the long-term use of cases with type 2 DM and cirrhosis. Similarly, observed changes in bacterial flora and decreased stool pH and beta-hydroxybutyrate may be associated with anti-proliferative effects on epithelial cells of colon that may potentially decrease the risk of carcinogenesis. Acarbose is poorly absorbed and systemic bioavailability is low. After oral administration, less than 2% of the unchanged drug enters into the circulation. Therefore there is no need for dosage adjustment in mild renal insufficiency. After a high carbohydrate meal, acarbose lowers the postprandial rise in blood glucose by 20% and secondarily FPG by 15% (120). Similarly, it lowers fasting and postprandial insulin levels. The initial improvement in blood glucose with acarbose tends to be modest, but efficacy steadily improves with the long-term use, and is maintained over several years without evidence of decreased effect. The beneficial effects of acarbose on serum lipids were also described with a dose-dependent manner (120), because dietary carbohydrates are key precursors of lipogenesis, and insulin plays a central role for postprandial lipid metabolism. Carbohydrate-induced postprandial triglyceride synthesis is reduced for several hours, so acarbose lowers plasma triglyceride levels (120). The same beneficial effect is also seen in non-diabetic patients with hypertriglyceridemia, and acarbose reduced LDL significantly, and HDL remained as unchanged in hyperinsulinemic and overweight patients with impaired glucose tolerance (IGT) (121). Significantly elevated levels of ursocholic acids in the stool appear to be the additive consequence of a decreased rate of absorption and increased intestinal motility due to the changes of intestinal bacteria. Acarbose may lower serum LDL by means of an increased fecal bifido bacteria, fecal biliary acids, and LDL uptake by the liver. Acarbose together with insulin was identified to be associated with a greater improvement in the oxidative stress and inflammation in cases with type 2 DM when compared with those received insulin alone (122). Similarly, acarbose may improve release of glucagon-like peptide-1, inhibit platelet activation, increase epithelial nitrous oxide synthase activity and nitrous oxide concentrations, promote weight loss, decrease BP, and eventually prevent endothelial dysfunction (120). So acarbose also prevents COPD and other atherosclerotic consequences in patients with excess weight even in the absence of IGT and DM (123, 124). According to our experiences, acarbose should be used in patients with COPD even in normal weight because there are nearly 20 kg of excess fat tissue between the upper and lower borders of normal weight in adults. Although some authors reported as opposite with us (125), acarbose should be considered as the first-line antidiabetic agent, and it is an effective pharmacological option for preventing of all consequences of excess fat tissue in whole body. Based on more than 40 years of clinical use of acarbose, numerous studies did not show any significant toxicity (126). On the other hand, acarbose has not any effect on appetite and eating habit.

As a conclusion, hardened RBC-induced capillary endothelial damage initiating at birth terminates with multiorgan failures in early years of life in the SCD. Excess fat tissue may be much more important than smoking and alcohol for atherosclerosis because excess weight-induced DM is the most common cause of CRD, and CHD and stroke are the main causes of deaths even in the COPD. The efficacy of acarbose to lower blood glucose by preventing breakdown of starch into sugar in the small intestine is obvious. Since acarbose is a safe, cheap, oral, and effective drug for excess weight, it should be advised in COPD because there are nearly 20 kg of excess fat tissue even between the upper and lower borders of normal weight in adults.

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