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Medical Journal
Gülhane Tıp Dergisi

Contents

REVIEW

ORIGINAL ARTICLES

CASE REPORTS

GÜLHANE MEDICAL JOURNAL
Gülhane Tıp Dergisi

DOI: 10.4274/gulhane.galenos.2024.55822
Gulhane Med J 2025;67(1):1-7

Redefining GERD management: The emerging role of potassium-competitive acid blockers

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Keywords: Gastroesophageal reflux, potassium-competitive acid blockers, proton pump inhibitors, reflux disease, heartburn

ABSTRACT

Gastroesophageal reflux is the regurgitation of gastric contents into the esophagus, while gastroesophageal reflux disease (GERD) denotes symptoms or mucosal damage due to recurrent reflux, manifesting as heartburn, acid regurgitation, and dysphagia. GERD's prevalence is lower in Asia (6-7%) than in Western countries (15-21%). Although not inherently dangerous, GERD can significantly reduce quality of life and cause complications, such as esophageal stricture and Barrett's esophagus. Proton pump inhibitors (PPIs) are the primary pharmacologic therapy, but approximately 40% of patients remain symptomatic. Long-term PPI use raises concerns regarding bacterial colonization, nutrient absorption, and other side effects. Potassium-competitive acid blockers emerge as a promising alternative that provides stronger acid suppression with potential benefits in refractory GERD cases and safety concerns associated with prolonged PPI use.

Introduction

Reflux of stomach contents into the esophagus is the cause of gastroesophageal reflux disease (GERD). GERD, on the other hand, is a condition in which gastric acid refluxes repeatedly into the esophagus, oropharynx, and/or respiratory tract, causing mucosal damage and/or distressing symptoms like dysphagia, acid regurgitation, and heartburn (1). GERD is generally less common in Asia than it is in Western nations. The prevalence in Western countries ranges from 15 to 21%, whereas in Asia, it is around 6-7%. GERD is frequently diagnosed by gastroenterologists, surgeons, and general practitioners (2-5).

GERD is classified into two categories: erosive esophagitis (EE), which is characterized by esophageal mucosa lesions that are visible on endoscopy, and non-erosive reflux disease (NERD), which does not have EE. Although not a serious disease, GERD can severely impair quality of life and productivity, comparable to or even lower than that of duodenal ulcers, angina pectoris, and mild heart failure (Figure 1). Untreated GERD can lead to severe consequences, such as Barrett's esophagus, ulceration, or stricture (6-8). Proton pump inhibitors (PPIs) are currently the preferred therapy for GERD. PPIs have a superior effect in resolving reflux complaints and mucosal repair compared to other medications, such as histamin-2 (H-2) blockers and mucoprotective agents. Even though PPI therapy is currently the first-line treatment for GERD, nearly 40% of patients still experience symptoms. Refractory GERD is defined as the presence of symptoms that have not improved with PPI therapy for at least 8 weeks (9). PPI use has been found to be less effective in some patients, particularly those with NERD. In addition, some publications have begun to doubt the safety of long-term use of PPI, which is known to increase the risk of bacterial colonization and infection, impaired nutrient absorption, and other non-specific side effects, such as dementia and chronic renal impairment (2,9-11).

The GERD consensus recommends a new gastric acid suppression drug that acts as a potassium blocker. Potassium-competitive acid blockers (P-CAB) work by inhibiting proton pump activity in the cytoplasmic tubulovesicle and secretory canaliculus, providing a more potent suppressive effect than PPIs (9).

Physiology of gastric acid secretion

Gastric acid is secreted by parietal cells located in the fundus and corpus of the stomach. Gastric acid is secreted to form acidic conditions in the gastric lumen (pH <2), and serves to kill bacteria, facilitate digestion, and absorb minerals such as phosphate, calcium, and iron. Food digestion is aided by the equilibrium of parietal cell secretion activators and inhibitors that protect the gastric and duodenal mucosa. Excessive gastric acid secretion can disrupt gastric mucosal integrity. Activators of the gastric acid secretion process include vagus nerve/ acetylcholine, gastrin, histamine, and ghrelin, whereas inhibitors include somatostatin and glucagon-like peptide 1 (12,13).

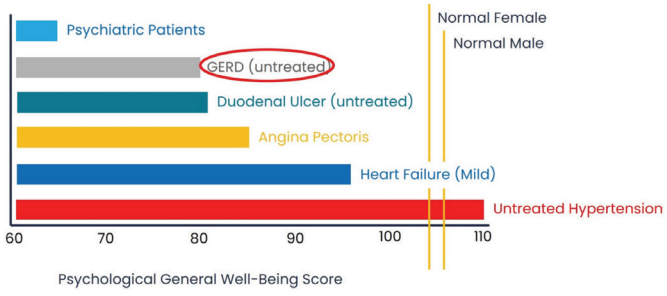

Figure 1. The impact of different medical conditions on quality of life (8)
GERD: Gastroesophageal reflux disease

The activator stimulates the fusion of tubulovesicles containing H^+/K^+ ATPase with the apical secretory canaliculi. The proton pump H^+/K^+ ATPase induces secretion by transporting H^+ ions to the gastric lumen to bind with Cl^- ions and form gastric acid. The entry of K^+ ions from the extracellular space into the cytoplasm of parietal cells occurs concurrently with the entry of H^+ ions into the gastric lumen. This mechanism, along with the sites targeted by acid-suppressing drugs, is illustrated in Figure 2. PPIs and P-CAB are two types of medications that target the H^+/K^+ ATPase pump. PPI acts on gastric parietal cells, covalently binding to the active H^+/K^+ ATPase and inhibiting the secretion of gastric acid, meanwhile, P-CAB works by competitively blocking potassium ions from binding to the H^+/K^+ ATPase, thereby preventing gastric acid secretion in a reversible manner (12,13).

Gastroesophageal reflux disease

GERD is a type of mucosal damage caused by the reflux of stomach contents into the esophagus, oropharynx, or respiratory tract (3,5). It leads to uncomfortable symptoms or complications such as heartburn, acid regurgitation, and dysphagia (3,5).

Etiology and pathophysiology

Esophageal reflux is a physiological condition that can occur in healthy individuals. The pathophysiology of GERD is associated with an imbalance between offensive and defensive factors of the esophageal defense system and gastric reflux material. This imbalance leads to pathologically recurrent

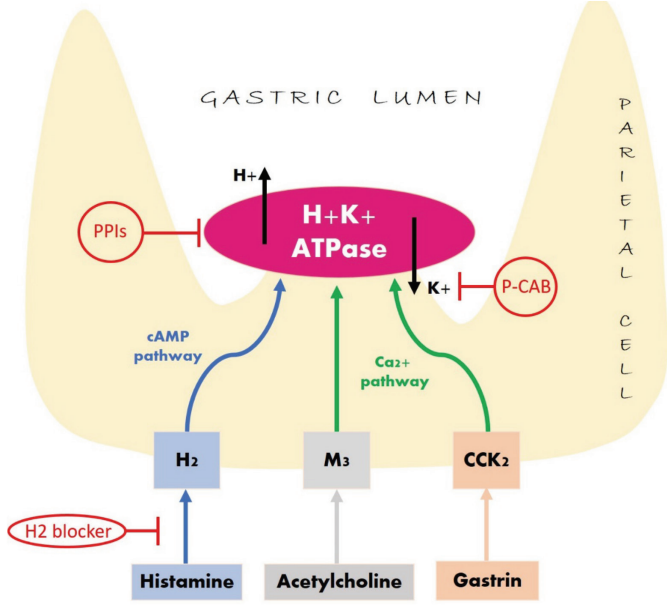

Figure 2. Mechanisms of action of gastric acid-suppressing agents (12,13)
PPIs: Proton pump inhibitors, P-CAB: Potassium-competitive acid blockers, cAMP: Cyclic adenosine monophosphate, Ca^{2+}: Calcium ions, M_3: M_3 muscarinic ACh receptor, H_2: Histamine H_2 receptor, CCK_2: Cholecystokinin receptor

esophageal reflux and causes esophageal mucosal damage. Gastric acid, pepsin, bile acids, and trypsin are considered offensive factors, whereas the lower esophageal sphincter (LES), esophageal clearance mechanisms, and epithelium are considered defensive factors (14,15).

The LES is an anatomical structure composed of smooth muscle cells of the esophagogastric junction (EGJ), separating the esophagus and stomach. Under normal conditions, the LES is in a state of contraction, maintaining high pressure in the zone above the stomach to prevent the migration of gastric reflux material into the esophagus. Physiologically, the LES undergoes transient relaxation during swallowing. In GERD, there is a weakness of the LES, and relaxation occurs without swallowing stimulation, causing gastric contents to flow into the esophagus. This mechanism is the most common cause (90%) explaining the incidence of GERD. Drug use, diet, hormone intake, and structural anomalies are among other factors that can impair LES function (14,15).

The mechanism of esophageal clearance involves the ability of the esophagus to rid itself of gastric reflux material, including bicarbonate in saliva, esophageal peristalsis, gravity, and salivary clearance. Under normal conditions, acidic gastric reflux material is cleared by esophageal peristalsis and neutralized by salivary bicarbonate. Saliva also contains growth factors, such as epidermal growth factor, which promote mucosal repair. Saliva's ability to neutralize stomach acid is compromised in GERD due to a disturbance in the mechanism of esophageal clearance, which allows stomach acid particles to come into contact with the esophagus. Repeated occurrences may cause esophagitis (14,15). The esophageal epithelium consists of cell membranes, intercellular junctions that limit the diffusion of H^+ ions into the esophageal tissue, and esophageal blood flow that supplies nutrients (oxygen and bicarbonate) and excretes H^+ ions and CO_2. Acidic gastric acid and pepsin contents, as well as alkaline duodenal contents of bile salts and pancreatic enzymes, can disrupt defensive mechanisms. Both of these cause damage to the gastric mucosa (15).

Risk factors

Several risk factors are significantly associated with GERD incidence. A family history of heartburn or GERD shows an increased risk as much as 3 times higher. Risk also increases with age, which is related to decreased LES tone. Anatomical abnormalities, such as hiatal hernia, may reduce the competence of the EGJ, increasing the risk of reflux and impairing the clearance of the esophageal refluxate. Obesity is a major risk factor for the emergence and progression of GERD. A decrease in body mass index by 3.5 points can reduce the frequency of GERD symptoms by as much as 40%. In addition to causing an increase in intra-abdominal pressure, increased progesterone hormone has a relaxing effect on the LES (3,16,17).

Some anti-hypertensive drugs, such as nitrates and calcium canal blockers, can decrease the LES tone. Alpha-and beta-adrenergic receptor agonists, theophylline and anti-cholinergics show similar actions. The use of non-steroidal anti-inflammatory drugs does not cause reflux but significantly increases the risk of esophagitis and stricture. Psychological stress can cause impaired esophagus motility. Alcohol consumption and smoking decrease LES tone. Some high-fat diets and soft drinks cause gastric distension, decreased LES, mucosal irritation, and slow gastric emptying (3,16).

Diagnosis

GERD is diagnosed based on clinical symptoms, response to acid suppression drugs, and objective examination, which includes endoscopy and pH monitoring of the esophagus. The symptoms of GERD are highly variable and are classified as typical, atypical, and extraesophageal. Typical symptoms are often observed after meals, aggravated by the recumbent position and improved by the administration of acid-suppressive medications (2,5).

Typical symptoms of GERD include heartburn and regurgitation. Heartburn is a substernal burning sensation that can radiate from the epigastrium to the upper neck, typically occurring after eating or in a lying position. Regurgitation is the return of gastric contents to the mouth, accompanied by a sour or bitter taste. Heartburn and regurgitation are GERD-specific symptoms with a specificity of up to 95%. These two symptoms can be the basis of a presumptive diagnosis and the cornerstone for starting empirical therapy (2,5,14).

Atypical symptoms of GERD include epigastric pain, dyspepsia, nausea, bloating, and burping. These symptoms are not specific and may be caused by other diseases, such as gastric ulcer and achalasia. The extraesophageal symptoms include chronic cough, asthma, laryngitis, and dental erosion. This may be due to the microaspiration of reflux material (2,5,14,15).

GERD is considered when heartburn and regurgitation symptoms are present. Additional objective examination may be considered in elderly patients who are unresponsive/refractory to acid suppression therapy, have a history of malignancy, have warning signs, and have a suspicion of Barret's esophagus. Some of the warning signs include dysphagia, odynophagia, anemia, hematemesis, and weight loss (5,14,18). An endoscopic examination of the upper gastrointestinal tract can be performed to assess the presence of lesions and the degree of complications. Most (75%) of the cases had no lesions on endoscopic examination, with 20-25% having EE and as many as 5-7% having Barret's esophagus (18). In patients with normal endoscopy, ambulatory reflux monitoring can provide confirming evidence. pH-impedance identifies all reflux, irrespective of acidity levels, and is widely regarded as the gold standard of

GERD diagnosis, as outlined in the Lyon Consensus. However, this test is generally not easily accessible, and interpretation is time-consuming (19).

Management

Chronic GERD necessitates long-term treatment, which includes lifestyle modification, medication, and surgery. Lifestyle modification includes weight loss in overweight and obese people, sleeping with a higher pillow, avoiding food consumption <3 hours before sleep, and eliminating stimulating foods, such as chocolate, caffeine, and alcohol (2,5,14,18).

In patients who do not improve with lifestyle changes, pharmacological therapy is recommended. The main drugs used to manage GERD are neutralizing or reducing stomach acid. PPIs are considered the most beneficial for both erosive and non-erosive GERD. PPIs are started once daily before meals and may be increased to twice daily if an inadequate response is observed. Night-time treatment may be considered to manage symptoms that occur at night. The addition of H-2 blockers may be considered when nighttime symptom control is not optimal with maximal PPI administration. There is limited data on the effects of prokinetic agents like metoclopramide and domperidone in GERD treatment (2,5,14,18,20).

Refractory gastroesophageal reflux disease

GERD that does not improve after at least 8 weeks of PPI therapy, supported by objective evidence, is referred to as refractory GERD. There are several causes of refractory GERD. Poor compliance and improper use of PPI medication should be evaluated in patients with suspected refractory GERD. PPI is a prodrug that requires gastric acid activation and should be taken 30-60 minutes before meals. A previous study stated that almost 100% of patients did not take the drug at the correct time, but rather more than 1 hour before a meal, during a meal, or before bedtime (17,21).

A syndrome with esophageal symptoms but no underlying structural, metabolic, or infectious cause is called functional esophageal abnormality. These disorders may be caused by increased mucosal sensitivity to mechanical and chemical stimulation. Functional esophageal abnormalities, weak acid reflux, and acid residues are the most common mechanisms of refractory GERD. Weak acid reflux causes a minimal decrease in pH, but reflux in large volumes may cause esophageal dilatation and induce reflux-related symptoms. Continued reflux may interfere with the healing process of the esophagus (21).

Potassium-competitive acid blocker

P-CABs are a relatively new category of acid-suppression drugs. The H^+/K^+ ATPase enzyme is in the final stage of gastric acid secretion and is the target of several anti-acid secretion drugs. P-CAB is one of the drugs that work by inhibiting the action of this enzyme by selectively acting as a competitive inhibitor of K^+ ions The binding of P-CAB is reversible (7,22,23).

P-CABs are available in tablets orally. The administration of food without or with food does not affect the bioavailability of the drug. The alkaline nature of these drugs causes them to accumulate at higher concentrations in the acidic gastric parietal cell canaliculi than in the plasma. There are several types of P-CABs, including vonoprazan, tegoprazan, and keverprazan, each with distinct pharmacokinetic characteristics. Vonoprazan binds to plasma proteins by 85-88% and is primarily metabolized in the liver to inactive metabolites and is excreted mostly (67%) through urine, whereas the rest is excreted through feces. In contrast, tegoprazan is minimally excreted through urine, accounting for less than 6%. Meanwhile, keverprazan is excreted in 36.3% of cases through urine and 7.33% through feces (23-25).

Efficacy of potassium-competitive acid blocker in gastroesophageal reflux disease

Patients with NERD were found to be less sensitive to PPI therapy; however, although P-CABs have proven effective for gastric acid suppression and show clear benefits in treating EE, their advantages for patients with NERD remain less certain. A study by Niikura et al. (9) found that 12 weeks of vonoprazan therapy can significantly improve the symptoms of NERD. Results from a South Korean trial involving 324 patients with NERD showed that the tegoprazan group achieved higher rates of complete heartburn resolution at 4 weeks than the placebo group (43-49% vs. 24%) (26). Esophageal mucosal lesions that are detectable during endoscopy are the hallmarks of EE. PPI medications have traditionally been the primary treatment for mucosal healing in EE. Although the American College of Gastroenterology does not specifically address the use of P-CABs in GERD, they acknowledge these medications as promising new treatment options. Some studies have indicated that vonoprazan is at least as effective as PPIs for healing EE, with some even showing superior efficacy. Additionally, other P-CABs, such as tegoprazan in Korean patients and keverprazan in Chinese patients, are non-inferior to PPI formulations for initial EE healing. This may be because P-CAB has a longer-lasting and more effective suppressive effect than PPI. As many as 99% of patients with EE achieved mucosal healing after 8 weeks of vonoprazan therapy (6,9,26). P-CAB is also known to reduce the frequency of symptoms in patients resistant to PPIs. The therapeutic effect of vonoprazan 20 mg was better than that of rabeprazole 20 mg, with a duration of therapy of 8 weeks (7).

Safety

Some studies have suggested that P-CAB is relatively safe. The majority of P-CAB safety data is gathered from vonoprazan studies, which reported excellent safety equivalent to anti-

secretory PPI formulations. The most common side effect is diarrhea. Other side effects that have been reported include nasopharyngitis, dyspepsia, headache, nausea, vomiting, and mild to moderate abdominal pain. Skin rash and erythema multiformity have been reported, but the incidences are rare. To date, there have been no reports of life-threatening side effects (22,27). In addition to vonoprazan, another type of P-CAB, tegoprazan, showed no significant difference from placebo regarding treatment-emergent side events in a 4-week trial on NERD (26). Another meta-analysis by Dong et al. (28) found that the tolerability of P-CABs, including vonoprazan, tegoprazan, and keverprazan, was comparable to that of lansoprazole. Although the study reported a slightly higher incidence of serious adverse events with P-CABs than with lansoprazole (P-CABs: 9.6% vs. lansoprazole: 9.3%), it is important to note that such events were rare.

Several P-CAB-type drugs have been developed since 1990, but many are not widely used because of their hepatotoxicity. Unlike the first generation, vonoprazan was found safer for the liver. One study stated that 4-8 weeks of vonoprazan treatment did not significantly induce abnormalities in aspartate aminotransferase and alanine aminotransferase. However, there are currently not many studies on this. Liver function should be monitored when using P-CAB (22,27).

P-CAB increases serum gastrin, pepsinogen 1, and pepsinogen 2 as feedback mechanisms for hypoadditivity. One study compared median gastrin levels 7 days after administering vonoprazan 20 mg twice daily and esomeprazole 20 mg twice daily. The median gastrin level was 529 pg/mL for vonoprazan, compared to 258 pg/mL for esomeprazole (25). Another study reported that the consumption of vonoprazan for 8 weeks did not have a significant effect on gastrin levels compared with the PPI group. Hypergastrinemia stimulates hyperplasia of parietal cells and ECL, causing hypersecretion of gastric acid and allowing the return of symptoms when the drug is discontinued (22). However, gastrin levels typically stabilize and return to normal immediately after therapy cessation. Although P-CABs exhibit nearly equivalent anti-secretory effects, they appear to cause varying degrees of hypergastrinemia, with vonoprazan producing higher levels than tegoprazan, furazan, and zestaprazan. The precise causes of this discrepancy remain unknown, and long-term studies are needed (29).

Proton pump inhibitors vs. potassium-competitive acid blockers

PPIs are currently the first-line therapy of choice for gastroesophageal reflux. However, the therapeutic efficacy of PPI is currently limited. PPI is unstable in an acidic atmosphere and requires an enteric-coated formulation to overcome this. P-CABs have better solubility and stability under acidic conditions, so they do not require enteric coating and can dissolve rapidly. This favors a rapid onset of action and maintains the inhibitory effect even in acidic environments. In addition, the effectiveness of PPI is altered by food intake, which is why it is recommended to take PPI 30-60 minutes before meals, whereas the action of P-CAB is not affected by food intake (7,13,22).

PPIs are activated in the acidic environment of the stomach, where they inhibit gastric acid production by forming a disulfide bond with the H^+/K^+ ATPase. However, the active form is unstable and easily degraded in such conditions. The half-life of PPI is also short at around 1-2 hours, whereas the half-life of P-CAB is longer at approximately 7 hours. As much as 25% of H^+/K^+ ATPase is synthesized daily and stimulated by the feeding process. This explains why multiple doses of PPI are required to achieve an adequate suppressive effect. Unlike PPI, P-CAB binds non-covalently to the H^+/K^+ ATPase, does not require activation, and can quickly suppress gastric acid in a single dose. It is also stable in acidic environments. In healthy male participants, tegoprazan showed greater efficacy and longer-lasting intragastric acid suppression than esomeprazole. Likewise, vonoprazan accumulates and resides in the stomach for a duration of >24 hours. The slow dissociation of vonoprazan gives a longer suppressive effect than that of PPI. Table 1 highlights the pharmacokinetic differences between several PPIs and P-CABs (7,13,22,26).

Genetic polymorphisms of the cytochrome P450 CYP2C19 cause differences in the efficacy of PPIs in some patients and are

Table 1. Comparison of the pharmacokinetic properties of PPIs and P-CABs (25,26,30,31)

	Esomeprazole	Pantoprazole	Vonoprazan	Tegoprazan
Prodrug	Yes, acid needed		No activation is needed, rapid onset of action	
Acid stability	No (enteric-coated)		Yes	
Dosage (mg)	20 mg, 40 mg	20 mg, 40 mg	10 mg, 20 mg	50 mg
Time to plasma concentration peak	1.5 hours	2-3 hours	2 hours	0.5-1.5 hours
Maximum inhibition of acid secretion	Multiple doses (3-5 days)		A single dose (faster with a higher dose)	
Plasma half-life	1-1.5 hours	1-1.9 hours	6-8.8 hours	3.7-5.4 hours
Liver metabolism	CYP2C19	CYP2C19, CYP3A4	Primarily CYP3A4	

PPIs: Proton pump inhibitors, P-CABs: Potassium-competitive acid blockers, mg: milligram

one of the causes of PPI resistance. In patients with extensive CYP2C19 metabolizer activity, PPI concentrations are lower, whereas drug levels are higher in patients with poor metabolizers because of low metabolic activity. The therapeutic effect was found to be higher in patients with poor metabolizers (84.6% compared to 45.8% in patients with extensive metabolizers). According to a study conducted in Indonesia, the most common types of metabolizers were intermediates (41.6%), followed by rapid (38.5%) and poor (19.9%) (32). CYP3A4 and non-oxidative enzymes (sulfotransferases) are among the enzymes that break down P-CAB. The metabolism of this drug is not influenced by CYP2C19, as shown in Table 1, so it is not influenced by genetic polymorphism and provides the same inhibitory effect on each individual (7,13,22).

Conclusion

GERD is one of the most prevalent conditions encountered by gastroenterologists, surgeons, and general practitioners. The condition is caused by the reflux of gastric contents into the esophagus. Although it is not a deadly disease, it can severely impair the quality of life and productivity. The first-line treatment for GERD is currently PPIs; however, in certain cases, especially NERD, the results are frequently inadequate. P-CAB, a new type of gastric acid suppression drug, is expected to provide a more potent effect than PPIs and can become one of the drugs of choice for GERD therapy.

Footnotes

Authorship Contributions

Concept: V.A.G., T.S., Design: V.A.G., Literature Search: V.A.G., T.S., Writing: V.A.G., T.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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Mapping and spatial analysis of hypertension and diabetes prevalence in selected rural South African communities

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ABSTRACT

Aims: The widespread prevalence of non-communicable diseases in rural South African communities is concerning. This study aimed to determine the number of cases of hypertension and diabetes reported in rural clinics during the period under review.

Methods: A cross-sectional population-based survey was conducted to determine the prevalence of hypertension and diabetes and the geographical distribution of healthcare facilities in rural communities in the North-West province. Hypertension and diabetes were defined as blood pressure ≥130/80 mm Hg and fasting blood glucose ≥126 mg/dL. The range of values for each district municipality (DM) were used to represent map densities and the number of patients screened for hypertension or diabetes.

Results: Hypertension and diabetes map densities were highest in the Bojanala DM and lowest in Dr. Ruth Segomotsi Mompati DM. The number of patients screened for hypertension was highest in the Dr. Ruth Segomotsi Mompati DM (11955-14940) and lowest in the Ngala Modiri Molema DM (11-2996). The number of patients screened for diabetes was highest in the Bojanala DM (12868-16083) and lowest in the Dr. Ruth Segomotsi Mompati DM and Dr. Kenneth Kaunda DM (1-3218).

Conclusions: Although higher numbers of hypertension and diabetes were reported in urban areas, the numbers were grossly low in rural areas. This difference may be associated with the lifestyle of the residents of each area and the uneven distribution of clinics and health centers for the diagnosis and management of these conditions.

Introduction

Worldwide, approximately 70% of all morbidities and mortality are caused by non-communicable diseases (NCDs) (1,2). These NCDs are major risk factors for stroke, myocardial infarction, blindness, and several other cardiovascular diseases (3). A report by the World Health Organization showed that more than 30% of the entire world population suffers from hypertension, whereas more than 10% suffers from diabetes (4). Unfortunately, the large numbers of morbidities and mortality due to NCDs are borne by low- and middle-income countries, where resources are scarce (2). Some reports indicate that approximately 75% of the people in low-and-middle-income countries will have hypertension or other NCDs by the year 2025 (5,6). Among the older population in most African countries, the prevalence is as high as 60%, and a higher prevalence has been reported in urban settings than in rural settings (7). For diabetes, the prevalence is documented as 67-77% in most parts of South Africa (8). Importantly, a study also reported a comorbidity association between hypertension and diabetes (9). This number is increasing (10) and mortality could increase by 2025 (11).

Studies have indicated the possible devastating impacts of the renewed health and behavioral transitions occurring in South Africa (12,13), which has led to an astronomical increase in the prevalence of hypertension, diabetes, and other NCDs (14). Health transitions have been attributed to a demographic shift from rural to urban centers caused by rural-urban migration (15,16). This rural-urban migration leads to dietary and lifestyle modifications and potentiates the population to develop lifestyle diseases (17,18). These transitions have been reported to change the dynamics of the prevalence of hypertension and diabetes and the use of available clinics in the provinces, typifying the situation in the North-West province of South Africa (19).

Medical geography is a relatively new field of study that characterizes the association between pathological and geographical factors that regulate the evolution of pathogens (20). Its use is still limited and uncommon in South Africa and most parts of Sub-Saharan Africa. Medical geography helps map and carry out spatial analyses of diseases and their spread within a locality, aiming to identify low-risk and high-risk regions of a disease (21). For example, in Luxemburg, a study reported geographical variations in the prevalence of hypertension with the highest odds ratio in the industrialized region of the country (22). This study aimed to determine the geographical presentation of hypertension and diabetes concerning the availability of public and private healthcare facilities in rural communities in the North-West Province of South Africa.

Methods

Study design

This was a cross-sectional population-based survey conducted at health clinics in the North-West province of South Africa between April 2015 and March 2016 to determine the distribution of health services in selected rural communities and the number of patients with hypertension and diabetes. There are four districts in the province. At each location, information was gathered using a data collection form detailing the number of clinics, the number of patients diagnosed with hypertension and diabetes, and any pertinent data. Hypertension and diabetes were defined as blood pressure ≥130/80 mmHg and fasting blood glucose ≥126 mg/dL respectively (23,24). Additionally, a Global Positioning System receiver was used to collect the geographical coordinates for each center in the study area. These coordinates were then linked to the attribute information collected at the centers and a spatial database containing health center locations and their characteristics was created.

Study locations

The survey was performed in eighty-eight local public and private healthcare facilities in the province. The research team visited 38, 26, 17, and 7 healthcare facilities in Bojanala, Kenneth Kaunda, Ngala Modiri Molema, and Dr. Ruth Segomotsi Mompati district municipalities (DM), respectively.

Dataset

Provincial names and boundaries, as well as their longitudes and latitudes, form the main dataset used in this study. Data were entered into GIS ArcMap and merged with clinical data analyses into one database using common codes for mapping and visualization. Geostatistical spatial analysis was employed to predict the spatial variation in hypertension and diabetes in the province (25).

Inverse distance weighting

Interpolation using inverse distance weighting (IDW) operates under the explicit assumption that objects closer to one another share more similarities than those farther apart (26). With evenly distributed points in an area, the IDW method is effective. In this study, greater weight was assigned to the points closest to the target location; thus, the allocated weights change as an inverse function of "p^{th} power of distance", where the power function (p) is a positive real number. The greater the values closest to the point to be interpolated, the greater the influence. The product of “allotted weights” and “measured values” for all sites was added to provide parameter prediction for the target location (26).

Hotspots analysis

Hotspot Analysis is an analytical technique that combines statistical and spatial methods to measure the concentration of specific elements or attributes. Concerning spatial interpolation, the Hotspot Analysis tool from ArcGIS calculates the Getis-Ord Gi* statistic for individual features in the dataset (27). The generated z scores and p values were used to identify high and low clustered values in space. This process assesses each feature while considering its context with neighboring features. A feature with a high value may be interesting but not necessarily be a statistically significant hotspot. For a feature to qualify as a statistically significant hotspot, it must have a high value and the surrounding features must possess similarly high values provided all points collected are equally dispersed and at equal intervals (27).

Kriging

Kriging is a stochastic geostatistical technique like inverse distance weighted averaging, where a linear combination of weights at known points is used to predict the value at unknown points. The kriging system is expressed as covariances, commonly derived by estimating and modeling a semi-variogram: a measure of the spatial correlation between two points (28). Kriging is a family of estimators used to interpolate spatial data, including ordinary, universal, and indicator kriging, co-kriging, and others. The choice of kriging depends on the data characteristics and desired spatial model. This study used ordinary kriging to predict unobserved values from observations obtained from nearby clinics. Ordinary kriging is the most common kriging type used in spatial data simulations, and it is considered the best because it minimizes the variance of the estimation error and is more accurate when the unobserved value is closer to the observed value (28).

Statistical Analysis

The range of values for each DM was used to represent map densities and the number of patients screened for hypertension or diabetes.

Ethics approval

This study was conducted following the guidelines for human experiments at North-West University (NWU), South Africa. This study is part of a larger study titled: NCDs, physical activities, and quality of life across different populations in the North-West province. The protocol for this study was approved by the NWU Ethics Committee (NWU-HREC) (registration number: NWU-00014-12-A9, date: 08.03.2012). All procedures for this study were carried out with strict adherence to the National Institutes of Health guidelines for human research.

Results

Density map of the North-West province districts for patients with hypertension and diabetes

The outcome is a less concentrated depiction of a phenomenon that is not portrayed through a sequence of distinct points but through an uninterrupted surface. The density map was found to be highest at the city centers of Bojalana District Municipality (BDM), Dr. Kenneth Kaunda District Municipality (DKKDM), and Ngala Modiri Molema District Municipality (NMMDM). This indicates the frequency of reported cases of hypertension compared with the available number of clinics in the more rural municipalities. There appeared to be a general reduction in density from city centers to suburbs. The density map was generally low at Dr. Ruth Segomotsi Mompati DM (DRSMDM). The Kernel density estimation in Figures 1a and 1b takes the value of the data assigned to a specific point and

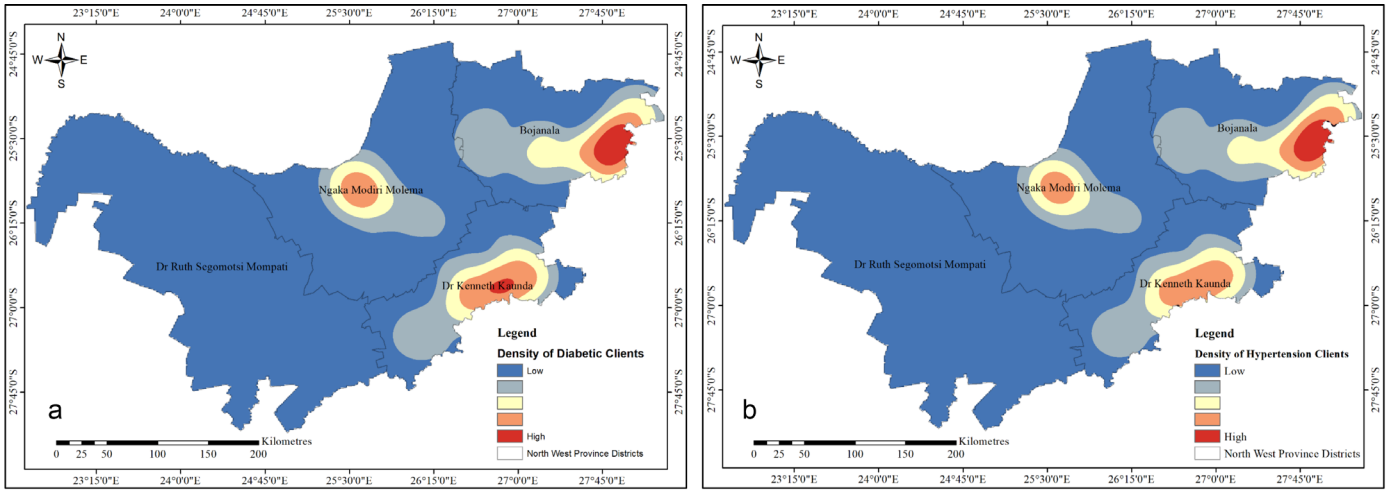

Figure 1. Density map for patients with (a) hypertension and (b) diabetes

spreads across a predefined boundary of the northeastern province. This density pattern was also observed in patients with diabetes, with higher concentrations observed in BDM, DKKDM, and NMMDM and lowest concentrations observed in DRSMDM. This density pattern indicates a possible link between the two studied NCDs.

Number of patients screened for hypertension and diabetes at various clinics in the districts

The study also reported the total number of patients who were screened for hypertension and diabetes at each district. The number of patients screened for hypertension was highest at the Dr. Ruth Segomotsi Mompati DM (11955-14940) and lowest at the Ngala Modiri Molema DM (11-2996). The number of patients screened for diabetes was highest at the Bojanala DM (12868-16083) and lowest at the Dr. Ruth Segomotsi Mompati and Dr. Kenneth Kaunda diabetes clinic (1-3218). This is illustrated in Figure 2a, 2b.

Hotspot map showing the prevalence of hypertension and diabetes

Figures 3a and 3b illustrate the hotspot map of the prevalence of hypertension and diabetes in the districts. The pattern was similar for hypertension and diabetes, with the prevalence highest at DKKDM, followed by BDM, DRSMDM, and finally NMMDM. The map of these hotspots also serves as another pointer to the possible link in the distribution of hypertension and diabetes in the district and the higher presence of these NCDs at urban centers.

Discussion

This study aimed to determine the geographical presentation of hypertension and diabetes in rural communities in the North-West province of South Africa. While a strategic plan to prevent the ever-increasing incidence and prevalence of NCDs like hypertension and diabetes had been developed more than

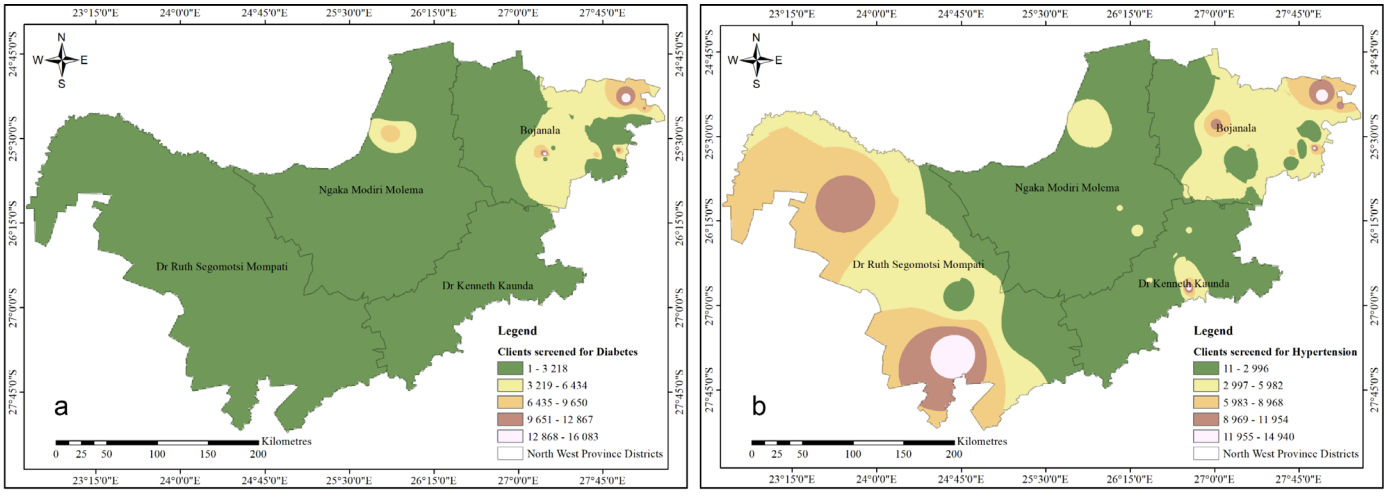

Figure 2. a, b) Number of patients screened for (a) hypertension and (b) diabetes at various clinics in the districts

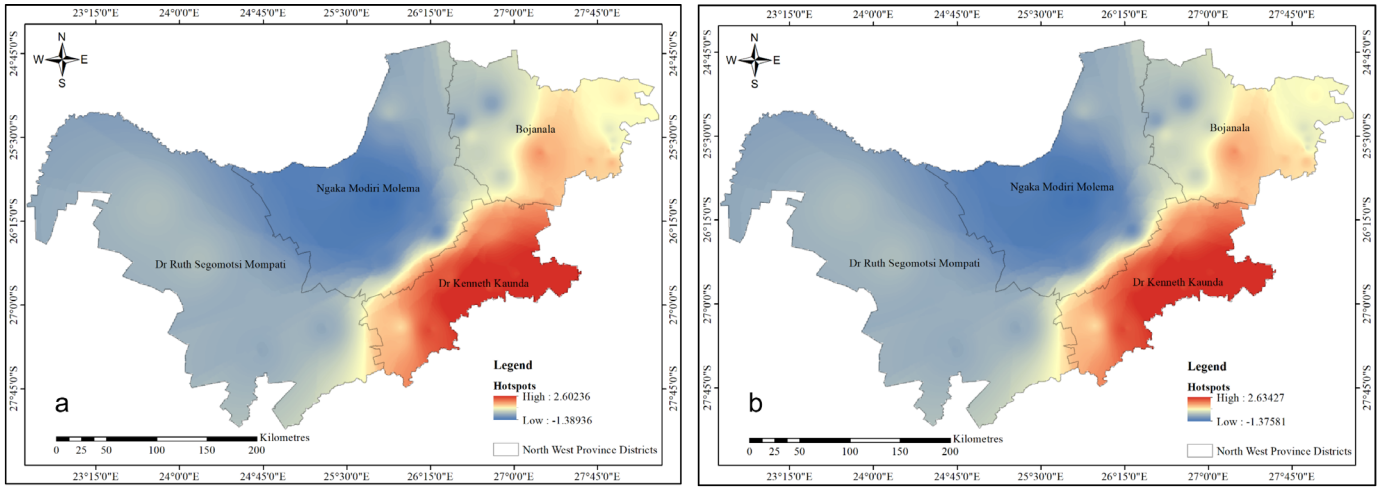

Figure 3. a, b) Hotspot map indicating the prevalence of (a) hypertension and (b) diabetes

a decade ago (29) in South Africa, the continuous increase appears to show a lack of understanding of the exact distribution of the affected patients and possible imbalance in the number of healthcare facilities and providers available to manage the conditions. This is the situation in the North-West province, and it explains why there is renewed interest in the likely factors responsible for the mismatch in the province (30). This study presents the observed uneven distribution of patients with either hypertension or diabetes, concerning the number of clinics in the North-West province of South Africa.

In this study, we observed that the density map for hypertension and diabetes showed higher concentrations of the two conditions in the relatively urban centers of Bojanala, Dr. Kenneth Kaunda, and Ngala Modiri Molema DM. It should be noted that these centers have the highest number of clinics in urban areas. The observed high densities could be due to the high population within the major towns in the different districts, as well as pull factors that contribute to the health risks associated with lifestyle diseases. This geographical distribution could also be due to the recently reported lifestyle transition characterized by increased adoption of urban and western lifestyles (7). Other authors have attributed this distribution to dietary transitions (6,7). The traditional diet has been abandoned because of urbanization and rural-urban migration for almost four decades (31). Thus, there appears to be a gradual shift from rural to urban centers (4,5,32), which typifies the situation in the province (7). A close look at the geographical distribution also revealed a high level of similarity between the density map for hypertension and that for diabetes in the entire province.

Importantly, even with fewer clinics in Dr. Ruth Segomotsi Mompati DM, more people were screened for hypertension than for diabetes. In contrast to this observation, however, the number of patients screened for both hypertension and diabetes at the Bojanala DM mirrors the available number of healthcare facilities. This implies that while the high number of cases reported in the Bojanala district could be due to the available number of clinics, the high number of patients screened for hypertension specifically at the Dr. Ruth Segomotsi Mompati district may be due to a clear-cut high number of cases in the district. Coincidentally, the number of patients screened for hypertension and diabetes was generally reduced at the Ngala Modiri Molema and Kenneth Kaunda DM compared with the available facilities. One major factor that could affect this distribution is the disparity in the level of education and wealth of the people in the province (33). Well-informed and educated people in major towns tend to have regular medical check-ups at public and private clinics (34). However, their counterparts in rural areas may prefer to use traditional herbs for treatment, as earlier studies have reported extensive use of herbal products by South Africans (35). A higher prevalence of hypertension and diabetes was reported in the Dr. Kenneth Kaunda DM, followed by Bojanala, Dr. Ruth Segomotsi, and Ngala Modiri Molema DMs. These are the core city centers dominated by educated people whose level of knowledge could directly affect the observed distribution (36,37) and where interprofessional care is commonly practiced in the management of conditions (38).

Based on these findings, there is an urgent need for a more pragmatic approach to managing the astronomical increase in the number of people with NCDs in the province. There may be a need to create policies to regulate nutritional and behavioral lifestyles at city centers while increasing the number of test centers and creating more awareness at rural centers to control the observed geographical distribution of hypertension and diabetes. However, it should be noted that most NCD data were collected and presented using surveying procedures, which might lead to under- or overestimation and are only applicable on coarse spatial scales (39).

This is one of the first studies in the Southern African region that directly used medical geography knowledge to describe a local challenge. The maps provide a real-time graphical representation of hypertension and diabetes in the province.

This study only reported the density maps, and the number of cases observed in the DM of hypertension and diabetes, among several other NCDs like cancer, chronic lung disease, and stroke. The nutritional and behavioral transition in the province is likely to affect the geographical distribution of these other NCDs. In addition, the study only presented the distribution within a short period of just one year. It would have been better if a report covering at least five years was available to provide a clearer picture of the distribution of NCDs in the province. Nonetheless, the report provides insight into the distribution of the two NCDs during the study period.

Conclusion

While higher numbers of hypertension and diabetes were reported in urban areas, the numbers were grossly low in rural areas. This difference may be associated with the lifestyle of the residents of each region and the uneven distribution of clinics and health centers for the diagnosis and management of these conditions.

Acknowledgments

The authors acknowledge the support from the Provincial Department of Health for their efforts in the collection of data for the study.

Ethics

Ethics Committee Approval: The protocol for this study was approved by the NWU Ethics Committee (NWU-HREC) (registration number: NWU-00014-12-A9, date: 08.03.2012).

Informed Consent: Consent form was filled out by all participants.

Footnotes

Authorship Contributions

Concept: A.A., U.U., M.A., Design: U.U., M.A., Data Collection or Processing: U.U., M.A., Analysis or Interpretation: A.A., U.U., S.B., Literature Search: A.A., U.U., Writing: A.A., U.U., S.B., M.A.

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Association between quality of life and visual characteristics in individuals with diabetic retinopathy

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ABSTRACT

Aims: To estimate the vision-targeted quality of life (QoL) in diabetic retinopathy (DR) patients and further correlate the National Eye Institute-Visual Functioning Questionnaire-25 (NEI-VFQ-25) score with demographic factors and visual function parameters.

Methods: This cross-sectional observational study included 92 patients with type 2 DR. The Marathi version of the NEI-VFQ-25 was used to assess QoL. Visual acuity (VA) for distance and near vision was assessed using the logMAR distance and near acuity chart, contrast sensitivity (CS) was assessed using a Pelli-Robson chart, and color vision was assessed using the Ishihara chart.

Results: The mean age was 65.08±17.56 ranging from 40 to 84 years participated in the study. Of the 92 patients with DR, 55.43% were male and 44.56% were female. The mean distance VA of the better eye was 0.7±0.29 logMAR. The mean near VA was 0.43±0.29 logMAR. The mean CS for the better eye was 0.95±0.50 log. The mean NEI-VFQ-25 composite score was 65.08±17.07. The subscales most affected were general health (50.7±20.16), mental health (52.22±25.03), and general vision (52.99±19.9).

Conclusions: QoL was significantly lower among patients with DR. Mental health, general health, general vision, and near vision were mostly affected. There was a significant association between the NEI-VFQ-25 score and age. The NEI-VFQ-25 score decreased with increasing age. Visual function parameters, including distance VA, near VA, and CS, were significantly associated with the NEI-VFQ-25 score.

Introduction

Diabetic retinopathy (DR) is a common complication of long-term and inadequately controlled diabetes mellitus (DM) (1). It is responsible for blindness and vision loss in individuals aged 60 years (2). It causes restrictions such as visual impairment, socially independent functional loss of work productivity, and economic loss due to treatment costs (3).

Impairment of vision and treatment costs due to DR can greatly impact patients' quality of life (QoL) and compel severe economic strain on society (4). Assessing health-related QoL (HR-QoL) provides better insight into the influence of disease and its treatment from a patient's viewpoint, which is not exposed in clinical assessment. Measuring QoL in affected individuals is highlighted in a patient-centric healthcare prototype (5).

In recent years, researchers in the health sciences have illustrated the imperative function of QoL in managing patients with diabetes. Worldwide, different studies in the past have revealed contradictory outcomes regarding QoL in these patients (6). According to previous studies, DR does not affect QoL (7,8). Nevertheless, some researchers have stated that there is a significant effect of visual impairment due to DR on patients' QoL (9-11). Therefore, determining QoL in patients with DR from different geographical locations is critical. Despite the ambiguity of obtaining the National Eye Institute-Visual Function Questionnaire-25 (NEI-VFQ-25) in the Indian language, few studies have been conducted in the Indian population, leading to disease and deteriorating QoL, which must be investigated. In a previous study using the Hindi translation of the NEI-VFQ-25, researchers from Pune found that DR negatively affects QoL (12). Although Marathi is Maharashtra's most widely spoken language, research on the QoL of people with DR in Pune, Maharashtra, has yet to be published using the Marathi-translated NEI-VFQ-25. This is the first study to assess VR-QoL in patients with DR from Pune, Maharashtra, employing the Marathi variant of the NEI-VFQ-25 and correlating these results with visual parameters. To evaluate vision-targeted QoL in patients with DR, to assess visual acuity (VA) and contrast sensitivity (CS), which are further correlated with the NEIVFQ-25 score.

Methods

Study design and setup

From January to March 2022, a cross-sectional observational study was conducted at the tertiary eye hospital. The study followed the Declaration of Helsinki, and the Institutional Review Board and Ethics Committee of Dr. D. Y. Patil Vidyapeeth provided ethical approval (re-reg. No. ECR/361/Inst/MH/2013/RR-16, date: 27.11.2019) for the study. The study involved 92 individuals diagnosed with type 2 diabetes and DR who met specific inclusion criteria. Additionally, the participants were required to provide informed consent and adhere to the study's prescribed protocol. Type 2 diabetes diagnosis was confirmed by thoroughly examining the patients' medical records. To be included in the study, the participants had to maintain stable glycemic control for 3 months, as indicated by HbA1c levels not exceeding 8%. Individuals with a history of severe diabetic ketoacidosis or hyperosmolar hyperglycemic states within the last 12 months were excluded. DR was categorized using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system. Ocular diseases other than DR, which may affect visual parameters, were excluded, such as aphakia, significant cataract (the cataract has been graded, followed by the World Health Organization simplified Cataract Grading system), corneal pathology, glaucoma, vitreous pathology, and retinal and optic nerve pathology. Participants who were either unwilling to participate, declined to complete the questionnaire, or submitted incomplete questionnaires were excluded from the study.

Participants' cognitive capacity was assessed using the Mini-Mental State Examination, which evaluates memory, attention, and executive function based on a minimum score. To maintain a specific focus on individuals predominantly affected by DR, it was imperative to exclude patients with illnesses that significantly impair cognitive function, such as Alzheimer's disease and other neurodegenerative diseases.

Language barriers hindering assessment understanding and completion were also grounds for exclusion. Individuals who are prescribed certain drugs may experience visual impairment as a result of probable adverse reactions. The study did not include medications that have the potential to impact visual functionality, such as corticosteroids, anticholinergics, antidepressants, isotretinoin, beta-blockers, oral contraceptives, and digoxin.

Data collection

Demographic information, such as age and gender, diabetes duration, and DR grade, was collected. Near VA (NVA), distant VA (DVA), and CS were examined and recorded. The ETDRS logarithm of the minimum angle of resolution (logMAR) chart was used to measure the best-corrected distance VA at a distance of 4 m. A standard retro-illuminator (the Lighthouse Chart lighting Unit from New York) was used for consistency of illumination. If the patients could not identify the peak line at a distance of four meters, the chart was moved by two and one meters until the patients achieved it. At a distance of 40 cm, the NVA was calculated as the smallest print that could be perceived by the patient with the finest corrective lenses using the logMAR NVA chart in an environment with controlled room illumination. A Pelli-Robson chart was employed to evaluate CS at a distance of 1 m and was tested binocularly to ensure that the chart luminance was within the manufacturer's recommended range of 60-120 cd/m^2. The Ishihara pseudoisochromatic plates, specifically plates 1-17, were used with all participants to detect any red-green color deficiency. This testing procedure was conducted under normal room lighting conditions at a distance of 75 cm, with participants using their best-corrected VA.

Questionnaire

This study utilized a Marathi translation of the NEI-VFQ-25 to assess participants' QoL. Initially, the NEI-VFQ-25 included 51 components designed to evaluate the impact of ocular diseases on an individual's functional activities and overall well-being (13). Subsequently, a concise version comprising 25 components was introduced. The well-established NEI-VFQ-25 questionnaire has undergone successful translation and validation in numerous languages. Self-assessment of vision-related functions was measured across 11 dimensions in the NEI-VFQ-25. These dimensions encompass general health, general vision, ocular discomfort, close and distant activities,

driving, color vision, peripheral vision, social functioning, role challenges, and dependence. Face-to-face interviews were conducted by one of the investigators at the hospital's outpatient department, following a consistent questionnaire administration method. Patients typically required approximately 10-15 minutes to complete the survey.

Statistical Analysis

Statistical Package for the Social Sciences 27.0.0 was used to perform all analyses on the collected data. Information was usually provided. The data followed a normal distribution. Descriptive statistics, independent t-tests, and analysis of variance (ANOVA) were used to compare the NEI-VFQ-25 composite scores between the groups. Pearson's correlation regression test was applied to illustrate the correlation between the NEI-VFQ-25 composite score and demographic (age and gender) and visual parameters (NVA, DVA, and CS).

Results

A total of 107 individuals with type 2 DR were initially selected for the study. However, after the initial ophthalmic assessment, 6 patients refused to complete the questionnaire, and 9 patients did not fully fill out the questionnaire. To ensure the integrity and completeness of our data, we excluded participants. Finally, 92 patients were examined with a mean age of 65.08±17.56 years, ranging from 40 to 84. The analysis revealed notable demographic traits and varying degrees of disease severity among the participants. A slight male predominance (51, 55.43%) was observed compared with a female predominance (41, 44.56%). The age distribution was fairly distributed, with the 60-69 age group having the highest representation (27.08%), followed by a relatively balanced distribution across the 40-49, 50-59, and 70-79 age groups (21.73%, 20.65% and 22.82%). The 80-90-year-old age group comprised the smallest proportion (7.60%) of participants. In terms of diabetes duration, most participants had the disease for 11-21 years (45.79%), followed by those with a history of more than 21 years (34.57%) and those diagnosed within the last 1-10 years (19.62%). DR severity varied, with proliferative DR (PDR) being the most common (46, 42.99%), followed by severe non- PDR (NPDR) (20, 18.69%), moderate NPDR (15, 14.01%), and mild NPDR (11, 10.28%).

Visual function

The mean DVA for the better eye was 0.7±0.29 logMAR, ranging from 0 to 1.3 logMAR. The mean NVA was 0.43±0.29 logMAR, ranging from 0 to 1.1 logMAR. The mean CS for the better eye was 0.95±0.50 log, ranging from 0.2 logs to 2.3 logs. Of the 92 patients, 81.31% had normal color vision, while 18.79% had color vision defects. The baseline characteristics of the visual functions are illustrated in Table 1.

Cronbach's alpha score for consistency

All subscales were calculated using Cronbach's alpha. A Cronbach's alpha is between 0.7 and 0.9 indicates high internal consistency. All items had a Cronbach's alpha of 0.98, indicating that the NEI-VFQ-25 instrument was internally consistent.

Score for the NEI-VFQ

The average NEI-VFQ-25 composite score was 65.08± 17.07. The most affected subscales were general health (50.7±20.16), mental health (52.22±25.03), general vision (52.99±19.9), near activities (55.61±27.81), and distance activities (58.60±21.75). However, the disease did not affect peripheral vision (82.24±21.72) and color vision (69.86±24.7). Higher scores were obtained for ocular pain (92.64±13.29) and driving (88.75±7.86). The NEI-VFQ-25 scores of the different subscales are illustrated in Table 2. The composite scores of different age groups and DR types are presented in Table 3. The difference in composite scores between age categories and types of DR was statistically significant (p=0.001).

Table 1. Baseline characteristics of the study participants

Visual functions	Mean, SD
DVA (logMAR)	0.7±0.29
NVA (logMAR)	0.43±0.29
CS (log)	0.95±0.50
Color vision	**Frequency and percentage**
Normal	75 (81.31%)
Defective	17 (18.79%)

DVA: Distance visual acuity, NVA: Near visual acuity, CS: Contrast sensitivity, SD: Standard deviation

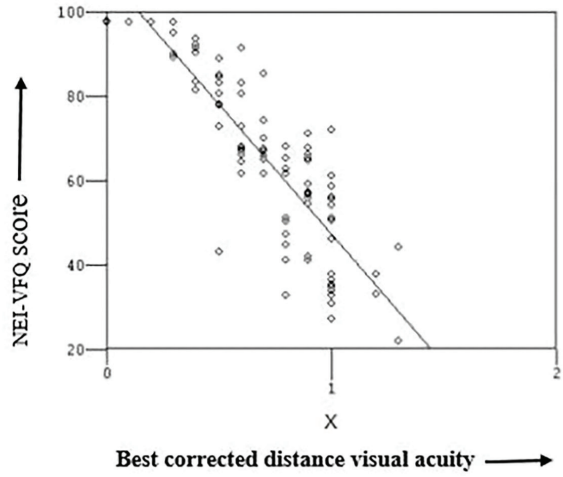

Figure 1. Correlation between NEI-VFQ and near visual acuity
NEI-VFQ: National Eye Institute-Visual Functioning Questionnaire

Association between NEI-VFQ-25 and demographic characteristics and visual functions

Demographic factors like age significantly correlated with the NEI-VFQ-25 composite score, whereas gender showed no significant correlation (Table 4). The NEI-VFQ-25 composite score demonstrated a notable link with DVA, NVA, and CS. Figure 1 illustrates a robust inverse relationship between DVA and the NEI-VFQ-25 score, indicating that as the logarithmic value of VA decreases, the NEI-VFQ-25 score increases. Conversely, Figure 2 presents a substantial correlation between CS and the NEI-VFQ-25 score, suggesting that an increase in the logarithmic measure of CS corresponds to an elevation in the NEI-VFQ-25 score. The better the VA, near vision, and CS were, the better the mean composite score.

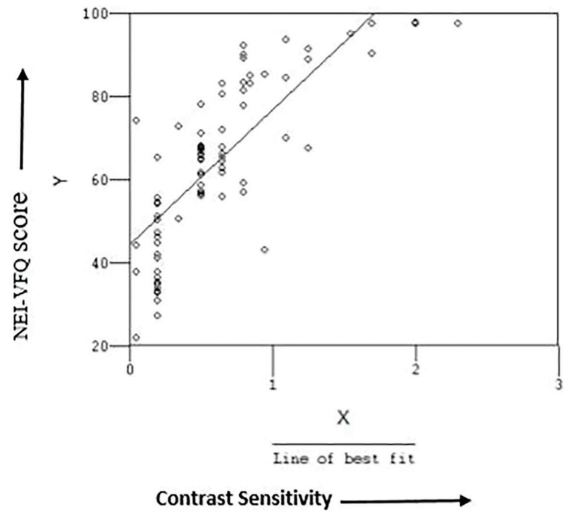

Figure 2. Correlation between NEI-VFQ and best-corrected distance visual acuity

NEI-VFQ: National Eye Institute-Visual Functioning Questionnaire

Table 2. Mean and standard deviation of NEI-VFQ-25 scores among the Indian populations

Domains	Present study (n=107)	Pawar et al. (12) (n=149)	Pereira et al. (20) (n=123)
General health	50.7±20.16	32.18±10.12	58.43±14.59
General vision	52.99±19.9	25.06±11.12	63.69±19.26
Ocular pain	92.64±13.29	63.78±12.36	89.10±13.32
Near activities	55.61±27.37	31.63±15.63	70.79±30.56
Distance activities	58.6±21.75	62.45±11.89	72.68±32.41
Social functioning	69.04±24.36	78.25±18.37	78.69±24.15
Mental health	52.22±25.03	56.25±14.39	71.71±28.77
Role difficulties	58.07±25.08	46.36±13.92	74.80±27.97
Dependency	59.66±26.08	66.31±12.83	77.17±27.93
Driving	88.75±7.86	52.79±10.87	48.84±42.63
Color vision	69.86±24.7	79.67±11.54	76.29±28.27
Peripheral vision	82.24±21.72	51.96±16.97	73.93±25.55
Composite score	65.08±17.07	-	73.93±25.55

NEI-VFQ-25: National Eye Institute-Visual Functioning Questionnaire-25

Table 3. Comparison of the NEI-VFQ-25 scores of demographic variables

Age group (years)	Composite score	p value
Gender		
Male	65.28±17.56	p=0.69
Female	64.82±17.88	
Age group		
40-49	90.00±11.95	
50-59	73.00±15.19	
60-69	60.24±18.80	p=0.0001
70-79	48.48±23.21	
80-90	34.14±21.98	
Severity of DR		
Mild NPDR	94.52±2.99	
Moderate NPDR	84.58±6.68	
Severe NPDR	75.87±8.90	p=0.001
PDR	51.44±12.96	

NEI-VFQ-25: National Eye Institute-Visual Functioning Questionnaire-25, DR: Diabetic retinopathy, NPDR: Non-PDR, PDR: Proliferative DR

Table 4. Association between the NEI-VFQ-25 composite score with demographic parameters and visual functions

Correlation between NEI-VFQ-25 scores and demographic parameters		
Demography	**Correlation coefficient**	**p values**
Age	-0.87	0.001
Gender	-0.012	0.9
Severity of DR	-0.80	0.001
Duration of DM	-0.81	0.001
Correlation between NEI-VFQ-25 and visual function		
Visual function	**Correlation coefficient (r)**	**p values**
DCVA	-0.85	0.001
NVA	-0.86	0.001
CS	0.79	0.001

NEI-VFQ-25: National Eye Institute-Visual Functioning Questionnaire-25, DR: Diabetic retinopathy, DM: Diabetes mellitus, DCVA: Distant corrected visual acuity, NVA: Near visual acuity, CS: Contrast sensitivity

Discussion

The main findings of the current study are as follows; patients with DR exhibited significantly lower QoL. The disease had an impact on general health, mental health, overall vision, near activities, and distance activities. Color and peripheral vision were least affected. The NEI-VFQ-25 score was strongly correlated with age and visual function.

HR-QoL in patients with DR can be assessed using various tools (3,10). According to previous reports, the NEI-VFQ-25 is an excellent tool for measuring the VR-QoL of patients with DR because it captures the psychological and emotional aspects of the disease and the visual purpose (3,14).

Previously, the NEI-VFQ-25 was employed in diverse populations to assess the QoL of subjects with different diseases (15,16). Therefore, in the present study, we used the Marathi-translated NEI-VFQ-25 to evaluate VR-QoL in patients with DR. This study provides evidence regarding the influence of demographic factors, including age and gender, duration of DM and severity of DR, and visual parameters, including DVA, NVA, and CS, on VR-QoL in patients with DR. The current research showed that DR dramatically affects patients' QoL, primarily affecting general health, vision, and mental health.

According to previous studies, women with DR have a significantly lower QoL than men (12,17). In the current study, women scored less than men, although the difference was not statistically significant. In the current analysis, no significant association was identified between the NEI-VFQ-25 composite score and gender, similar to previous research (18,19). On the contrary, some studies have found lower QoL scores among females than males (12,17). These differences may be due to geographical distribution and cultural variations. Patients aged 40-50 years recorded the lowest QoL scores, according to Pawar et al. (12), whereas those aged 81-90 years reported the highest QoL. The current investigation revealed a negative relationship between the NEI-VFQ-25 composite score and age, consistent with previous studies (20,21). The severity of DR has a significant impact on QoL. As the severity of DR progresses, the NEI-VFQ-25 score shows significant deterioration. Previous studies on QoL scores between the NPDR and PDR groups found no significant differences (21,22). In the present study, the PDR group had significantly lower QoL scores than the NPDR group, similar to a study by Pereira et al. (20). The duration of DM was significantly correlated with the NEI-VFQ-25 composite score. Çetin et al. (22) and Pereira et al. (20) reported similar findings.

The current study showed that VA and NEI-VFQ-25 scores were significantly correlated with patients with DR. When VA was amplified, NEI-VFQ-25 scores were also amplified. This finding is similar to that of previous studies (12,22). Along with contributing to poor VA, poor scores on the NEI-VFQ-25 may indicate a lack of CS, as it has become a routine method for assessing visual function in a clinical setup further (23). The present study also revealed an association between CS and QoL. This finding supports the NEI-VFQ-25's validity for assessing visual function in individuals with DR.

According to the current study, general health was the most significantly affected by DR, followed by general vision and mental health. Pereira et al. (20) also reported the same findings in their study. Hence, the mere existence of DR in patients with diabetes significantly influences their overall health perception. The decrease in the overall vision rating is attributed to the intensity of DR. The fact that people with diabetes had DR influenced how they thought about their well-being. The mental health domain reflects concern, dissatisfaction, lack of control over events, and worry about possible stigma associated with vision.

Ocular pain had the highest mean value in the present study, which is consistent with previous research findings (8,20). Pereira et al. (20) reported that the driving subscale had the lowest average score; in the present study, a higher score in the driving subscale was obtained. The driving subscale was incorrectly estimated because of a low response rate; most individuals use public transportation (20).

There is not enough long-term follow-up in this study to track the development of DR and how it affects QoL over time. To fully comprehend the long-term effects of DR severity and changes in visual function on QoL, longitudinal research is required. Color vision defects may affect the CS. The current study did not assess the relationship between CS and the NEI-VFQ-25 score after excluding patients who had color-vision impairments, which could have affected the findings. Thorough ophthalmological examinations are required to eliminate these potential influences.

Conclusion

Patients with DR had considerably worse QoL. The general vision, general health, and mental health subscales scored the lowest. The NEI-VFQ-25 score was significantly associated with age; with increasing age, the score decreased. Visual function parameters, including DVA, NVA, and CS, were significantly associated with the NEI-VFQ-25 score. Poorer the visual function, poorer the NEI-VFQ-25 score.

Ethics

Ethics Committee Approval: The study followed the Declaration of Helsinki, and the Institutional Review Board and Ethics Committee of Dr. D. Y. Patil Vidyapeeth provided ethical approval (re-reg. No. ECR/361/Inst/MH/2013/RR-16, date: 27.11.2019) for the study.

Informed Consent: Consent form was filled out by all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.P., S.K., S.B., Concept: R.P., S.K., S.B., Design: R.P., S.B., Data Collection or Processing: R.P., S.B., Analysis or Interpretation: R.P., S.K., Literature Search: R.P., S.K., S.B., Writing: R.P., S.K., S.B.

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Juvenile osteochondral lesions of the talus: need for surgery and surgical treatment results

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Keywords: Juvenile, osteochondral lesion, talus, ankle, treatment

ABSTRACT

Aims: Juvenile osteochondral lesions of the talus (JOLTs) are complex lesions affecting the articular cartilage and subchondral bone of the talus. This study aimed to assess the need for surgical intervention following conservative management of JOLTs and to evaluate the early outcomes after surgery.

Methods: This retrospective study identified patients aged 18 years or younger who were surgically treated for JOLTs at our institution from 2018 to 2021. The surgical treatment indication was conservative treatment failure. Patients were followed up for 2 years using the visual analog scale (VAS) and American Orthopedic Foot and Ankle Society (AOFAS) score.

Results: The study included 12 patients with a median age of 15 (10-17) years. All lesions were stage 2-3 at initial presentation. Conservative treatment failed in 8 of 12 patients (67%), and these patients underwent surgical treatment. The median pre-operative and follow-up AOFAS scores were 39.5 (21-75) and 88 (51-100), respectively. The median pre-operative and follow-up VAS scores were 8 (5-9) and 2 (0-9), respectively.

Conclusions: The success rate of conservative treatment of JOLTs was lower than expected. This study showed early success of surgical treatment of JOLTs.

Introduction

Osteochondral lesions of the talus (OLTs) are complex injuries involving the articular cartilage and subchondral bone of the talus, often associated with persistent ankle pain and disability (1). OLTs primarily affect individuals between the ages of 10 and 40 years, with a peak incidence during the second decade of life (1). The reported incidence of OLTs ranges from 0.9-6.5% (2,3). These lesions develop before the closure of the growth plates and are referred to as juvenile osteochondral lesions of the talus (JOLTs). Although several theories regarding the etiology of OLTs exist, none have been universally accepted. OLTs often occur following acute ankle sprain or chronic ankle instability but may also be idiopathic (4-6).

The limited literature on OLTs has led to the application of adult OLT treatment protocols in pediatric cases. Although no standardized conservative treatment guidelines exist, conservative management is typically the first-line approach for JOLTs (7,8). The traditional conservative protocol includes immobilization and non-weight bearing, with or without non-steroidal anti-inflammatory drugs, followed by progressive

weight-bearing exercises to restore flexibility, strength, and balance. Previous studies have suggested that osteochondral lesions heal more effectively in younger patients due to open growth plates (9). However, recent studies have challenged this view, reporting high failure rates with conservative treatment (10,11).

This study aimed to assess the need for surgical intervention following conservative management of OLTs in children and to evaluate the early outcomes of surgical treatment in pediatric patients.

Methods

Study design and patient selection

This study included patients younger than 18 years at the time of the JOLTs diagnosis and at least 1 year of follow-up data. The exclusion criteria were closed growth plates and incomplete data. The Ethics Committee of Marmara University Faculty of Medicine approved the study protocol (protocol code: 09.2021.662, date: 02.07.2021). This study followed the principles outlined in the Declaration of Helsinki for research involving human subjects.

Data collection

Demographic (age, gender, height and weight), clinical (history of trauma, onset of symptoms, treatment initiation and method) and radiological data were collected from the hospital records.

The Berndt-Harty classification was used to grade lesions on plain radiographs (12). Lesion size and localization were evaluated using magnetic resonance imaging. All patients initially underwent conservative treatment for at least 6 months (Table 1). This protocol included immobilization and non-weight-bearing for 6 weeks, followed by gradual weight-bearing, physiotherapy, joint mobilization, and exercises to improve flexibility and strength. Additional treatments included personalized insoles, invasive ultrasound, and activity modification. Patients refrained from sports until symptoms resolved.

Patients unresponsive to conservative treatment underwent arthroscopically assisted surgery performed by the same surgeon. Standard two-port ankle arthroscopy with the patient in the supine position was performed to assess the lesion's size and stability.

Post-operatively, the two patients who underwent malleolar osteotomy were fitted with a short leg splint, and mobilization was allowed with crutches, avoiding weight-bearing on the operated foot. After approximately 1 week, the splint was removed, and a supervised exercises program was initiated for progressive joint mobility. No splint was applied for patients requiring only arthroscopic treatment. However, weight-bearing was restricted for 4-6 weeks, depending on the lesion size and the patient's body mass index. Six weeks post-operatively, gradual weight-bearing with crutches was permitted. Once full weight-bearing was achieved, progressive functional strengthening and activity-specific protocols were initiated. Typically, patients resume physical activities approximately 6 months after surgery.

The patients were followed clinically and radiographically for 2 years. Clinical follow-up included assessments using the visual analog scale (VAS) and American Orthopedic Foot and Ankle Society (AOFAS) scores.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, New York). Descriptive statistics included number, percentage, median, and minimum and maximum values. The normality of VAS and AOFAS outcomes was tested using the Shapiro-Wilk test, which revealed non-normal distributions. The Mann-Whitney U test was used for between-group comparisons. A p value <0.05 was considered statistically significant.

Results

Descriptive statistics

The study included 12 patients (4 men and 8 women). The median age at diagnosis was 15 (10-17) years. All patients presented with stage 2-3 lesions, and no stage 4 lesions were observed. Table 1 shows the descriptive data. Conservative treatment was unsuccessful in 8 of 12 patients (67%) who required surgical intervention. In addition, nine patients (75%) had a history of trauma.

Arthroscopic shavers and microfracture techniques were used in six patients to excise damaged cartilage and stimulate the subchondral bone. In two patients with intact but unstable lesions, medial malleolar osteotomies were performed with grafting and bioabsorbable screw fixation (Table 2).

The median baseline AOFAS score of patients treated conservatively was 31.5 (11-75), which improved to 39.5 (17-100) at the 2-year follow-up (p=0.687). The median baseline VAS score of these patients was 6.5 (5-9), which decreased slightly to 6 (0-9) at the final follow-up (p=0.496).

Among the surgically treated patients, the median pre-operative AOFAS score was 39.5 (21-75), which improved significantly to 88 (51-100) at the 2-year follow-up (p=0.0036). Similarly, the median pre-operative VAS score was 8 (5-9), which improved to 2 (0-9) at the final follow-up (p=0.011). Of the eight patients who underwent surgery, seven (87.5%) achieved a successful outcome. No minor or major complications were reported, and no reoperations were performed. Although reoperation was recommended for the patient (12.5%), the patient declined.

Table 1. Demographic data and outcomes of patients treated conservatively

Case	Sex	Age	BMI	Side	Trauma history	AOFAS baseline/lost control	VAS baseline/last evaluation
1	F	12	18.8	R	+	21/100	8/0
2	F	15	18.6	R	+	74/87	6/3
3	M	10	21.2	L	-	14/17	7/6
4	F	15	27.2	L	+	11/19	9/5
5	F	14	22.5	R	+	25/25	6/6
6	F	14	25.4	R	+	32/25	6/8
7	F	15	36.7	R	+	65/58	6/6
8	M	17	30.1	L	+	24/21	7/9
9	F	17	24.5	R	+	75/75	5/5
10	M	16	21.6	R	+	57/58	9/9
11	F	13	27.1	R	-	67/48	6/8
12	M	16	26.6	L	-	31/31	7/8

BMI: Body mass index, AOFAS: American Orthopedic Foot and Ankle Society scale, VAS: Visual analog scale, F: Female, M: Male, R: Right, L: Left

Table 2. Demographic data and outcomes of patients undergoing surgical treatment

Case	Sex	Age	BMI	Side	Trauma history	AOFAS baseline/conservative treatment/last treatment	VAS baseline/ conservative treatment/ last treatment	Surgical treatment
1	F	14	22.5	R	+	25/25/88	6/6/2	Arthroscopic debridement and microfracture
2	F	14	25.4	R	+	32/25/88	6/8/2	Arthroscopic debridement and microfracture
3	F	15	36.7	R	+	65/58/88	6/6/2	Arthroscopic debridement and microfracture
4	M	17	30.1	L	+	24/21/100	7/9/0	Arthroscopic debridement and microfracture
5	F	17	24.5	R	+	75/75/51	5/5/9	Arthroscopic debridement and microfracture
6	M	16	21.6	R	+	57/58/100	9/9/0	Arthroscopic debridement, medial malleolar osteotomy, and the osteochondral fragment fixed with a bioabsorbable screw
7	F	13	27.1	R	-	67/48/88	6/8/1	Arthroscopic debridement and microfracture
8	M	16	26.6	L	-	31/31/68	7/8/4	Arthroscopic debridement, medial malleolar osteotomy, and the osteochondral fragment were fixed with a bioabsorbable screw (this patient had a three-year history of pain and had received 6 months of conservative therapy before surgery).

BMI: Body mass index, AOFAS: American Orthopedic Foot and Ankle Society scale, VAS: Visual analog scale, F: Female, M: Male, R: Right, L: Left

Discussion

OLTs are more common in adolescents than in adults or children. However, there is limited knowledge regarding optimal treatment protocols and outcomes of JOLTs in pediatric patients (13). The primary finding of this study was the success rate of conservative treatment in JOLTs, which was lower than expected (33.3%), requiring surgical intervention in most patients.

Despite previous studies suggesting that JOLTs have higher spontaneous healing potential and lower rates of joint degeneration than adult cases (7,14,15), the present findings highlight the limited success of conservative treatment, particularly for advanced lesions (16). Previous studies have reported varied outcomes with conservative treatment (14,15). Lam and Siow (14) achieved 100% good to excellent outcomes in six patients with JOLTs treated non-surgically, whereas Higuera et al. (15) observed favorable results in 68% of cases treated conservatively. However, Heyse et al. (10) reported a 39% success rate in conservative treatment. The authors noted that non-surgical treatment led to poor outcomes in patients with stage 3 OLT lesions and older children. Similarly, Kim et al. (11) achieved successful results in 37 (67%) of 55 JOLTs managed conservatively. However, only six (16.2%) out of 22 patients with stage 3 lesions responded favorably, with success rates decreasing in older patients. In line with these findings, our study observed successful outcomes in only four (33.3%) of the 12 patients who underwent conservative treatment for at least 6 months. These findings emphasize the need for close follow up of pediatric OLT patients treated conservatively.

Surgical treatment is the next step when conservative management fails or when there are unstable stage 4 lesions (7,8,15,17). A variety of arthroscopic and open-surgical methods are available for the treatment of JOLT. The choice of surgical procedure depends on the surgeon's experience and the lesion's location, depth, and size (18,19). Common surgical interventions include bone marrow stimulation techniques (drilling and microfracture), fixation of displaced subchondral bone fragments, and tissue transplantation (e.g., mosaicplasty, osteochondral allograft, or autologous chondrocyte implantation). Carlson et al. (20) performed arthroscopic bone marrow stimulation in 22 patients with JOLTs and described a surgical algorithm based on arthroscopic evaluation. The size and stability of the lesions were assessed using direct visualization and arthroscopic probes. In the cases of stable lesions, translator drilling was performed under fluoroscopic guidance to preserve the cartilage layer. If the lesion was unstable, excision followed by translator drilling and microfracture was performed to promote fibrocartilage formation. The authors report satisfactory clinical outcomes with minimal ankle osteoarthritis progression at a minimum follow-up duration of 2 years. Pallamar et al. (21) reported on 30 patients (32 joints) treated for osteochondritis dissecans of the immature talus over a mean follow-up period of 6 years. Retrograde drilling was performed for stable lesions; fixation was used for unstable lesions with intact cartilage. In cases of cartilage damage, microfracture or osteochondral allografts were used, depending on the lesion size. The study found that stable OLTs treated with drilling resulted in better clinical and radiographic outcomes and lower joint degeneration rates in fixation and reconstruction procedures for unstable lesions.

Positive short-and long-term outcomes have been reported following microfracture treatment (22-24). However, some researchers caution against the potential for fibrocartilage formed through microfracture to lead to osteoarthrosis over time (16,25). Ferkel et al. (25) reported worsened clinical scores in six patients (35%) 5 years after treatment, although these findings pertain to adults. Long-term outcomes of pediatric surgical treatment remain unclear. Körner et al. (26) reported a reoperation rate of 25.9% in 27 patients after a mean follow-up of 31 months and attributed this high rate to the closure of the distal tibia and fibular physis. However, younger age and an open tibial physis are associated with better healing potential (27). Perumal et al. (7) observed clinical improvement in all patients (100%) and radiographic improvement in 11 patients (85%) at a 1-year follow-up of 13 patients (1 of whom underwent open arthrotomy and 12 of whom underwent arthroscopic retrograde drilling. Minokawa et al. (28) also reported significant clinical improvement in six patients (eight ankles) who underwent retrograde drilling. In our study, six patients with cartilage lesions underwent arthroscopic debridement and microfracture, whereas two patients with intact cartilage had their osteochondral fragments fixed using bioabsorbable screws. The VAS and AOFAS scores improved in seven patients who underwent arthroscopic surgery (success rate: 87.5%). One patient experienced deteriorating outcomes despite standard arthroscopic cartilage debridement, microfracture, and post-operative rehabilitation. During follow-up, the patient experinced progressive worsening of pain and functional outcomes but rejected reoperation. These findings and recent studies in the literatıre suggest that arthroscopic surgery is highly effective in the early management of JOLT, although long-term outcomes remain to be determined.

The most common cause of OLTs is ankle trauma. A recent systematic review found that osteochondral lesions occurred in 45% of ankle fractures, with nearly half involving the talus. Ferkel et al. (25) reported that 37 (74%) of 50 patients with OLTs had a history of trauma. Kramer et al. (29) found that 38 (35%) of 109 OLT cases in patients aged ≤18 years had a traumatic origin. Similarly, Letts et al. (8) identified trauma in 19 (79%) of 24 pediatric patients with OLTs. In our study, nine out of 12 patients (75%) had a documented history of trauma, supporting the widely accepted notion that ankle osteochondritis dissecans is primarily trauma-induced.

This study has several limitations. The retrospective design of the study and the small sample size hinder the generalizability

of the findings, as talus osteochondral lesions are less common in adolescents than in adults. Additionally, a follow-up period of 2 years is insufficient to assess medium to long-term outcomes or to determine the optimal surgical procedure. Finally, a single surgeon proformed because the operations the results might require external validity.

Conclusion

This study demonstrated that conservative treatment of JOLTs achieved a lower success rate than anticipated. Although conservative management is the initial treatment approach, close monitoring is necessary because the likelihood of success is limited. When conservative treatment fails, surgical intervention is required. This study highlighted favorable early outcomes of arthroscopic surgery for JOLTs, although further research is needed to evaluate long-term outcomes.

Ethics

Ethics Committee Approval: The Ethics Committee of Marmara University Faculty of Medicine (protocol code: 09.2021.662, date: 02.07.2021) approved the study protocol.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.Ç., Concept: O.Ç., K.S.I., Design: O.Ç., K.S.I., Data Collection or Processing: O.Ç., K.S.I., Analysis or Interpretation: O.Ç., Literature Search: O.Ç., Writing: O.Ç., K.S.I.

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Comparison of the effectiveness of vestibular rehabilitation on disability and balance in patients with chronic unilateral and bilateral vestibular hypofunction

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ABSTRACT

Aims: This study evaluated the effectiveness of supervised vestibular rehabilitation on disability and balance by comparing patients with chronic unilateral vestibular hypofunction (UVH) and bilateral vestibular hypofunction (BVH).

Methods: This retrospective study included patients aged 18-65 years diagnosed with chronic vestibular hypofunction and underwent a supervised vestibular rehabilitation program. We excluded patients with a history of central nervous system disease, central vestibular pathology, systemic disease, and neck disorders that may cause dizziness and balance disorders, psychiatric disease, cognitive disorder, visual dysfunction, and vestibular disorder with a fluctuating course. The outcome measures were the differences between the Dizziness Handicap Inventory (DHI) for disability and the Berg Balance Scale (BBS) for balance-fall risk scores before and after the rehabilitation program in patients with UVH vs. BVH.

Results: The study included 24 UVH [age, mean±standard deviation (SD): 50.0±12.3 years, women: 75%] and 14 BVH patients (age, mean±SD age: 53.8±12.1 years, women: 64.3%). Baseline demographic characteristics, DHI and BBS scores were similar in the two groups. We observed improvements in DHI (UVH: 67.25±10.43 vs. 51.50±17.03, $p<0.05$; BVH: 63.00±21.12 vs. 44.57±22.90, $p<0.05$) and BBS [UVH: 49 (43.0-51.75) vs. 50.5 (44.75-52.75), $p<0.05$; BVH: 42.07±9.35 vs. 47.86±6.65, $p<0.05$] scores in the two groups after the rehabilitation program. On the other hand, there were no between-group differences in the changes in DHI (UVH: -15.75±13.28 vs. BVH: -18.43±15.79, $p>0.05$) and BBS [UVH: 2 (0-5) vs. BVH: 4 (1.0-9.25), $p>0.05$] scores.

Conclusions: This study found that a supervised 4-week vestibular rehabilitation program was similarly effective in chronic UVH and BVH in disability and balance improvement.

Introduction

Vestibular hypofunction is characterized by impaired vestibular functions due to partial or complete involvement of the peripheral or, rarely, the central vestibular system (1,2). Patients with vestibular hypofunction complain of symptoms such as dizziness, visual and gaze disorders, balance disorders, unsteadiness during walking and standing, and oscillopsia, depending on the type of involvement (unilateral or bilateral) (3,4). Chronic vestibular asymmetry manifests with symptoms and findings such as head movement-induced symptoms, gait instability, oscillopsia, spatial disorientation, and impaired navigation in patients with unilateral vestibular hypofunction (UVH) (1). In contrast, imbalance and oscillopsia with head movement are among the most common symptoms in patients with chronic bilateral vestibular hypofunction (BVH)

(1). Oscillopsia, postural instability, and falls are more frequent among patients with BVH (5).

Vestibular hypofunction negatively affects patients' quality of life and activities of daily living (1). Falls are a serious complication in patients with vestibular hypofunction (6). Considering the consequences on quality of life and overall disease burden, proper diagnostic and therapeutic measures may reduce the adverse outcomes of vestibular hypofunction (7).

Rehabilitation practices have long been used in patients with vestibular hypofunction, with increasing evidence of their effectiveness (5). Exercise programs to improve gaze stability, developed on the concept of vestibulo-ocular reflex (VOR) adaptation and substitution, habituation exercises that aim to reduce symptoms by repeatedly exposing the patient to provocative stimuli, exercises and practices to improve balance and gait quality, and their combinations, are recommended on a person basis (1,5). A recently published clinical guideline strongly recommends vestibular physical therapy in patients with chronic UVH and those with chronic BVH, along with supervised vestibular rehabilitation for patients with peripheral vestibular hypofunction (1).

Although vestibular rehabilitation is recommended and beneficial in patients with both UVH and BVH, most studies have shown that patients with UVH benefit more from vestibular rehabilitation (5).

However, only a limited number of studies have evaluated the effectiveness of supervised vestibular rehabilitation on disability and balance in patients with chronic vestibular hypofunction and have compared the rehabilitation effectiveness in patients with UVH and BVH (1).

We hypothesized that vestibular rehabilitation would benefit patients with chronic vestibular hypofunction and that patients with UVH would benefit more from vestibular rehabilitation than patients with BVH. Therefore, the present study aimed to evaluate the effectiveness of a supervised vestibular rehabilitation program on disability and balance in patients with chronic UVH vs. chronic BVH.

Methods

Study design and participants

This retrospective study included patients with chronic vestibular hypofunction who received a vestibular rehabilitation program at a tertiary center between November 2022 and November 2023. Demographic and clinical data, including age, gender, body mass index, and disease duration, were recorded using the medical records.

The inclusion criteria were age between 18 and 65 years and confirmed diagnosis of chronic vestibular hypofunction according to the video head impulse test [VOR gain of less than 0.7 for the semicircular canal (1)] by the otorhinolaryngology and neurology departments. The exclusion criteria were a history of central nervous system disease, central vestibular pathology, systemic disease that may cause dizziness and balance disorders, or neck disorder that may cause dizziness and balance disorders, being diagnosed with a psychiatric disease, cognitive impairment, impairment in visual functions, or vestibular disorder with a fluctuating course (e.g., Meniere's disease). We compared the results obtained in patients with UVH vs. BVH. The study protocol was approved by the Ethics Committee of Ankara Bilkent City Hospital (decision no: E2-23-5922, date: 27.12.2023). The study conforms to the principles of the Declaration of Helsinki.

Treatment protocol

The vestibular physical therapy program consisted of 12 sessions in 4 weeks. Sessions were planned thrice weekly, and each session lasted 45 minutes under the supervision of the same physiotherapist experienced in vestibular rehabilitation. All patients regularly participated in vestibular physical therapy sessions.

The vestibular physical therapy program included gaze stabilization exercises (e.g., eyes focus on a fixed target while the head moves-VORx1, eyes focus on a moving target while the head and target move in opposite directions-VORx2), habituation exercises, and balance and gait training (e.g., Romberg, tandem, single leg stance, walking with head turns, doing a secondary task while walking), based on the diagnosis, symptoms, and functional status. Therapy sessions consisted of gaze stabilization exercises for approximately 15-20 minutes, habituation exercises (if necessary) for approximately 10 minutes, static and dynamic balance, and gait training for approximately 15-20 minutes with a 5-minute rest period between different exercise types.

Clinical assessment

The outcome measures in the present study were the Dizziness Handicap Inventory (DHI) and Berg Balance Scale (BBS) scores, which were routine before and after a vestibular rehabilitation program (1).

Patients' self-perceived disability due to vestibular disease were evaluated using the DHI scores (8). The DHI is a 25-item test with three domains (functional, emotional, and physical). The scores vary between 0 and 100, with higher scores showing greater perceived handicap due to dizziness. The validity and reliability of the DHI in Turkish patients were performed (9), and the Cronbach alpha values of all sub-dimensions were 0.67 and 0.82.

The balance and fall risk were evaluated using the BBS scores (10). The BBS yields a score between 0 and 56 from 14 activities, with higher scores indicating better balance. The validity and reliability of the Turkish version of the BBS were performed (11), and the intra-class intraclass correlation

coefficient and inter-rater reliability were 0.98 and 0.97, respectively.

Outcome measures

The outcome measures were the differences between the DHI for disability and the BBS for balance-fall risk scores before and after the rehabilitation program in patients with UVH vs. BVH.

Statistical Analysis

Statistical analysis was performed using the SPSS for Mac version 20.0 software (SPSS Inc, Chicago, IL, USA). Descriptive data were expressed as mean±standard deviation (SD) and median (25-75%) values for continuous variables and numbers (%) for categorical variables. The normal distribution of data was assessed using the Shapiro-Wilk test. Intragroup comparisons before and after treatment were performed using the Wilcoxon signed-rank test for non-normally distributed variables and the paired samples t-test for normally distributed variables. Inter-group comparisons were performed using the Mann-Whitney U test for non-normally distributed continuous variables, the independent samples t-test for normally distributed continuous variables, and the Chi-square test for categorical variables. The results were considered statistically significant for $p<0.05$.

Results

Demographic and clinical characteristics

The study included 24 patients with UVH [age, mean±SD: 50.0±12.3 years, 75% women] and 14 patients diagnosed with BVH (age, mean±SD: 53.8±12.1 years, 64.3% women). Baseline demographic characteristics, DHI scores, and BBS scores were similar between the two groups (Table 1).

Intragroup comparisons

There were significant improvements in post-treatment DHI and BBS scores ($p<0.05$) (Table 2) in both groups.

Comparison of the inter-groups

We observed no significant difference between the two groups in terms of changes in DHI and BBS scores ($p>0.05$) (Table 3).

Table 1. Clinical and demographic data of the groups at baseline

	UVH (n=24)	BVH (n=14)	p
Age (years)	50.0±12.3[a] 51.5 (42.5-60.75)[b]	53.8±12.1[a] 58 (49-61.25)[b]	0.243
Sex, n (%) **Women** **Men**	 18 (75.0) 6 (25.0)	 9 (64.3) 5 (35.7)	0.488
BMI (kg/m²)	27.26±7.14[a] 25.16 (22.71-30)[b]	27.28±5.56[a] 26.76 (23.94-29.35)[b]	0.515
Disease duration (month)	11.08±6.34[a] 9 (6-14.25)[b]	12.29±7.47[a] 12 (5.75-19.5)[b]	0.806
DHI	67.25±10.43[a] 67 (60-76)[b]	63.00±21.12[a] 73 (41.5-79)[b]	0.411
BBS	46.08±7.29[a] 49 (43.0-51.75)[b]	42.07±9.35[a] 42.5 (35.5-50.25)[b]	0.192

UVH: Unilateral vestibular hypofunction, BVH: Bilateral vestibular hypofunction, BMI: Body mass index, DHI: Dizziness Handicap Inventory, BBS: Berg Balance Scale
[a]: Mean±standard deviation, [b]: Median (25-75%)

Table 2. Pre-treatment and post-treatment DHI and BBS scores

	Pre-treatment	Post-treatment	p
DHI			
UVH (n=24)	67.25±10.43[a] 67 (60-76)[b]	51.50±17.03[a] 54 (36.5-66)[b]	<0.001*
BVH (n=14)	63.00±21.12[a] 73 (41.5-79)[b]	44.57±22.90[a] 51 (25-66.5)[b]	0.001*
BBS			
UVH (n=24)	46.08±7.29[a] 49 (43-51.75)[b]	49.21±4.62[a] 50.5 (44.75-52.75)[b]	0.001*
BVH (n=14)	42.07±9.35[a] 42.5 (35.5-50.25)[b]	47.86±6.65[a] 49 (45-53.25)[b]	0.001*

UVH: Unilateral vestibular hypofunction, BVH: Bilateral vestibular hypofunction, DHI: Dizziness Handicap Inventory, BBS: Berg Balance Scale
*: Significant difference, [a]: Mean±standard deviation, [b]: Median (25-75%)

Table 3. Comparison of changes in DHI and BBS scores between groups

	UVH (n=24)	BVH (n=14)	p
DHI	-15.75±13.28[a] -16 (-21.5, -8)[b]	-18.43±15.79[a] -19 (-23, -9)[b]	0.58
BBS	3.13±4.31[a] 2 (0, 5)[b]	5.79±5.09[a] 4 (1.0, 9.25)[b]	0.08

UVH: Unilateral vestibular hypofunction, BVH: Bilateral vestibular hypofunction, DHI: Dizziness Handicap Inventory, BBS: Berg Balance Scale
[a]: Mean±standard deviation, [b]: Median (25-75%)

Discussion

The results of the present study showed that supervised 4-week vestibular rehabilitation had similar positive effects on disability and balance in patients with both chronic UVH and chronic BVH.

There are several studies on the efficacy of vestibular rehabilitation in patients with chronic UVH. A randomized controlled study showed that a customized vestibular rehabilitation postively affected disability and balance in patients with chronic UVH (12). In the present study, similar to the abovementioned study, vestibular rehabilitation was effective in improving disability and balance in patients with chronic UVH.

A recently published guideline strongly recommends supervised vestibular physical therapy for individuals with peripheral vestibular hypofunction (1). Another study reported that customized supervised rehabilitation was superior to a home-based exercise program in patients with chronic UVH (13). A retrospective study that evaluated the effectiveness of vestibular rehabilitation on walking ability and balance in patients with chronic UVH reported that multiple interventions by a physical therapist in a rehabilitation program were more beneficial than a single intervention (14). A retrospective study reported that a closely monitored vestibular rehabilitation program was superior to home exercises in patients with vestibular hypofunction (15). In the present study, in patients with chronic vestibular hypofunction, a physiotherapist-supervised rehabilitation program improved balance and disability within 4 weeks. Compared with studies in the literature, a relatively shorter time to reach effectiveness in the present study may be explained by the increased frequency of sessions and the supervision of a physiotherapist. These results indicate that vestibular rehabilitation implemented under the supervision of a physiotherapist can augment effectiveness by improving treatment compliance and motivation. However, comprehensive studies comparing the effectiveness of exercises performed under the supervision of a physiotherapist, home exercises, and combined exercises are needed to support this interpretation.

Vestibular rehabilitation programs are also suitable for patients with peripheral BVH (1). On the other hand, patients with UVH benefit more from vestibular rehabilitation than those with BVH (5,16).

A few studies evaluated the effectiveness of vestibular rehabilitation programs in patients with chronic BVH and UVH. Maslovara et al. (17) reported that a home exercise program improved functionality and confidence in activities in chronic UVH and BVH, being more favorable in chronic UVH. Karapolat et al. (18) reported that a weekly vestibular rehabilitation program for 8 weeks in a vestibular rehabilitation unit and a home exercise program similarly improved disability and balance in patients with unilateral and bilateral vestibular dysfunction. The present study's findings are in agreement with the study by Karapolat et al. (18). Similar positive improvements in disability and balance were observed with 4-week supervised vestibular rehabilitation in both groups, possibly because the rehabilitation program was personally tailored and supervised 3 days a week. The results suggest that increasing the frequency of the supervised vestibular rehabilitation program and supervision of a physiotherapist can yield more positive results in a shorter period.

The retrospective study design, lack of long-term follow-up data, and relatively small sample size are some of the limitations of the present study. On the other hand, the strength of the present study is that it is one of the few studies that comparatively evaluate the effectiveness of supervised vestibular rehabilitation in patients with chronic UVH and BVH.

Conclusion

In conclusion, the results of the present study indicate that the supervised 4-week vestibular rehabilitation program is effective in patients with both chronic UVH and those with chronic BVH and has similar positive effects on disability and balance. Further randomized controlled studies with long-term follow-up in larger patient groups are needed to determine the optimal rehabilitation program for patients with chronic vestibular hypofunction.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Ankara Bilkent City Hospital (decision no: E2-23-5922, date: 27.12.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: Ö.K., B.B.B., C.Ç., Design: Ö.K., B.B.B., C.Ç., Data Collection or Processing: Ö.K., B.B.B., C.Ç., B.A., Analysis or Interpretation: Ö.K., B.B.B., B.A., Literature Search: Ö.K., B.B.B., Writing: Ö.K., B.B.B., C.Ç., B.A.

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Virgin coconut oil reverses atrazine and diabetes-induced lipid profile derangements in male Wistar rats

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ABSTRACT

Aims: We assessed the ameliorative effect of virgin coconut oil (VCO) following atrazine (ATZ) and diabetes-induced lipid profile derangements in rats.

Methods: Male Wistar rats (n=35) in the test group were divided into five groups (n=7): Groups 1, 2, and 3 received 10 mL/kg distilled water, 10 mL/kg VCO, and 123 mg/kg ATZ, respectively. Group 4 consisted of the untreated diabetic animals and Group 5 consisted of diabetic animals treated with 10 mL/kg of VCO for 2 weeks. The recovery group rats (n=35) were divided into five groups (n=7): Groups 1 and 2 received 10 mL/kg of distilled water and VCO, respectively. Groups 3, 4, and 5 received 123 mg/kg ATZ for 2 weeks. After 2 weeks, Group 1, Group 2, and Group 3 continued the initial treatment, whereas Group 4 and Group 5 received 10 mL/kg of VCO and 10 mL/kg of distilled water, respectively. Blood samples were collected after 2 weeks.

Results: From Group 1 to Group 5 in the test group, differences were observed in high-density lipoprotein cholesterol (HDL-C) levels (56.20±0.86 mg/dL, 66.00±0.71 mg/dL, 42.60±0.93 mg/dL, 33.80±1.16 mg/dL, and 52.60±1.17 mg/dL, respectively, $p<0.05$) and low-density lipoprotein cholesterol (LDL-C) levels (39.20±1.16 mg/dL, 44.00±1.52 mg/dL, 69.80±0.37 mg/dL, 75.20±0.86 mg/dL, and 61.60±1.29 mg/dL, respectively, $p<0.05$). In the recovery group, HDL-C levels were higher in Group 4 than in Group 3 (40.40±0.51 mg/dL vs. 32.20±0.80 mg/dL, $p<0.001$), LDL-C levels were lower (45.40±0.87 mg/dL vs. 66.60±1.08 mg/dL, $p<0.001$).

Conclusions: ATZ and diabetes mellitus induction reduced HDL and increased LDL levels, which were reversed by VCO administration.

Introduction

Environmental pollutants are taken into the body by inhalation, swallowing, or skin contact (1). They have devastating effects on human health, causing diseases like diabetes mellitus (DM) (2). The high prevalence of DM is of great concern not only for human health but also for its social and economic implications and burden on national development. Genetic predisposition, overnutrition, and physical inactivity play key roles in the etiology of DM. Nevertheless, neither these well-recognized risk factors nor genetic predispositions can explain the rapid rise in the prevalence of DM. Increased manufacturing rate of pollutants coincides with the prevalence of diabetes (3),

constituting new risk factors for this multi-factorial disease. Thus, understanding how environmental risk factors influence the development and progression of DM can lead to further improvements in public health. Atrazine (ATZ) is one of the most widely used herbicides that was reported to be above the limits in water bodies (4). The Environment Protection Agency classifies ATZ as class 3 toxicity on a scale of 1-4 (scale 1 as the most toxic). ATZ is an endocrine-disrupting pesticide by the US Environmental Protection Agency (5). The primary target of ATZ in humans and animals is the endocrine (hormonal) system (6), which could ultimately disrupt the regulatory and metabolic activities of the body.

Virgin coconut oil (VCO) is an unprocessed oil obtained from the mature and fresh kernel of the coconut fruit by mechanical or natural means, with or without mild heat (7). VCO is rich in lauric acid, an essential fatty acid that transforms into monolaurin acid which is an anti-viral and anti-parasite (8). VCO shows hypoglycemic actions by enhancing glucose, insulin, and estrogen metabolism (9) and by ameliorating oxidative stress induced in type 1 DM-induced rats (10). VCO also ameliorates low-density lipoprotein (LDL) in diabetes-induced male rats (11) and restores ATZ-deranged glucose transporter-4 receptors in male Wistar rats (12).

Because plasma lipid level follow-up and proper diet are paramount in preventing the prevalence of certain risk factors (e.g., obesity) associated with DM (11), VCO's effects on high-density lipoprotein may be used in the management and prevention of diabetes and possibly ATZ toxicity. Thus, this study aimed to test the effects of VCO administration following ATZ and diabetes-induced lipid profile derangements in rats.

Methods

Experimental design and groups

Adult male Wistar rats (180-200 g) maintained at the animal house unit of the Department of Physiology, Faculty of Basic Medical Sciences, University of Calabar were kept in a well-ventilated space to acclimatize, fed with rat chow, and allowed water "ad libitum" for two weeks. After the acclimatization period, the animals were weighed, and fasting blood glucose levels were measured before commencing the experimental treatment.

The rats were randomly divided into two main experimental groups (the test and recovery groups), with 35 rats in each group. The experiments lasted two weeks in the test group and four weeks in the recovery group.

The rats in the test group were randomly divided into five subgroups of 7 animals (n=7) and fed oral gavage. Group 1 served as the healthy controls and received 10 mL/kg distilled water. Group 2 received 10 mL/kg VCO, and Group 3 received 123 mg/kg (20% of lethal dose) ATZ. Group 4 consisted of untreated diabetic animals and Group 5 consisted of diabetic animals treated with 10 mL/kg of VCO. The animals were examined after 2 weeks, and blood samples were collected (Table 1).

During the two weeks, 35 rats in the recovery group were also divided into five subgroups of 7 rats (n=7) and received the following treatments: Group 1 served as healthy controls and received 10 mL/kg body weight of distilled water, Group 2 received 10 mL/kg of VCO, and Group 3, Group 4, and Group 5 received 123 mg/kg of ATZ. After 2 weeks, the animals were re-treated for recovery and were treated as follows: Group 1 continued the initial treatment, receiving 10 mL/kg body weight of distilled water; Group 2 received 10 mL/kg of VCO; Group 3 received 123 mg/kg of ATZ; Group 4 received 10 mL/kg of VCO; and Group 5 received 10 mL/kg of distilled water. After two weeks of the recovery treatment period, the animals were sacrificed and blood samples were collected (Table 1).

Experimental procedures

Induction of diabetes mellitus

Diabetes was induced intraperitoneally using 150 mg/kg body weight of alloxan monohydrate (13). Polyuria and glucosuria were observed for approximately 48 hours. After 72

Table 1. Experimental groups and treatments

Groups	Treatments		
	Test group (n=35)	Recovery group (n=35) (4 weeks)	
	2 weeks	1st 2 weeks	2nd 2 weeks
Group 1* (n=7)	10 mL/kg of distilled water	10 mL/kg of distilled water	10 mL/kg of distilled water
Group 2* (n=7)	10 mL/kg of virgin coconut oil	10 mL/kg of virgin coconut oil	10 mL/kg of virgin coconut oil
Group 3* (n=7)	123 mg/kg (20% of lethal dose) of atrazine	123 mg/kg (20% of lethal dose) of atrazine	123 mg/kg (20% of lethal dose) of Atrazine
Group 4** (n=7)	10 mL/kg of distilled water	123 mg/kg (20% of lethal dose) of atrazine	10 mL/kg of virgin coconut oil
Group 5** (n=7)	10 mL/kg of virgin coconut oil	123 mg/kg (20% of lethal dose) of atrazine	10 mL/kg of distilled water

*Normal rat, ** Diabetic rat

hours, diabetes was confirmed with a blood glucose level of 180-200 mg/dL and above using a glucometer (ACCU-CHECK Active) and ACCU-CHECK compatible glucose test strips.

Virgin coconut oil preparation

VCO was extracted from mature dried coconut using a modified wet extraction method (14). The solid endosperm of mature coconut was crushed into a thick slurry. Approximately 500 mL of water was added to the slurry and squeezed through a fine sieve to obtain coconut milk. The resultant coconut milk was left for approximately 18 hours to facilitate the gravitational separation of the emulsion. Demulsification produced layers of an aqueous phase (water) at the bottom, an oil phase in the middle layer, and an emulsion phase (cream) on top. The cream on the top was removed, and the oil was scooped and warmed for about 5 minutes to remove moisture. The obtained oil was then filtered and stored at room temperature.

Median lethal dose

The toxicity of ATZ was assessed using Lorke's method (15), involving the administration of the chemical to the animals and observation for mortality within 24 hours, which was achieved as follows:

a. Twelve Swiss albino mice were fasted and weighed.
b. The animals were subgrouped into four groups for graded intraperitoneal doses of 1250 mg/kg (1.25 g/kg), 1000 mg/kg (1.00 g/kg), 750 mg/kg (0.75 g/kg), and 500 mg/kg (0.50 g/kg).
c. The administration was based on body weight, and the experimental mice were examined 24 hours after dosage administration.
d. There were physical signs of toxicity in the groups administered with doses of 1,250, 1,000, and 750 mg/kg, and mortality was recorded.
e. No physical signs of toxicity or mortality were recorded in animals administered a 500 mg/kg dose (Table 2).

Evaluation of the lipid profile

Measurement of high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and very low-density lipoprotein-cholesterol concentrations

We used a Cell Biolabs HDL-C and LDL-C/VLDL-C assay kit [United States (USA)] to measure the HDL-C, LDL-C, and VLDL-C levels (16).

Preparation of high-density lipoprotein cholesterol, low-density lipoprotein-cholesterol, and very low-density lipoprotein-cholesterol fractions

First, 200 µL of serum and 200 µL of precipitation reagent were added to a microcentrifuge tube and mixed well with cortexin. The mixture was incubated for 5-10 minutes at room temperature (20-25°C) for precipitation and centrifuged at 2000 x g (5000 rpm) for 20 min (the pellet should be visible). The supernatant (HDL-C fraction) was carefully transferred into a new tube, leaving the pellet (LDL-C/VLDL-C fraction). The pellet was resuspended and dissolved in 400 µL of phosphate-buffered saline and mixed well to ensure that the pellet (LDL-C/VLDL-C fraction) was completely dissolved before testing.

Assays for high-density lipoprotein cholesterol and low-density lipoprotein-cholesterol levels

First, 50 µL of the diluted cholesterol standard or sample was added to a 96-well microtiter plate. Then, 50 µL of the prepared cholesterol reaction reagent was added and mixed thoroughly. The wells were covered to protect them from light and incubated for 45 minutes at 37 ºC. The plate was immediately read with a fluorescence microplate reader equipped for excitation in the 530-570 nm range and emission in the 590-600 nm range.

Estimation of total cholesterol concentration

We used a Cell Biolabs total cholesterol (TC) assay kit (USA) to measure TC levels as described by Ghezzi et al. (16).

Assay procedure

First, 50 µL of the diluted cholesterol standard or sample was added to a 96-well microtiter plate. Then, 50 µL of the pre-pared cholesterol reaction reagent was added and mixed thoroughly. The plate was covered to protect it from light and incubated for 45 minutes at 37 ºC. The plate was immediately

Table 2. Dosages of lethal concentrations

Dose-1250 mg/kg		
Mice	**Body weight**	**Dosage**
T_1	25.60 g	0.64 mL
T_2	25.23 g	0.63 mL
T_3	26.04 g	0.66 mL
Dose-1000 mg/kg		
Mice	**Body weight**	**Dosage**
T_4	28.18 g	0.56 mL
T_5	27.63 g	0.55 mL
T_6	24.45 g	0.49 mL
Dose-750 mg/kg		
Mice	**Body weight**	**Dosage**
T_7	26.37 g	0.40 mL
T_8	27.53 g	0.41 mL
T_9	22.90 g	0.34 mL
Dose-500 mg/kg		
Mice	**Body weight**	**Dosage**
T_{10}	19.70 g	0.20 mL
T_{11}	21.40 g	0.21 mL
T_{12}	27.60 g	0.28 mL

read with a spectrophotometric microplate reader in the 540-570 nm range. The cholesterol concentration was calculated by comparing the sample absorbance values with the cholesterol standard curve. The study was approved by the Local Ethics Committee for Animal Experiments (decision no: 022PY30417, date: 27.06.2017).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY: USA, released 2011). The data were analyzed using the one-way analysis of variance followed by Tukey's post-hoc test and expressed as mean±standard error of mean. A p-value <0.05 was considered significant.

Results

High-density lipoprotein cholesterol levels in the test groups

There was a significant increase in the HDL-C levels in Group 2 compared with Group 1 (66.00±0.71 mg/dL vs. 56.20±0.86 mg/dL, p<0.001), and in Group 3 compared with Group 1 and Group 2 (42.60±0.93 mg/dL vs. 56.20±0.86 mg/dL, p<0.001 and 66.00±0.71 mg/dL, p<0.001, respectively). There was a reduction in HDL-C levels In Group 4, compared with Groups 1, 2, and 3 (33.80±1.16 mg/dL vs. 56.20±0.86 mg/dL, 66.00±0.71 mg/dL, and 42.60±0.93 mg/dL, p<0.001, respectively). HDL-C levels significantly increased in Group 5, compared with Group 3 and Group 4 (52.60±1.17 mg/dL vs. 42.60±0.93 mg/dL, and 33.80±1.16 mg/dL, p<0.001, respectively) (Table 3).

High-density lipoprotein cholesterol levels in the recovery group

HDL-C levels decreased significantly in Group 3 compared with Group 1 and Group 2 (32.20±0.80 mg/dL vs. 57.52±0.35 mg/dL, and 66.25±0.82 mg/dL, p<0.001, respectively). HDL-C levels increased in Group 4 compared with Group 3 (40.40±0.51 mg/dL vs. 32.20±0.80 mg/dL, p<0.001) but decreased when compared with Group 1 and Group 2 (40.40±0.51 mg/dL vs. 57.52±0.35 mg/dL and 66.25±0.82 mg/dL, p<0.001, respectively). There was no significant difference in the HDL-C levels between Group 5 and Group 3 (p=0.204), while it was significantly lower than in Group 1, Group 2, and Group 4 (p<0.001 for all) (Table 4).

Low-density lipoprotein-cholesterol levels in the test groups

The mean values for LDL-C levels were 39.20±1.16 mg/dL, 44.00±1.52 mg/dL, 69.80±0.37 mg/dL, 75.20±0.86 mg/dL and 61.60±1.29 mg/dL in Group 1, Group 2, Group 3, Group 4, and Group 5, respectively. There was a significant increase in LDL-C levels in Group 2 compared with Group 1 (p=0.044). There was an increase in LDL-C levels in Group 3 compared with Group 1 and Group 2 (p<0.001, for both). LDL-C level was also higher in Group 4 than in Group 1 (p<0.001), Group 2 (p<0.001), and Group 3 (p=0.02). LDL-C level decreased significantly in Group 5 compared with Group 3 and Group 4 but remained higher than in Group 1 and Group 2 (Table 3).

Table 3. Comparison of HDL-C, LDL-C, and TC levels among the test groups (n=35)

Groups	Group 1 (n=7)	Group 2 (n=7)	Group 3 (n=7)	Group 4 (n=7)	Group 5 (n=7)
HDL-C (mean±SEM)	56.20±0.86	66.00±0.71[a]	42.60±0.93[a,b]	33.80±1.16[a,b,c]	52.60±1.17[b,c,d]
LDL-C (mean±SEM)	39.20±1.16	44.00±1.52	69.80±0.37[a,b]	75.20±0.86[a,b,c]	61.60±1.29[a,b,c,d]
TC (mean±SEM)	39.80±1.16	44.40±1.08[a]	65.60±1.03[a,b]	72.20±0.86[a,b,c]	58.60±1.29[a,b,c,d]

a= p<0.05 vs. Group 1, b= p<0.05 vs. Group 2, c= p<0.05 vs. Group 3, d= p<0.05 vs. Group 4.
HDL-C: High-density-lipoprotein cholesterol, LDL-C: Low-density-lipoprotein cholesterol, TC: Total cholesterol, SEM: Standard error of the mean

Table 4. Comparison of HDL-C, LDL-C, and TC levels among the recovery groups (n=35)

Groups	Group 1 (n=7)	Group 2 (n=7)	Group 3 (n=7)	Group 4 (n=7)	Group 5 (n=7)
HDL-C (mean±SEM)	57.52±0.35	66.25±0.82[a]	32.20±0.80[a,b]	40.40±0.51[a,b,c]	34.40±0.51[a,b,d]
LDL-C (mean±SEM)	39.82±1.78	44.32±1.65	66.60±1.08[a,b]	45.40±0.87[a,c]	56.80±1.46[a,b,c,d]
TC (mean±SEM)	40.00±1.20	44.55±0.84[a2]	73.00±0.71[a,b]	57.40±0.51[a,b,c]	64.20±0.80[a,b,c,d]

a= p<0.05 vs. Group 1, b= p<0.05 vs. Group 2, c= p<0.05 vs. Group 3, d= p<0.05 vs. Group 4.
HDL-C: High-density-lipoprotein cholesterol, LDL-C: Low-density-lipoprotein cholesterol, TC: Total cholesterol, SEM: Standard error of the mean

Low-density lipoprotein-cholesterol levels in the recovery group

LDL-C levels increased significantly with continuous use of ATZ in Group 3 compared with Group 1 (66.60±1.08 mg/dL vs. 39.82±1.78 mg/dL, p<0.001), and Group 2 (66.60±1.08 mg/dL vs. 44.32±1.65 mg/dL, p<0.001). LDL-C level was higher in Group 4 than in Group 1 (45.40±0.87 mg/dL vs. 39.82±1.78 mg/dL, p=0.016), but lower than in Group 3 (45.40±0.87 mg/dL vs. 66.60±1.08 mg/dL, p<0.001). LDL-C levels were higher in Group 5 than Group 1 (p<0.001), Group 2 (p<0.001), and Group 4 (p<0.001) but lower than Group 3 (p<0.001) (Table 4).

Total cholesterol levels in the test groups

There was a significant increase in TC levels in Group 2 compared with Group 1 (44.40±1.08 mg/dL vs. 39.80±1.16 mg/dL, p=0.044). TC levels were significantly higher in Group 3 than in Group 1 and Group 2 (65.60±1.03 mg/dL vs. 39.80±1.16 mg/dL, p<0.001, and 44.40±1.08 mg/dL, p<0.001, respectively). A significant increase in TC levels was observed in Group 4 compared with Group 1 (p<0.001), Group 2 (p<0.001), and Group 3 (p=0.020). There was a decrease in TC levels in Group 5 compared with Group 3 and Group 4 (58.60±1.29 mg/dL vs. 65.60±1.03 mg/dL, p<0.001, and 72.20±0.86 mg/dL, p=0.001, respectively) but an increase in TC levels compared with Group 1 and Group 2 (58.60±1.29 mg/dL vs. 39.80±1.16 mg/dL, p<0.001, and 44.40±1.08 mg/dL, p<0.001, respectively) (Table 3).

Total cholesterol levels in the recovery group

There was an increase in the TC levels in Group 3 compared with Group 1 and Group 2 (73.00±0.71 mg/dL vs. 40.00±1.20 mg/dL, p<0.001, and 44.55±0.84 mg/dL, p=0.026, respectively). Following VCO administration, TC levels in Group 4 decreased when compared with Group 3 (57.40±0.51 mg/dL vs. 73.00±0.71 mg/dL, p<0.001) and increased when compared with Group 1 and Group 2 (57.40±0.51 mg/dL vs. 40.00±1.20 mg/dL, p<0.001, and 44.55±0.84 mg/dL, p<0.001, respectively). TC levels in Group 5 were lower than Group 3 but higher than Group 1 (p<0.001), Group 2 (p<0.001), and Group 4 (p=0.001) (Table 4).

Discussion

This study determined the effects of VCO treatment in diabetes and ATZ-induced lipid profile derangements in rats. ATZ decreased HDL-C levels and increased LDL-C and TC levels, which reversed after VCO treatment. VCO administration for 14 days did not alter LDL-C and TC levels in control rats, suggesting that VCO did not negatively impact the lipid profile in healthy animals. Dyslipidemia in diabetes is characterized by reduced HDL-C and elevated LDL-C or triglyceride (TG) levels (17,18). The current findings are in agreement with a study by Eleazu et al. (19) that also reported no alterations in lipid profiles in healthy rats fed with 5 mL/kg VCO for 21 days. Margata et al. (20) reported that rats fed VCO and hydrolyzed VCO had higher TC levels than rats administered atorvastatin. Famurewa et al. (21) also reported that 10% and 15% VCO supplementation for 35 days considerably reduced TC, TG, LDL-C, and VLDL-C levels, accompanied by a significant increase in HDL-C levels, compared with the control rats. Nevin and Rajamohan (22) observed that VCO supplementation improved TG and LDL-C levels but not serum and tissue HDL-C levels. In another study, VCO reduced serum TC and prevented LDL-C oxidation, a vital process in atherosclerotic plaque formation (14). It was suggested that approximately 60% of the medium-chain fatty acids, pre-dominantly lauric acid and myristic acid (52% and 15%, respectively (23), present in VCO and may mediate the beneficial effect of VCO on lipid metabolism. The discrepancy in these results could be due to the length of the experiments and the different doses administered, as also suggested by Famurewa et al. (21). The results of this study indicated alterations in the lipid profiles of ATZ-treated and diabetic rats compared with healthy rats fed distilled water and VCO.

We observed a significant reduction in the HDL-C levels in Group 4. HDL-C is “The good cholesterol” because it is a free radical scavenger that can prevent lipoprotein peroxidation. High levels of HDL-C have been considered a good indicator of a healthy heart (20). Hypertriglyceridemia and low levels of HDL-C are the most common lipid abnormalities related to DM (24). This finding is in line with the studies by Sheweita et al. (25) and Sadri et al. (26) that also reported a significant decrease in HDL-C levels in streptozotocin-induced diabetic rats compared with healthy rats. Upon administration of VCO to the treated diabetic rats in Group 5, we observed a significant increase in the HDL-C levels compared with Group 4, which was the untreated diabetic group, indicating that the administration of VCO to diabetic rats helped increase their HDL levels. VCO has anti-oxidant, hypolipidemic, and anti-thrombotic properties (27), supporting the study by Margata et al. (20) that reported an improvement in HDL-C levels in dyslipidemic rats following VCO administration. Feoli et al. (28) also reported an increase in HDL levels in rats fed coconut oil (CO). When VCO was administered for longer, HDL-C levels may be restored to normal in diabetic rats because a slight enhancement was noticed in Group 2 compared with Group 1.

LDL-C and TC levels increased in Group 4; however, LDL-C and TC levels decreased after VCO treatment in Group 5. Thus, although diabetes is associated with an increased lipid profile, VCO administration can mitigate lipid derangement over time (29). This finding is consistent with a previous study that showed the anti-atherogenic and hypocholesterolemic activity of VCO (22). Another research group reported the hypolipidemic and anti-peroxidative effects of CO proteins in hypercholesterolemic rats fed a high-fat diet (30). The beneficial effects of CO on reducing

circulating lipoprotein levels and lipoprotein disposition may be associated with its biologically active polyphenol compounds (30,31). VCO has numerous beneficial effects on health, including reducing total cholesterol, TG, and phospholipid levels (32). The decreased TC and LDL-C levels in the VCO-treated group suggested reduced lipolysis by hormone-sensitive lipase due to increased insulin secretion or sensitivity (19).

ATZ administration in Group 3 caused a significant decrease in HDL-C levels, whereas there was a concomitant elevation in TC and LDL-C levels. This finding is consistent with a report by Mohammad et al. (33) that also observed a similar disruption in lipid profile after ATZ supplementation. This observation could result from the down-regulation of the steroidogenic activity of cholesterol, a precursor for steroidogenesis that decreases the end products and cholesterol production (34). The increase in serum LDL-C levels may be associated with the inhibition of scavenger receptor β1 by ATZ, as suggested by Pogrmic et al. (34). The inhibition of the scavenger receptor β1 increases LDL-C levels (35), whereas its overexpression decreases LDL-C levels (36). Such lipid profile changes may be related to the toxic effects of ATZ on lipid metabolism.

In the recovery groups, we observed that VCO supplementation did not significantly increase HDL-C levels in Group 4 compared with Group 5, although there was a marginal increase, which may be associated with the length of the recovery period of the experiment. However, LDL-C levels decreased in Group 4, which possibly contributed to recovery after VCO administration (22). Other studies reported that VCO supplementation considerably reduced TC, TG, LDL-C, and VLDL-C levels while increasing the HDL-C levels, which were higher than those of the controls (21,22). VCO also restored lipid parameters in hyperlipidemic animal models (20,21). Mohammad et al. (33) reported that clomiphene citrate treatment resulted in a dose-dependent improvement in serum lipid levels, a decrease in serum cholesterol, TG, LDL-C, and VLDL-C levels, and an increase in serum HDL-C levels in male and female rats (33). Ngala et al. (37) observed increases in TC levels with groundnut oil (GO) and CO administration. In addition, LDL-C levels increased in the CO group, HDL-C levels increased in the GO and CO groups, and TG levels increased in the GO group. Although TC levels increased in the CO group, cardiovascular risk decreased.

The polyphenol fraction from VCO has an advantage over other oils in reducing LDL-C oxidation (22). Several studies have revealed the anti-oxidant activity of polyphenolic substances, especially in red wine and olive oil (38). These polyphenolic compounds might trap reactive oxygen species in aqueous components such as plasma and interstitial fluid of the arterial wall, thereby inhibiting LDL oxidation and showing anti-atherogenic activity. In addition, these compounds can reverse cholesterol transport and reduce intestinal cholesterol absorption (39). The cholesterol-lowering activity of VCO may be partly attributed to this process. Previous research has demonstrated the mitigation of ATZ and diabetes-induced oxidative stress by VCO administration by enhancing deranged oxidative stress markers such as superoxide dismutase, catalase, and glutathione peroxidase (40).

This study has several limitations. First, we did not determine the fatty acid content of the samples. Second, we did not perform a phytochemical analysis of the active components of VCO.

Conclusion

In conclusion, this study elucidated diabetes- and ATZ-induced lipid profile derangement and confirmed the role of VCO in restoring the deranged lipid profile.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee for Animal Experiments (decision no: 022PY30417, date: 27.06.2017)

Informed Consent: Not required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.H.O., E.J.A., D.E.E., Concept: T.H.O., E.J.A., E.E.B., I.U.U., J.U.D., A.E.A., H.P.U., Design: T.H.O., E.J.A., E.E.B., I.U.U., D.E.E., J.U.D., S.A.T., J.I.O., A.E.A., H.P.U., Data Collection or Processing: T.H.O., E.E.B., I.U.U., J.U.D., J.I.O., Analysis or Interpretation: E.J.A., I.U.U., D.E.E., J.I.O., A.E.A., Literature Search: T.H.O., E.J.A., E.E.B., I.U.U., D.E.E., J.U.D., J.I.O., S.A.T., A.E.A., H.P.U., Writing: T.H.O., E.E.B., I.U.U., J.U.D., S.A.T., H.P.U.

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Potentially inappropriate medications in geriatric patients attending a tertiary care hospital in South India: an observational cross-sectional study

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ABSTRACT

Aims: The aim of this study was to assess drug therapy, possible drug-drug interactions, and potentially inappropriate medications (PIMs) in the geriatric age.

Methods: This was a cross-sectional study with prospective enrollment for 12 months. The study population consisted of geriatric patients admitted to the general medicine department. We defined polypharmacy as the concurrent use of more than 5 medications daily. The American Geriatrics Society Beers 2019 criteria were used to identify PIMs. Drug-drug interactions were identified using a drug interaction checker and categorized into mild, moderate, and severe.

Results: The study included 96 patients (mean age: 70.5±7.8 years, men: 61.5%). Seventy-three patients (76.0%) had polypharmacy. A total of 73 (12.1%) PIMs were identified. Among the 605 medications prescribed 63 (10.4%) potential drug-drug interactions were identified. The percentages of mild, moderate, and severe interactions were 43.5%, 43.5%, and 12.9%, respectively.

Conclusions: In this Indian setting study, while the rate of polypharmacy was high, the rate of PIMs and drug-drug interactions were lower. Vigilance is required to identify drug interactions and PIMs in older adults to avoid adverse drug effects.

Introduction

The world has witnessed the phenomenon of population aging as never before. Initially, an increase in the older adult population was seen only in developed countries; however, even developing countries are having the same challenge. The World Health Organization (WHO) states that by 2050, 80% of older adults will live in low-and middle-income countries. The 2011 population census found that there are nearly 104 million older adults (aged 60 years or above) in India, consisting of 53 million women and 51 million men. The proportion of older adults increased from 5.6% in 1961 to 8.6% in 2011. The United Nations World Population Aging Report 2019 asserts that population

aging is a human success story, reflecting the advancement of public health, medicine, economic, and social development and their contribution to disease control, injury prevention, and reducing the risk of premature death. Simultaneously, this also draws our attention to the need for better healthcare services for older adults. In this era of advancements in the medical management of diseases, one of the challenges faced by physicians in the field of geriatric care is the increased number of medications prescribed for multiple ailments, which results in polypharmacy. Polypharmacy refers to the simultaneous use of multiple medications, including prescription medications, over-the-counter medications, and complementary medications (1). There is a lack of a universally accepted cutoff for the number of drugs to define polypharmacy. The numbers range from ≥2 to ≥11 drugs in various sources. However, concurrent use of more than 5 medicines is one of the most followed definitions (2). Polypharmacy increases the risk of adverse drug events, unfavorable drug interactions, and medication non-adherence (3). It is also associated with increased hospitalization, falls, frailty, cognitive impairment, and mortality in geriatric patients (4). Additionally, potentially inappropriate medications (PIMs) in older adults aggravate the risk of adverse events. PIMs refer to the medication prescribed to a patient in whom the risk of the drug outweighs the benefit (3,5). The increase in morbidities with the passing age contributes to polypharmacy and the use of PIMs. Recent studies have shown an increased incidence of frailty associated with the prescription of PIMs (6-8). A systematic review and meta-analysis by Ma et al. (9) concluded with a bidirectional association between frailty and the use of PIMs. The risk of adverse health outcomes, such as adverse drug reactions, hospitalization, and overall mortality, increases with the number of PIMs prescribed, according to the results of a meta-analysis (10). Hence, scrutiny of the medications prescribed to the geriatric population is considered essential. The present study determined the number of medications, potential drug-drug interactions and PIMs in a South Indian sample (11,12).

Methods

This was a cross-sectional study that prospectively enrolled geriatric inpatients from the Department of Medicine of Kasturba Medical College, Manipal, India, a tertiary care hospital. The study was performed from August 2019 through August 2020. The Institutional Ethics Committee of the Kasturba Medical College and Kasturba Hospital approved the study protocol (IEC number: 312/2019, date: 18/06/2020) that was also registered at the Clinical Trial Registry of India (CTRI/2019/07/020438). Participants provided informed consent and the study protocol conforms to the principles of Helsinki.

The study included men or women aged 60 years or older because the United Nations uses this cutoff to classify elderly (13).

The data were collected from the medical records. The study followed three phases:

Phase 1

We first reviewed the case sheets of all older adult patients aged >60 years admitted to the hospital. The primary cause (s) of admission, comorbidities, drugs, and any adverse drug reactions or drug-drug interactions were recorded. Polypharmacy was defined as the concurrent use of more than 5 medications daily (1,2). We also followed the definition given by Kaufman et al. (14), who categorized the patients into four groups of medication count <4, 5-9, 10-14 and >15.

Phase 2

The drugs entered in the first phase were categorized or tabulated according to the Beers screening tool to alert doctors to right treatment (START)/screening tool of older persons' prescriptions (STOPP) criteria (11,12).

Phase 3

Medical review and clinical evaluation were performed based on the number of adverse drug reactions, drug interactions, and possible recommendations for drugs/therapy/regime according to the Beers Criteria (11,12).

Considering prescription details from patient records, the prevalence and frequency of drug-drug interactions and potentially dangerous drug interactions were assessed using computer-based checks available online on the internet (15). Drug interactions were recorded with the following information: drug name, the drug(s) it is interacting with, and the severity of the drug interaction. The severity of drug interactions was graded as mild, moderate, and severe as follows:

Mild: Minimally clinically significant. Minimize risks; assess risks and consider alternative drugs; take steps to circumvent interactions; and/or establish a monitoring plan.

Moderate: Moderately clinically significant. Typically, avoid combinations; use only under special circumstances.

Severe: Highly clinically significant. Avoid combinations; the risk of interaction outweighs the benefit.

Statistical Analysis

The required sample size was calculated with the WHO Epi Info software using the formula $n=4\ pq/d^2$ (n=sample size, p=proportion anti-cipated to have participation in the study, q=1-p, d=absolute precision). With a 50% of participation rate and a relative certanity of 10% at a 95% confidence level, a minimum number of 96 patients was required.

The collected data were recorded as a Microsoft Office Excel 2016 and analyzed using Jamovi version 2.3 statistical software. The descriptive statistics used were proportions and percentages. Mann-Whitney U test was used to compare the average number

of drugs between the two sexes. The Kruskal-Wallis test was used for comparisons across three or more groups. A p-value of <0.05 was considered statistically significant.

Results

The study included 96 patients (mean age: 70.5±7.8 years, men: 61.5%). Fifty-six patients (58.3%) had hypertension, 40 (41.6%) had diabetes mellitus, and 12 (12.5%) had chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD).

a. Polypharmacy

The percentage of patients on ≤4, 5-9 and ≥10 medications was 23.9%, 69.7% and 6.3%, respectively (Table 1). According to the Kaufmann criteria, the prevalence of polypharmacy (defined as prescription of ≥5 drugs) was 76.1%.

Among patients having polypharmacy, 93.1% were between 60 and 80 years of age (Table 1). There was no statistically significant difference in the number of medications prescribed across age groups (60-70 years, 70-80 years and >80 years) (p=0.580). Similarly, there was no statistically significant difference between sexes (p=0.440).

b. Drug interactions

Using the Beers Criteria (11,12) and a drug interaction checker, the potential drug interactions were predicted and classified as mild, moderate and severe. We identified 63 (10.4%) potential drug interactions. Of them, 43.5%, 43.5% and 12.9% were mild, moderate and severe, respectively. Pantoprazole-cyanocobalamin (9.7%) and aspirin-furosemide (9.7%) were the most frequently noted mild interactions. The most frequent moderate interactions were those of aspirin-furosemide and aspirin-sodium bicarbonate, accounting for 11.1% of the total moderate interactions. Table 2 shows the drugs associated with severe interactions. Among the serious drug interactions, azithromycin-ondansetron interaction had a higher frequency.

Table 1. Distribution of patients according to number of medications and age-group distribution of polypharmacy

Distribution of patients according to the number of medications	
Number of medications	Number (%)
≤4 medications	23 (23.9)
≥5-9 medications	67 (69.7)
≥10 medications	6 (6.3)
Age wise distribution of polypharmacy among patients (total patients on polypharmacy=73)	
Age group(years)	n (%)
60-70	39 (53.4)
71-80	29 (39.7)
81-90	5 (6.8)

c. Potentially inappropriate medications

The total number of PIMs identified in the collected data was 73 (12.1%). The number of repeated PIMs was 20 (27.4%). The most frequently identified PIMs were diuretics (70.8%), tramadol (29.2%), and levetiracetam (19%), followed by aspirin (14.3%) (Tables 3, 4).

Furthermore, the PIMs were categorized as inappropriate for most adults (Table 3), drugs inappropriate for certain diseases (kidney disease) (Table 4), and drugs to be used with caution (Table 4).

Discussion

This study was conducted among patients aged 60 years who were admitted to medical wards to assess polypharmacy, PIMs, and potential drug interactions. The prevalence of polypharmacy was 76.0%. Out of these, most patients (91.8%) fell in the category of 5 to 9 drugs. The remaining patients were prescribed ≥10 drugs. The prevalence of polypharmacy in older adults varies widely across regions, health conditions, and healthcare settings. A cross-sectional analysis conducted on the age group >65 years in 17 European countries and Israel showed a prevalence of polypharmacy in the range of 26.3-39.9% (16). In a prospective cohort of individuals aged >65 years in Sweden, the prevalence of polypharmacy and excessive polypharmacy (>10 drugs) was 44% and 11.7%, respectively (17), while a study on Koreans aged >65 years reported a prevalence of 86.4% (18). We found a high prevalence of polypharmacy in our study sample, similar to previously conducted studies. The WHO recommends that the average number of medications an older adult should take is between 1.3 and 2.2 (19). The average number of drugs in the present study was 6.3, much higher than the recommended number.

The comorbidities commonly associated with geriatric patients with polypharmacy in our study were type 2 diabetes mellitus, hypertension, CKD, and COPD. This finding is in agreement with a previously reported higher rate of polypharmacy in diabetes, hypertension, and heart disease (20). According to a study conducted by Hosseini et al. (21), hypertension, depression, and dementia were the most prevalent diseases associated with polypharmacy. In our patients, CKD and COPD were recorded at high rates.

Most interactions we identified were of mild or moderate grade, not requiring discontinuation. The most common interactions were pantoprazole-cyanocobalamin (the former reduces the gastrointestinal absorption of latter), aspirin-furosemide (aspirin reduces furosemide's action by pharmacodynamic antagonism), aspirin-furosemide (aspirin increases and furosemide reduces serum potassium levels; final effect being unpredictable) and aspirin-sodium bicarbonate (aspirin level increases in parallel with augmented tubular

Table 2. List of drugs associated with severe drug-associated interactions

Drugs with severe interactions	Interaction	Number (%)
Azithromycin x ondansetron	The QTc interval increases	3 (33.3)
Clonidine x diltiazem	Sinus bradycardia	1 (11.1)
Ondansetron x nortriptyline-pregabalin	The QTc interval increases	1 (11.1)
Heparin x warfarin	Increased anti-coagulation bleeding	1 (11.1)
Methylprednisolone x tolvaptan	Methylprednisolone decreases the effect of tolvaptan	1 (11.1)
Clopidogrel x rabeprazole	Rabeprazole decreased the effects of clopidogrel	1 (11.1)
Ceftriaxone x enoxaparin	Ceftriaxone enhances the anti-coagulant effect of enoxaparin	1 (11.1)

Table 3. Medications inappropriate for most adults

Drug	Number (%)
Levetiracetam	8 (19)
Aspirin (in cardiac disease)	6 (14.3)
Glimepiride	5 (11.9)
Clonidine	4 (9.5)
Pregabalin	4 (9.5)
Digoxin	3 (7.1)
Ibuprofen	2 (4.8)
Pentazocine	2 (4.8)
Lorazepam	2 (4.8)
Quetiapine	2 (4.8)
Clonazepam	2 (4.8)
Escitalopram	1 (2.4)
Amiodarone	1 (2.4)

Table 4. Potentially inappropriate medications in drug-disease interactions that may exacerbate the disease and drugs to be used with caution

Drug-disease (kidney disease)	
Drug	**Number (%)**
Dabigatran	3 (42.9)
Enoxaparin	2 (28.6)
Duloxetine	1 (14.3)
Ciprofloxacin	1 (14.3)
Drugs to be used with caution among older adults	
Drugs	Number (%)
Diuretics (spironolactone, furosemide, eplerenone)	17 (70.8)
Tramadol	7 (29.2)

reabsorption due to increased pH by sodium bicarbonate). Among the severe drug interactions, azithromycin-ondansetron was prescribed to three patients. The concurrent use of these two drugs that cause QT interval prolongation may carry a risk of ventricular arrhythmia.

Previous studies have shown that the most common drugs involved in drug interactions were those used to treat cardiovascular diseases and psychotropic agents (22-25). Similarly, the present study showed that drugs used for cardiovascular diseases, specifically anti-thrombotic agents, were involved in the majority of the drug interactions.

The most common PIMs were diuretics, levetiracetam, and tramadol. Notably, medications such as digoxin, diuretics, and tramadol were labeled for use with caution in patients with kidney disease, while others like aspirin (in cardiac disease) and dabigatran were indicated as potentially inappropriate due to their interactions with specific conditions. In a previous study conducted in a similar setting, proton pump inhibitors and anti-histamines comprised the majority of PIMs (26). According to a systematic review of the global prevalence of PIMs among older adults, benzodiazepines were the top prescribed drug class (27). Similarly, a population-based cohort study reported benzodiazepines, followed by proton pump inhibitors, as the most common PIMs in older adults (28). However, in the present study, diuretics, levetiracetam, and tramadol were the most common PIMs. We analyzed PIMs using the American Geriatrics Society 2019 Updated AGS Beers Criteria (11,12) that may not be most suitable for an Indian setting. On the other hand, it should be noted that the American Geriatrics Society Beers Criteria was updated subsequently in 2023 (29).

This study aimed to obtain data with the help of structured proforma and analyze the same data to examine the medications prescribed to the geriatric population to minimize adverse drug reactions by cross-checking the lists and informing physicians of any potentially inappropriate combinations. The prescribers appreciated the report provided on potential drug interactions and PIMs as it would make them more vigilant and aware of several drug interactions and inappropriate medications generally overlooked. Integrating tools like the Beers Criteria and drug interaction checkers into hospital ordering systems could serve as invaluable resources, providing real-time alerts and enabling informed decision-making for safer medication dispensation. While it is used in the United States, its adoption in other countries could significantly enhance medication safety practices, providing proper adaptation and integration into existing healthcare infrastructures. Other tools available to assist in the evaluation of medication regimens like STOPP and START

criteria, Turkish inappropriate medication use in the elderly criteria, and ARMOR (Assess, Review, Minimize, Optimize, Reassess), can be implemented according to the suitability of the health care setting and put into practice (30-33). Moving forward, systematic medication reviews and educational initiatives for healthcare providers can further improve prescribing practices and promote patient safety in geriatric care settings.

This study has several limitations. First, the data collection was difficult in some instances because of the coronavirus disease. Second, although the sample size was not small, outcome rates, particularly the rate of PIMs, were low. Third, the tools to assess drug interactions and PIMs were not validated in the local context. Fourth, the results may not be generalized to other populations and settings, including primary and secondary care facilities.

Conclusion

In this Indian setting study, the rate of polypharmacy was high, but the rate of PIMs and drug-drug interactions were low. Hence, scrutiny of the medication list in older adults is of utmost importance to check for PIMs, polypharmacy, and drug interactions to provide the maximum benefit of the medications, avoid adverse drug effects, and minimize health care costs. Continuing medical education programs may help alleviate prescriptions of PIMs in geriatric patients.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of Kasturba Medical College and Kasturba Hospital (IEC number: 312/2019, date: 18/06/2020).

Informed Consent: Informed consent was obtained from the participants.

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Footnotes

Authorship Contributions

Concept: A.M.V., M.K.K., Design: A.M.V., M.K.K., Data Collection or Processing: N.R., S.S., Analysis or Interpretation: A.M.V., N.R., S.S., M.K.K., Literature Search: A.M.V., N.R., S.H., S.S., Writing: A.M.V., N.R., S.H., S.S., M.K.K.

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Aspergilloma of maxilla in an immunocompromised patient: A multidisciplinary approach

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Keywords: Maxilla, fungal osteomyelitis, aspergilloma, maxillectomy, immunocompromised

ABSTRACT

Aspergillosis is a rare, invasive, rapidly progressive, and life-threatening fungal disease of the maxillofacial region and what makes the disease sinister is its indolent course and ability to cause death (16%). Early diagnosis and treatment are essential for such infections. We here report a case of an elderly male patient with diabetes mellitus, cardiac disease, and kidney failure who was diagnosed with aspergilloma with osteomyelitis of the right maxilla. Treatment was based on the comorbidities and the clinical, radiological, and histological features of the lesion.

Introduction

Globally, mycotic infections of the paranasal sinuses are on the rise, associated with an increasing incidence of coronavirus disease-19 and the number of individuals with compromised immune systems. Aspergillosis has been recognized as a fungal disease since Katzenstein et al. (1) discovered it in 1983, although its diagnosis, course of treatment, and classification remain unclear. Aspergillus is a part of the phylum Ascomycota.

Although Aspergillus species are diverse, only a few thermotolerant species can infect humans opportunistically and cause aspergillosis. The most prevalent subtype is aspergilloma. It is characterized by a non-invasive chronic fungal sinusitis that frequently occurs in the maxillary antrum of healthy individuals. The disease has an ominous quality because of its slow course and the possibility of mortality. Mortality may be as high as 16% (2). We here present a case of aspergilloma of the maxilla, managed by a multidisciplinary team owing to a compromised immune system.

Case Presentation

A 75-year-old male patient was admitted with a chief complaint of pain followed by pus discharge from the right maxilla for 8 months. The patient had a history of tooth extraction 10 months ago, followed by gradual onset, progressive, and continuous pain. His history was relevant for type 2 diabetes mellitus for 20 years and ischemic heart disease and chronic kidney disease for 5 years. On physical examination, there was pus discharge from a previous extraction socket on the right, upper labial vestibule (Figure 1a). Serum urea (72.7 mg/dL), creatinine (2.2 mg/dL), sodium (134 mmol/L), potassium (5.30 mmol/L), and chloride (104.9 meq/L) were measured. A chest X-ray was normal. A cardiologist, nephrologist, and endocrinologist were counseled. An incisional biopsy revealed ulcerated mucosa lined by granulation tissue and subepithelium with an abundance of mixed inflammatory cell infiltrates with numerous bacterial colonies with sulfur granules and radiating filaments, suggesting actinomycosis. The colonies were observed in dead bony spicules, suggesting osteomyelitis of the maxilla secondary to actinomycosis species. A contrast-enhanced computed tomography scan revealed moderate circumferential thickening with few areas of hyperdensity and erosion involving the anterior and posterior walls of the right maxillary sinus, extending to the right orbital floor. The intramedullary erosion involved the maxillary premolar and molar alveolar processes (Figure 2). The patient underwent aggressive surgical debridement and primary closure under general anesthesia, though with high cardiac risk (Figure 1b). The final histopathological report suggested aspergilloma with osteomyelitis and a bony sequestrum in the right maxilla. Multiple sections of hematoxylin and eosin (H&E) staining and periodic acid-Schiff (PAS) staining showed fibro-collagenous tissue bits lined by respiratory mucosa with seromucous glands, hemorrhage, dead bone fragments, and calcification with clumps of thin, acute-angled branching septate hyphae and an area of necrosis (Figure 3). The post-operative recovery of the patient was favorable.

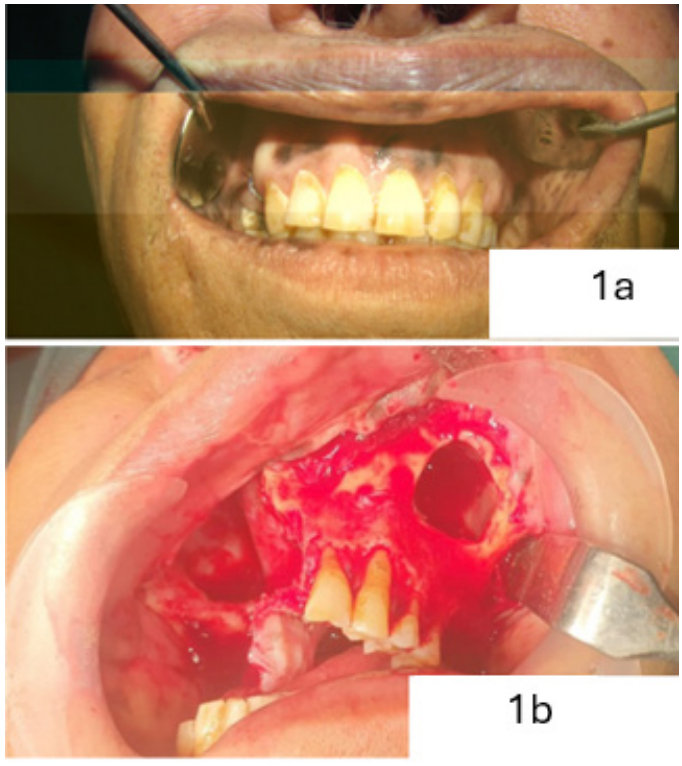

Figure 1. (a) Intraoral sequestrum noted in 16 regions. (b) Intraoperative image

Discussion

The priest botanist Micheli (3) was the first to mention aspergillosis in 1729. In 1893, Mackenzie (4) published the first report of maxillary sinus aspergillosis. Its local invasiveness and types 1 and 3 hypersensitivity responses are linked with its pathogenicity. Of all rhinosinusitis diagnoses, 6-9% are related to fungal sinusitis. In the head and neck area, the maxillary sinus is the most common location (87.8%), followed by the sphenoid sinus coming in second (5).

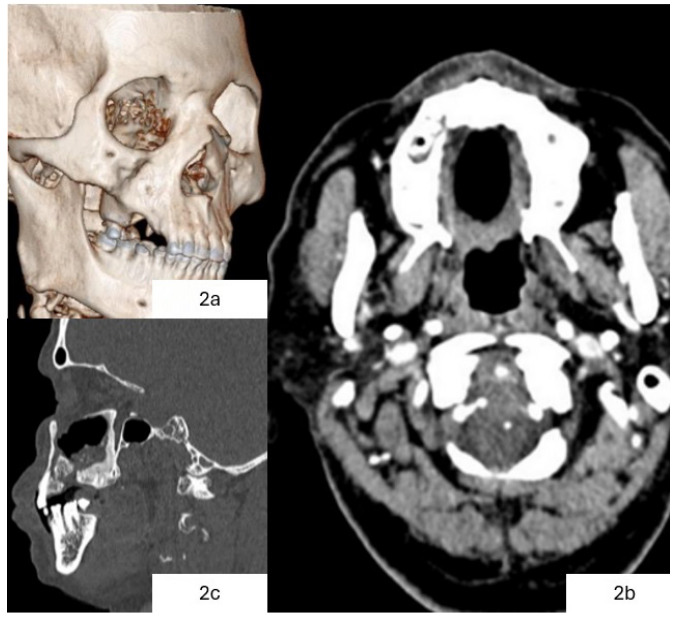

Figure 2. Contrast-enhanced computed tomography images. (a) 3D reconstructed image. (b) Axial section. (c) Sagittal section

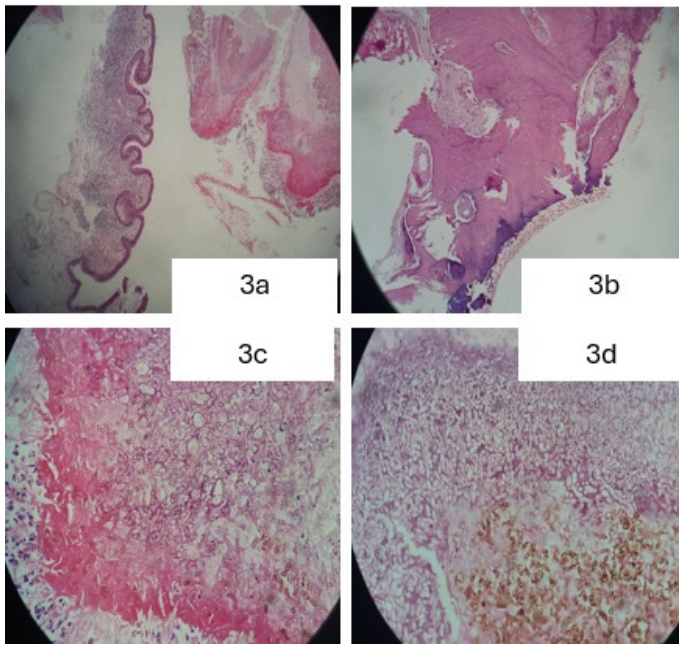

Figure 3. Histopathological images. (a, b) H&E staining in 10X magnification of the respiratory mucosa with seromucous glands, hemorrhage, and dead bone fragments. (c) H&E staining in 100X. (d) PAS staining in 100X
H&E: Hematoxylin and eosin, PAS: Periodic acid-Schiff

Despite its rarity, orofacial aspergillosis can have disastrous effects when the immune system is impaired due to uncontrolled diabetes, lymphomas, leukemia, renal failure, long-term steroid usage, and acquired immunodeficiency syndrome (5,6). The clinical manifestations include nasal congestion, headache, purulent or blood-stained discharge from the nose, and pain in the orbital region. Ocular involvement can occur and presents with chemosis, ptosis, proptosis, conjunctival suffusion, sore eyes, blurred vision, and visual loss associated with retinal artery thrombosis (7). In the present patient, although there was purulent leakage to the oral cavity from a removed socket, there was no sign of ocular involvement.

Radiographically, it appears as a region with a density comparable to iron, resembling a foreign mass within a uniformly clouded maxillary sinus. The affected area may show sinus cavity opacification, mucosal thickening, or erosion of the underlying bone (8). Common histological fungi stains are Grocott methenamine silver (GMS) and PAS. The GMS stain has a signal-to-noise problem because it stains not only the fungi but also the inflammatory cells (lysosomes) and tissue reticulin despite being more sensitive than the PAS stain (9). The small benefit of PAS staining is that it makes the morphology of the tissue next to the fungus easier to see; however, this issue may be overcome by applying an H&E counterstain and GMS stain. When viewed under 10X and 100X, histopathological sections show fibro collagenous tissue bits lined by respiratory mucosa with seromucous glands, hemorrhage, dead bone fragments, and calcification with clumps of thin, acutely angled branching septate hyphae with areas of necrosis (9).

Treatment for fungal infection includes sequestrectomy, wound debridement, and anti-fungal drug regimens, including amphotericin B, voriconazole and posaconazole (10). In aspergilloma of the maxillary sinus, the surgical approach has some advantages compared with functional endoscopic sinus surgery by enabling complete removal of the fungus, drainage of the remnant sinus cavity, and prevention of recurrence (11). However, our patient underwent only aggressive surgical debridement and did not receive any anti-fungal therapy because of his compromised renal condition.

Conclusion

Aspergillosis is a rare, invasive, life-threatening fungal disease of the maxillofacial region, particularly in immunocompromised patients. The present immunocompromised patient was accurately diagnosed and aggressively managed with a multidisciplinary team.

Ethics

Informed Consent: Informed written consent for publication was obtained from the patient.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: D.S., V.A., N.K. Concept: D.S., V.A., N.K. Design: D.S., V.A., N.K. Data Collection or Processing: D.S., T.M., Analysis or Interpretation: D.S., T.M., Literature Search: D.S., T.M., Writing: D.S., T.M.

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Acute abdomen with perforated viscus: A case of intestinal T-cell lymphoma, not otherwise specified

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ABSTRACT

Small bowel lymphoma is a rare disease with nonspecific presentation. Intestinal T-cell lymphoma, not otherwise specified, is an aggressive lymphoma type with a poor prognosis and may be widespread upon presentation. We report a case of a 72-year-old man who presented with abdominal pain and was diagnosed with a small bowel tumor. Small bowel resection with primary anastomosis was performed. We highlighted the importance of high clinical suspicion when diagnosing such disease and tumor aggressiveness.

Introduction

Primary gastrointestinal (GI) lymphoma accounts for about 1-4% of all GI malignancies (1). Approximately 90% of GI lymphoma cases are of the B-cell lineage, with the rest indicating Hodgkin lymphoma and T-cell lymphoma (2). World Health Organization 2022 classification classifies intestinal T-cell lymphomas as (I) enteropathy-associated T-cell lymphoma (EATL), (II) monomorphic epitheliotropic intestinal T-cell lymphoma, (III) indolent T-cell lymphoproliferative disorder of the GI tract, (IV) intestinal T-cell lymphoma, not otherwise specified (ITCL-NOS), and (V) indolent natural killer cell lymphoproliferative disorder of the GI tract. The prognosis

is different in each lymphoma type; therefore, prompt diagnosis and treatment are crucial to achieve a cure (3). Therapeutic management requires a multidisciplinary approach, and surgery is necessary in patients with complications like perforation or hemorrhage.

Case Presentation

A 72-year-old man with a past diagnosis of hypertension was admitted with fever and worsening abdominal pain for 2 days. The pain was colicky, localized on the left side, with no radiation. He had frequent colicky abdominal pain for 1 month, loss of appetite, and weight loss. He reported no recurrent fever or other GI symptoms. He was of medium build, had pallor, and was mildly dehydrated. The abdomen showed tenderness in the left hypochondrium with a vague palpable mass. The blood tests showed leucocytosis ($23x10^9$/L), anemia (8.3 g/dL), increased ALP (476 U/L), lactate dehydrogenase (LDH) (557 U/L, tumor markers like carcinoembryonic antigen, was normal (1.0 ng/mL). Computed tomography (CT) scan showed a heterogenously enhanced small bowel mass with multiple enlarged mesenteric lymph nodes (Figure 1). He was pre-diagnosed with a sealed perforated small bowel tumor.

The patient underwent exploratory laparotomy, which showed a small bowel tumor, a small perforation covered with slough, and multiple enlarged mesenteric nodes 30 cm from the duodenojejunal junction. Another intraluminal mass was noted 20 cm distally from the terminal ileum. Segmental bowel resection was performed on both tumor sides, with primary anastomosis; however, proximal enlarged mesenteric nodes could not be completely resected because they were fixed and close to the mesenteric vessels (Figure 2).

Post-operatively, his recovery was complicated by cardiac events and sepsis caused by hospital-acquired pneumonia. During approximately 1 month of hospital stay, he developed intestinal obstruction, and the CT scan showed an enlarged mesenteric node with tumor progression and obstruction in the small bowel. Unfortunately, he succumbed to illness 40 days after the initial surgery.

Histopathological assessment showed diffuse tumor infiltration within the submucosa, extending into the serosa and causing perforation in the jejunum. Both tumors were reported as aggressive intestinal T-cell lymphoma, not otherwise specified (ITCL-NOS). Tumor cells were positive for CD3, CD2, CD4, and CD8, perforin with high Ki67, and negative to CD20 and CD56 (Figure 3).

Consent to participate in this case report was provided by the patient's next of kin.

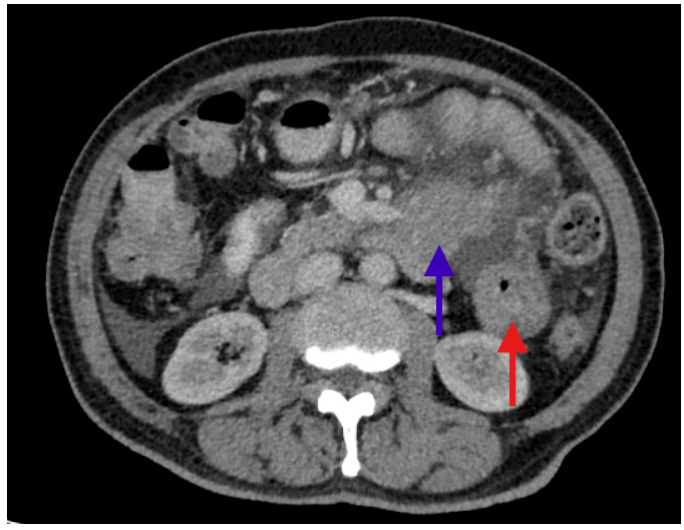

Figure 1. Preoperative contrast-enhanced computed tomography scan of the abdomen. The blue arrow denotes enlarged mesenteric nodes. The red arrow denotes an intraluminal heterogeneous mass at the proximal small bowel

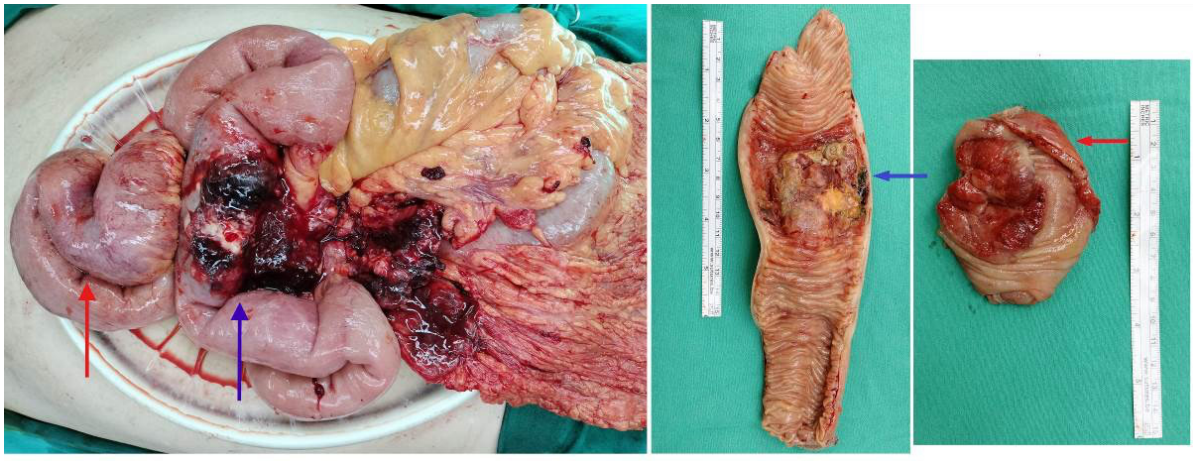

Figure 2. Left: Intraoperative findings during exploratory laparotomy. The blue arrow denotes the jejunal tumor site with multiple enlarged mesenteric nodes. The red arrow denotes the site of the intraluminal mass felt at the distal ileum. Right: Bivalved specimen showing an ulceroinfiltrative mass at the intraluminal bowel, Blue arrow: Jejunal specimen, Red arrow: Terminal ileum specimen

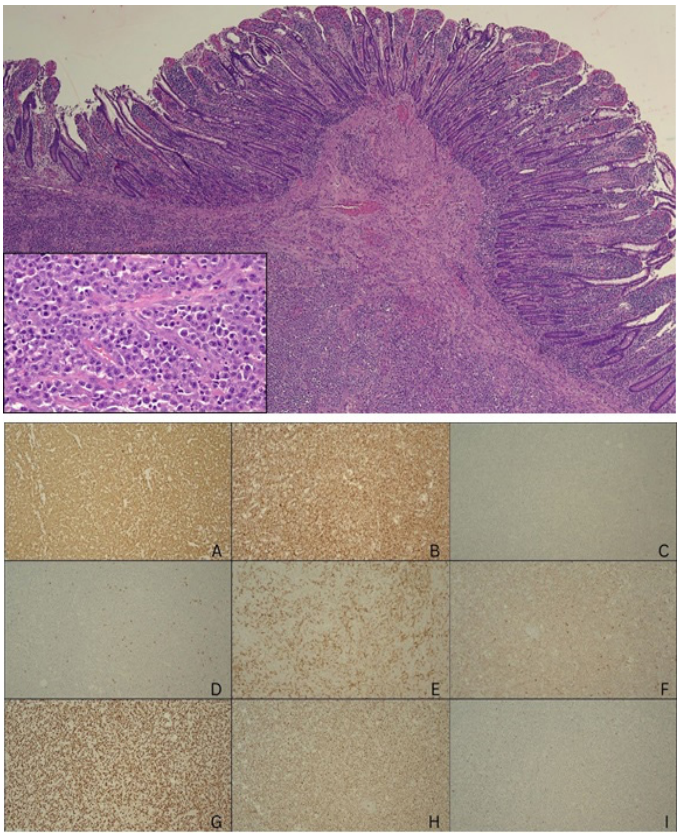

Figure 3. Above: The small bowel with intact mucosa. The tumor cells appear to push the muscularis mucosae without infiltration into the lamina propria of the villi in this field but not in other areas (H and E, 40x) that resulted in perforation (not shown). Inset: Tumor cells are pleomorphic, medium to large in size, irregular vesicular nuclei and large nucleoli, and moderate in amount of cytoplasm. Mitoses are easily seen (H and E, 400x). Below: Immunohistochemistry (x100): A-CD3 positive; B-CD2 positive; C-CD20 negative; D-CD5 negative; E-CD4 positive; F-CD8 positive; G-Ki67 (about 80-90%); H-Perforin positive; I-CD56 negative

Discussion

About 30-40% of all extranodal non-Hodgkin lymphomas occur in the GI tract (4). The most frequently affected sites are the stomach (50-60%), followed by the small bowel (20-30%) (4). Small bowel lymphoma is commonly discovered incidentally in asymptomatic patients, whereas others may present with intestinal obstruction, GI bleeding, perforation, and intussusception (4). Our patient presented with nonspecific abdominal symptoms like pain for a month before the symptoms worsened due to perforation.

Certain tumor subtypes display proclivity toward specific sites, such as mucosa-associated lymphoid tissue lymphoma in the stomach, mantle cell lymphoma (MCL) in the terminal ileum, jejunum, and colon; EATL in the jejunum; and follicular lymphoma in the duodenum (2). Small bowel lymphoma behaves more aggressively than gastric lymphoma (1). ITCL preferentially involves the jejunum with a higher tendency to cause perforation than others (2). In our patient, the tumor involved the jejunum and distal ileum, with complications of perforation at the proximal tumor site.

CT can be used to diagnose small intestinal lymphomas; however, it has a low specificity for small intestinal lesions (1). In our patient, the CT scan that was performed to evaluate the abdominal pain was able to detect a small bowel mass. However, there exist no pathognomonic features on CT to diagnose lymphoma based on imaging alone.

Surgical intervention for gastric and colon lymphoma should be delayed until tumor-related complications (5). The management of GI lymphoma requires a multidisciplinary approach of a radiologist, pathologist, once-hematologist, radiotherapist, and gastroenterologist (6). A previous study reported better prognosis in B-cell subtypes of non-Hodgkin lymphoma and those who underwent systemic chemotherapy and surgical resection compared with surgery alone (1). Hong et al. (5) reported higher morbidity and mortality rates in patients who underwent emergency surgery, but the current study showed no significant differences in early mortality or severe surgery-related complications.

Gross specimens of B-cell lymphoma tend to be fungating or ulcerofungating, whereas T-cell lymphoma tends to appear more ulcerative or ulceroinfiltrative (7). ITCL-NOS is a diagnosis of exclusion and refers to a heterogeneous group of T-cell lymphoma without specific morphologic or phenotypic criteria of other entities (3). They are usually aggressive and may present as widespread disease (3). In immunohistochemistry, tumor cells were positive for CD8 and negative for CD5 (7). As in our case, an aggressive ITCL-NOS diagnosis was made based on histopathological assessment, and other T-cell lymphoma subtypes were ruled out. In a series by Tian et al. (8), patients with prevalent B-cell pathological types had better long-term survival after surgery, whereas T-cell lymphoma and MCL had poor prognosis regardless of whether surgery before chemotherapy or emergency surgery was performed. Risk factors associated with survival included poor performance status, advanced disease stage, bulky disease, extranodal involvement, elevated LDH level, and higher Ki67 proliferative index, where their presence confers lower overall survival (7).

Conclusion

Small bowel lymphoma is rare and requires high suspicion because of a nonspecific presentation and symptoms. Presentation as an acute surgical complication is beneficial in localized disease. The present patient posed diagnostic challenges in small bowel lymphoma because of its rarity and nonspecific presentation.

Ethics

Informed Consent: Consent to participate was granted by the patient's next of kin.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: W.W.L., A.D.Z., M.Z.M.Y., F.A.H., Literature Search: W.W.L., Writing: W.W.L., A.D.Z., M.Z.M.Y., F.A.H.

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Diverse diagnoses in esophageal perforation: Comparative insights from three cases

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ABSTRACT

This case series highlights diverse etiologies and management strategies for esophageal perforation through three illustrative cases: Foreign body ingestion, achalasia cardia, and iatrogenic perforation. Data were retrospectively reviewed, including patient history, diagnostic findings, treatments, and outcomes. Each case was managed differently, based on the patient's presentation, disease severity, and long-term needs. Esophageal perforation requires prompt diagnosis and individualization to address its varied etiologies and prevent complications. This series emphasizes the critical role of timely intervention in achieving favorable outcomes.

Introduction

Esophageal perforation is a rare but potentially life-threatening condition characterized by full-thickness disruption of the esophageal wall. Prompt diagnosis and management are critical because of the high risk of severe complications, such as mediastinitis, sepsis, and multi-organ failure. The condition can arise from various etiologies with unique clinical challenges requiring different management strategies. Common causes include traumatic injuries from foreign body ingestion, iatrogenic injuries during medical procedures, and spontaneous ruptures, such as in Boerhaave syndrome.

Despite advances in diagnostic and therapeutic techniques, esophageal perforation remains a clinical challenge because of its varied presentations and the rapid progression of associated complications. Timely recognition and appropriate intervention are essential for improving patient outcomes and reducing morbidity and mortality.

This case series aimed to highlight the diverse etiologies and management strategies for esophageal perforation in three illustrative cases. Each case provides insight into different aspects of the condition, including diagnostic challenges and treatment approaches. By examining these cases, we aimed

to underscore the importance of individualized patient care and the need for a multidisciplinary approach to patients with esophageal perforation.

Case Presentations

Case 1: A 64-year-old man with chronic obstructive airway disease was admitted for exacerbation of chronic airway disease with fluid overload. In the ward, he complained of dysphagia and chest discomfort. Before admission, his relative claimed he had a bowl of fish soup at home. Esophagogastroduodenoscopy (EGD) revealed a large, hard fish scale stuck in the distal esophageal mucosa. The tumor was removed but left a 2-cm linear esophageal tear. A gastrostomy tube was inserted with endoscopy guidance. The patient was ordered to receive strict nil oral treatment and to feed via a gastrostomy tube. Repeat EGD after 3 months showed healing of the esophageal tear, and the patient was allowed to eat orally after gastrostomy tube removal (Figure 1).

Case 2: A 34-year-old man with a history of chronic dysphagia for the past 14 years was admitted for pneumonia and right-sided thoracic empyema. Computed tomography (CT) of the thorax revealed a grossly distended esophagus with circumferential wall thickening involving the mid and lower parts and right lung empyema. EGD showed pooling saliva within the esophagus with distal esophageal perforation. Endoscopic naso-enteral tube (ENET) insertion was performed, followed by ultrasound-guided drainage of empyema. He recovered slowly but was discharged home after the removal of the chest drain. Six months later, the patient underwent a Heller cardiomyotomy (Figure 2).

Case 3: A 49-year-old female patient complaining of chronic epigastric pain and intermittent vomiting for 5 months after undergoing open surgery for a bile duct stone. Clinical examination revealed a tender mass over the epigastric region. Contrast-enhanced computed tomography of the abdomen revealed gossypiboma in the stomach. An attempt to remove the abdominal pack endoscopically was successful. Nevertheless, the patient developed chest pain, shortness of breath, and subcutaneous emphysema over the neck. CT thoracoscopic examination revealed extensive pneumomediastinum and pneumopericardium, bilateral pleural effusion, and subcutaneous emphysema. Urgent endoscopy revealed distal esophageal wall perforation with multiple erosions along the esophagus and gastric wall defects. She underwent left thoracotomy and exploratory laparotomy and received parenteral nutrition and enteral feeding after the insertion of an ENET (Figure 3).

Discussion

Different etiologies leading to esophageal perforation

Esophageal perforation is associated with various etiologies. The first case involved a 64-year-old man who developed esophageal perforation after ingesting a large fish scale, which is a common cause in adults due to accidental ingestion of sharp objects. The second case highlighted a 34-year-old man with a 14-year history of achalasia cardia, which led to a distended esophagus and eventual perforation, demonstrating that chronic esophageal conditions can predispose patients to perforation. The third case involved a 49-year-old woman who experienced iatrogenic perforation from a retained surgical item (gossypiboma) following bile duct surgery, highlighting the risks associated with surgical procedures and the importance of surgical vigilance. Recent studies have shown that iatrogenic instrumentation is the leading cause (59%), followed by spontaneous perforation (15%) and foreign body ingestion (12%). Other etiologies include trauma, surgical injury, and tumor (1).

Similarities in clinical presentation

Regardless of etiology, mechanism, and extent of injury, there were similarities in clinical presentations. All three patients were admitted with dysphagia, a common symptom of esophageal perforation due to obstruction, inflammation, or structural damage. Each case also involved chest discomfort

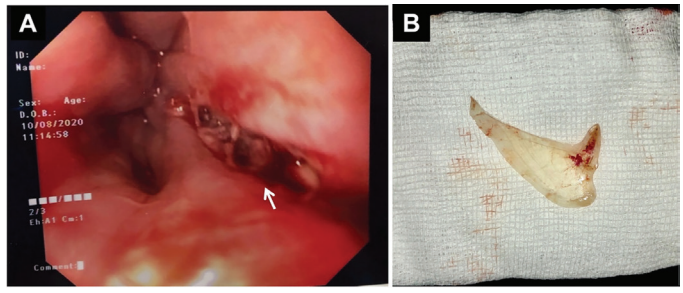

Figure 1. (A) Linear tear at the distal esophageal, measuring 2 cm after removal of fish scale. (B) Hard fish scale retrieved by endoscopy

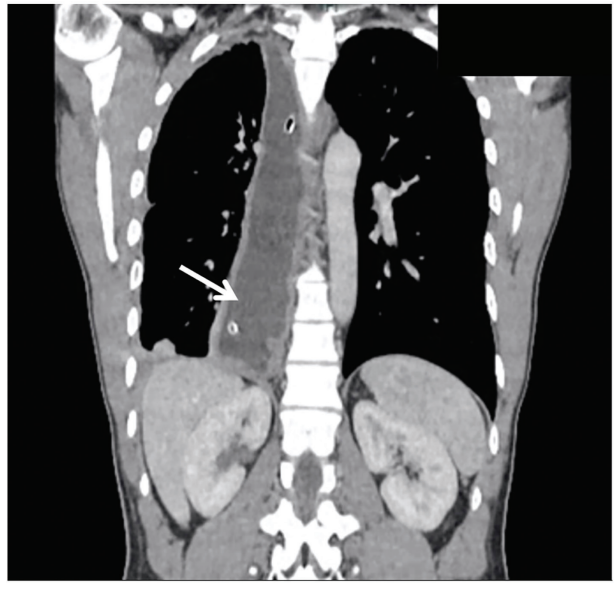

Figure 2. CT thorax post-drainage; showing residual right lung empyema with mega-esophagus
CT: Computed tomography

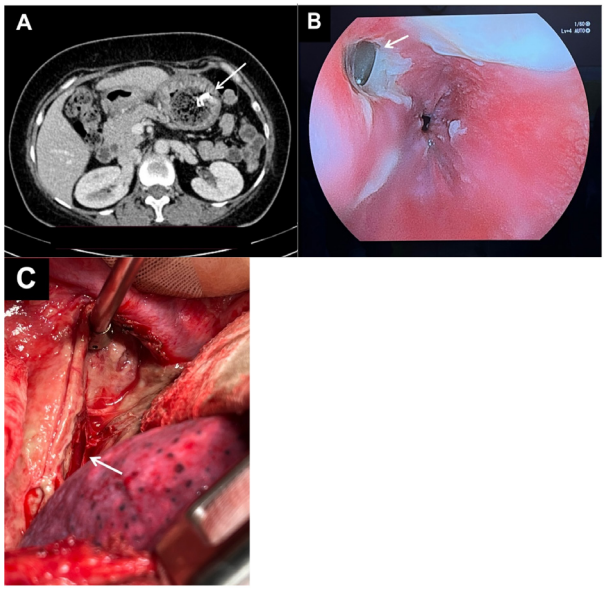

Figure 3. (A) Spongiform-like mass with hyperdense linear structure in the stomach. (B) Left distal esophageal wall perforation, 1 cm in diameter with surrounding slough 2 cm from cardioesophageal junction. (C) Distal esophagus perforation 1 cm in diameter with localized pus collection. Slough surrounded the left lower lobe of the lung

or pain, reflecting the severe irritation and possible mediastinal involvement typical of esophageal perforation. Other symptoms related to esophageal perforation include subcutaneous emphysema, epigastric pain, fever, and tachycardia (2). Symptoms may be masked by medical problems like respiratory infections or cardiac diseases. A high index of suspicion is crucial for subtle complaints or clinical findings. Chronic complaints should not be overlooked, and a thorough assessment is needed to lead to a diagnosis. Early diagnosis is critical, and a delay from perforation diagnosis to diagnosis may increase the mortality rate and worsen patient outcomes.

Differences in diagnostic challenges and management strategies

Due to various clinical presentations and etiologies, diagnosis remains a challenge, and management will differ on a case-by-case basis. In cases of foreign body ingestion, the diagnostic challenge lies in identifying the foreign body and its removal, which can be managed effectively with endoscopy. Post-removal care focused on preventing infection and ensuring esophageal healing through strict oral and gastrostomy tube feeding. In the case of esophageal perforation due to chronic illness, the challenge was to distinguish between chronic achalasia symptoms and acute perforation. The management involved addressing both the acute perforation with ENET insertion and empyema drainage and the underlying achalasia with subsequent Heller cardiomyotomy. The third case scenario was challenging because the diagnostic challenge was multifaceted and involved initial identification of the gossypiboma and subsequent complications (pneumomediastinum, pneumopericardium). The management required a combination of endoscopic and surgical interventions, followed by careful post-operative care with parenteral and enteral nutrition.

Clinical implications

The diversity of etiologies necessitates a high index of suspicion for esophageal perforation in patients presenting with chest pain and dysphagia. Prompt and accurate diagnosis is crucial because delays can lead to significant morbidity and mortality. This series highlights the importance of individualized management strategies tailored to the specific cause and clinical scenario.

Challenges and considerations

Management strategies are challenging, depending on the etiology, severity of injury, and patient condition. The principle of managing esophageal cancer is to eliminate the source of infection, drainage contamination, anti-biotics, nutritional support, and restoration of the continuity of the alimentary tract (3).

Conclusion

Esophageal perforation requires prompt, tailored management. This case series emphasizes the importance of early diagnosis and appropriate intervention for ensuring optimal patient outcomes. Further research is required to establish standardized protocols for managing diverse presentations.

Ethics

Informed Consent: Consent form was filled out by all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.T.Y., M.N.M.H., H.A.R., Consept: M.T.Y., Data Collection or Processing: M.T.Y., H.A.R., Analysis or İnterpretation: M.T.Y., M.N.M.H., H.A.R., Literature Search: M.T.Y., M.N.M.H., Writing: M.T.Y.

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