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Editor in Chef

Dear Readers,

As we commemorate the 103rd anniversary of the Victory Day on August 30, the turning point of our independence struggle, we once again express our wish for a world where peace prevails and human life is valued as it deserves.

The month of September also heralds the beginning of a new academic year. We extend our best wishes for a productive and successful year to all students and academics, from secondary to higher education, under the illuminating guidance of science. As members of the medical community dedicated to advancing human health and quality of life, we remain committed to sustaining our scientific productivity and our openness to innovation in this new term.

With this enthusiasm, we are pleased to present to you the third issue of the Gülhane Medical Journal in 2025. This issue features original research, reviews, and valuable case reports in the field of medicine, and we hope it will open new horizons for our readers.

We sincerely thank our authors for enriching our journal with their contributions, our editors for their meticulous efforts, and our esteemed readers for their continued interest and support.

Best regards,

M. Ali Gülçelik, M.D., Prof.
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The impact of fermented foods and microbiota modulation on colorectal cancer

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ABSTRACT

Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality worldwide. Chemotherapy, immunotherapy, and surgical interventions are the available CRC treatment options. Nevertheless, they have limited effects on overall survival while causing serious side effects. Therefore, alternative interventions that complement the available treatment options are required. Fermented foods contain bioactive components that exhibit antioxidant and anti-inflammatory effects. They are also effective in modulating the microbiota and regulating the immune system, with living/non-living microorganisms and metabolites such as short-chain fatty acids produced by these microorganisms. This review article outlines the potential of using fermented foods in CRC.

Introduction

Colorectal cancer (CRC) begins as a benign adenomatous intestinal polyp in the colon epithelium. It can progress to high-grade dysplasia, invasive adenocarcinoma and eventually to advanced adenoma with metastasis to distant organs such as the liver (1). It is the third most prevalent cancer worldwide, accounting for approximately 10% of all cancers. By 2020, Europe had the highest CRC incidence, followed by Australia and New Zealand, and the highest mortality rates were in Eastern Europe (2). CRC mainly affects people aged 50 years and older (2) and the average age for CRC diagnosis in a population-based study including seven European nations was 71.1 years (3). The burden of CRC is estimated to reach 3.2 million additional cases annually by the year 2040, reflecting a

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63% increase, along with 1.6 million deaths each year, marking a 73% rise (2).

Modifiable lifestyle factors, including physical activity, diet, smoking, and alcohol consumption, can affect both CRC incidence and survival. The report of the World Cancer Research Fund and the American Institute for Cancer Research concluded that consumption of fruits, vegetables, nuts/seeds, calcium, milk, yogurt, β-carotene, vitamin E, vitamin C, and dietary fiber is protective effects against the risk of CRC, while the consumption of alcohol and processed and red meat significantly increases the CRC risk (4).

Fermented foods include kefir, boza, yogurt, vinegar, bread, sausage, soy sauce, beer, wine, kombucha, and pickles (5). The main goal of the fermentation of foods, which dates back to the time before Christ, is to preserve food by increasing its longevity without spoilage. So far, fermented foods have proven to have favorable effects on atherosclerosis, metabolic syndrome, inflammatory bowel diseases, colon cancer, depression, anxiety, and neurodegenerative diseases (6).

There is a need for less-toxic therapies in cancer treatment. Fermented foods show anticancer properties through modulation of the host immune response and reduction of oxidative damage (7). This review aims to explore the impact of fermented foods on CRC based on current literature and to assess the effectiveness of incorporating them into the diet to prevent and manage CRC.

1. Colorectal cancer

Colorectal carcinogenesis is a multifactorial neoplastic disease involving genetic and environmental factors. The pathophysiological mechanisms of colorectal carcinogenesis include aberrant cell proliferation, differentiation, resistance to apoptosis, invasion of adjacent structures by colorectal tumor cells, and distant metastasis (8).

Different mutations affect disease progression and survival in CRC. Mutations in the DNA mismatch repair system are usually associated with alterations in oncogenes and tumor suppressor genes such as Kirsten rat sarcoma viral oncogene homolog (KRAS), alpha isoform of the p110 catalytic subunit of the phosphatidylinositol 3-kinase, adenomatous polyposis coli (APC), and tumor protein p53 (TP53) (1). The Wingless-related integration site (WNT) signaling pathway, a major mediator of stem cell activation, is the most commonly dysregulated oncogenic pathway in CRC, with the most frequently mutated gene in sporadic CRC being APC, a crucial component of this system (9). Most patients with colorectal adenomas have early APC gene mutations and activating mutations of the KRAS oncogene and later inactivating mutations of the tumor suppressor genes TP53 and mothers against decapentaplegic homolog 4 cause the condition to proceed to carcinoma (8). In addition, the proinflammatory state triggered by the transcription factor nuclear factor kappa B (NF-κB) is among the most significant pathways in CRC progression. Most risk factors linked to CRC, such as grilled meat, saturated fatty acids, fried meals, stress, and pollutants, have been found to activate this transcription factor (10).

1.1. Gut microbiota in colorectal cancer

The gut microbiome plays critical roles in the digestion of nutrients, regulation of host immunity, gut hormone production, neurotransmission, toxin removal, and drug metabolism (11). *Firmicutes*, *Proteobacteria*, *Bacteroidetes*, and *Actinobacteria* are the most common bacterial phyla in the human gut, while *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Ruminococcus*, *Peptostreptococcus*, *Faecalibacterium*, *Eubacterium,* and *Peptococcus* are the most prevalent species (12). The microbial community in a healthy gut is diverse, stable, resistant, and resilient. On the other hand, an unhealthy gut microbiota has low abundance, lacks diversity, and shows signs of commensalism (13). Disturbed equilibrium of bacteria within the gut can result in heightened inflammation and the emergence of multiple ailments, encompassing ailments affecting the gastrointestinal tract, metabolism, immune system, and brain (12).

The microbiota might activate CRC via oxidative stress, genotoxicity, virulence factors, and epigenetic alterations (8). The “driver-passenger” model proposes that the microbiota contains two types of bacteria: bacterial drivers (pathogens) that initiate carcinogenesis and passengers (pathobionts), which, though less abundant in the intestinal tract, provide advantages due to their prevalence in the tumor microenvironment. As the tumor environment changes, pathobionts become more numerous than the drivers and can infiltrate the disrupted colonic tissue (14).

Multiple studies have found that certain types of bacteria are more common in patients with CRC than in healthy individuals. In a systematic review, *Fusobacterium-enterotoxigenic Bacteroides fragilis (ETBF)*, *Salmonella, Clostridium,* and *Peptostreptococcus* have been linked to CRC development (15). In another systematic review, patients with adenoma showed increased frequencies of *Fusobacteria*, *Proteobacteria*, and *Bacteroidetes* phyla in their mucosa-associated microbiota and fecal luminal microbiome (16). *Prevotella copri, Bacteroides vulgatus,* and *Ruminococcus torques* were detected at a higher frequency in the CRC group compared to the control group in a meta-analysis of data from France, China, and the USA (17). These bacteria may activate various signaling pathways leading to the transformation of normal intestinal epithelium into malignant cells and may influence carcinogenesis by inducing the expression of inflammatory cytokines (15).

Fusobacterium nucleatum

Fusobacterium nucleatum (F. nucleatum), frequently detected in CRC tissues and feces, may take part in the occurrence and progression of the disease by promoting the proliferation and metabolism of cancer cells, causing a proinflammatory tumor environment, inhibiting anti-cancer immune responses, causing genetic and epigenetic lesions, and promoting metastasis and chemoresistance (18). It was also associated with reduced survival (19). In a recent study, Zepeda-Rivera et al. (20) identified *F. nucleatum* subspecies animalis C2 as a subspecies enriched in the microbiome of CRC patients. The also found that, in mice treated with this subspecies, the number of intestinal adenomas was higher. A study that analyzed 100 paired tumors and normal tissues showed higher *F. nucleatum* colonization in cancerous tissue than in normal tissue. The authors also observed positive correlations between the amount of *F. nucleatum* and the expression of tumor necrosis factor (TNF)-a and Interleukin 6 (IL-6) genes (21).

There is ongoing debate about whether *F. nucleatum* has a causal relationship with CRC. It was suggested to have a triggering effect on precancerous lesions such as hyperplastic polyps and adenomas, potentially leading to CRC (21,22) and promoting an oncogenic and inflammatory response through its virulence factor-*F. nucleatum* adhesin A**,** which interacts with E-cadherin and activates the β-catenin pathway. Based on the available evidence, some researchers argue that *F. nucleatum* is more likely to be a cause of rather than a consequence of CRC (22).

1.2. Relationship between colorectal cancer, gut microbiota, and immunity

Key players in determining the immunological response include the gut microbiota, innate immune system, macrophages and dendritic cells, acquired immune system, T and B lymphocytes, and gut-associated lymphoid tissue. The gut microbiota plays a role in combating harmful pathogens by activating T cells, producing antibodies, and releasing antimicrobial substances like short-chain fatty acids (SCFA) (23). Additionally, it aids in the maturation of immune cells, facilitating the immune response and playing a crucial part in establishing and maintaining the host's immune system (24).

The gut microbiota can also impact antitumor immunity in several ways. Microbial elements or pathogen-associated molecular patterns can boost the activity of antigen-presenting cells through pattern recognition receptors like toll-like receptors (TLRs), elevate cytokine production by immune cells, and indirectly affect immune responses through metabolites generated by microorganisms (25). For example, when TLR4 is overexpressed, it may promote tumor development by increasing the expression of inflammatory cytokines. However, when TLR4 signaling activates TNF-related apoptosis-inducing ligand, a strong inducer of tumor cell death, cytokine expression with anti-cancer effects increases (26).

Oxidative cellular damage and chronic inflammation may be key players in CRC development (10). While the bacteria such as *F. nucleatum*, *Candida albicans*, *ETBF*, and polyketide synthases + *Escherichia coli* can inhibit antitumor immunity, others such as *A. Muciniphila*, *Lactobacillus plantarum, Ruminococcus gnavus*, and *Blautia producta* can promote antitumor immunity (24). Pathogens with pro-tumorigenic effects can induce tumor formation by activating intracellular oncogenic growth through hyperactivation of the WNT-β-catenin pathway, triggering the release of inflammation-promoting cytokines such as bacterial metabolites, IL-17 and TNF (27). A study conducted with tumor, peritumor, and intact tissue samples from different parts of the colon of Mexican CRC patients reported significantly lower IL-23 levels in tumor samples and a non-significant increase in IL-17 and IL-10, suggesting that the IL-23/IL-17 pathway contributes to the onset and progression of CRC (22).

Gut microbiota influences cancer immunotherapy, particularly immune checkpoint inhibitors (ICIs), by shaping antitumor immune responses (28). *Alistipes shahii*, *B. Fragilis*, *Faecalibacterium* spp., and *Eubacterium limosum* enhance the response to immunotherapy (29). Enhanced comprehension of the synergy mechanisms between ICI treatment and the intestinal microbiome and the accurate identification of immunostimulatory and immunosuppressive strains or pathways hold promise for individualized medicine strategies (28).

2. Fermented foods

The International Scientific Association for Probiotics and Prebiotics defined fermented foods as "foods made through desired microbial growth and enzymatic conversions of food components" (30). Fermented foods are categorized based on live microorganism content. While some fermented foods contain live microorganisms (e.g., kefir, sour cream, most cheeses, yogurt, miso, natto, boza), others do not (e.g., pasteurized fermented vegetables, vinegar, bread, soy sauce, sausage, some kombucha, distilled spirits, most beer and wine, and roasted chocolate beans). They can be categorized into types (e.g., cereals, dairy products, meat products, legumes, beverages, fish products, fruit, and vegetable products) and diverse commercial products (e.g., fermented animal protein, fermented vegetable protein), as well (5).

Fermented foods are produced through a process known as fermentation, which involves the activity of bacteria, yeasts, and mycelial fungi. These microorganisms' presence, suitable substrate, and environmental conditions, including temperature,

pH, and moisture content, are essential for food fermentation (31). Traditional food fermentation relies on the natural microbiome in the food or from previously fermented products, whereas commercial food production systems utilize starter cultures to ensure consistent product quality (32).

Current fermentation processes include lactic acid bacteria (LAB), alcoholic fermentation, alkaline fermentation and mixed fermentation (33). Throughout the fermentation process, the concentration of numerous crucial vitamins such as B2, B9, B12, and K, SCFAs, conjugated linoleic acid (CLA), γ-aminobutyric acid, bioactive peptides, and phenolic compounds increases (6). Fermentation is a natural strategy that enhances the appearance, taste, and odor of food with protein, vitamins, and essential amino acids while potentially reducing tannins and phytic acids that limit nutrient availability by reducing the nutritive value of foods (34).

2.1. Fermented foods and microbiota modulation

Fermented foods may interact with the gut microbiota via its microbiome or substances existing within its matrix by delivering nutrients that encourage or inhibit components of the gut microbiota or establishing members of the food microbiome as gut residents and/or engaging with the resident gut microbiota (32). Microorganisms within fermented foods (yogurt, kefir, cheese, and kimchi) are known to survive gastrointestinal transit and are alive when consumed (30). However, some fermented foods undergo further processing, such as pasteurization, baking, or filtering that kills the live microorganisms. The quality and quantity of these methods differ according to the production methods, storage conditions, and durability (34).

2.2. Fermented foods in colorectal cancer

The consumption of fermented milk and its derivatives in CRC has interested researchers because it forms a part of everyday diets. There is evidence that fermented dairy products can lower the risk of CRC. A meta-analysis comprising 61 studies revealed that fermented dairy products significantly reduce the risk of bladder cancer, CRC, and esophageal cancer (35). A meta-analysis that evaluated the relationship between fermented dairy products and CRC reported an inverse correlation between cheese consumption and CRC incidence. Yogurt consumption was also associated with a lower risk of CRC, attributed to the probiotic content of yogurt (36). The combination of two large-scale case-control studies [the Johns Hopkins Biofilm Study and the Tennessee Colorectal Polyp Study (TCPS)] indicated that daily and occasional yogurt consumption in the TCPS was associated with a reduced chance of hyperplastic polyps (37).

LAB genera frequently found in fermented milk and its products include *Lactobacillus, Lactococcus, Enterococcus, Pediococcus*, and *Streptococcus* and are considered “generally recognized as safe" (38). The microorganisms involved in fermentation enhance health by partially breaking down lactose, proteins, and lipids in milk, producing peptides, free fatty acids, and CLA, and improving digestibility (39). Hence, incorporating fermented dairy products into consumption habits may be an effective and low-cost strategy for preventing CRC (36). A clinical study on the impact of a 10-week intervention with 100 grams of fermented kimchi daily on the gut microbiota in 32 volunteers with normal colon, simple adenoma, and advanced colon adenoma found that the intervention resulted in significant changes in the diversity of the fecal microbiome. The same study also showed increased fecal *Cyanobacteria, Acinobacteria, Clostridiumsensu, Gastronaeophillales, Turicibacter* content in patients with advanced colon adenoma following intervention, whereas fecal *Enterococcua Roseburia, Bifidobacterium* spp., *Corynebacteriaceae,* and *Akkermansia* content reduced significantly in patients with advanced colon adenoma (40). The beneficial effects of fermented foods in human studies (35-37) and preclinical studies (41,42) include the induction of apoptosis, inhibition of cancer cell proliferation, suppression of carcinogenic signaling pathways like WNT-β-catenin, and prevention of tumor progression by reducing proinflammatory cytokine production. Combining chemotherapy with fermented food intake alleviates histological changes such as colonic shortening and spleen enlargement (43). Preclinical studies have proven the adjuvant effects of fermented foods by reducing the side effects of chemotherapy (43,50). The effects of fermented foods on CRC are summarized in Table 1 (animal models) and Table 2 (cell models).

Conclusion

Alternative treatments with fewer side effects are necessary for CRC treatment. Bioactive compounds with antioxidant properties and SCFAs, which play a central role in regulating the intestinal microbiota, increase with fermentation. Fermented foods may be beneficial in preventing and treating CRC by modulating the intestinal microbiota and immunity through the metabolites produced by the bacteria they contain. Fermented foods are considered safe and effective in microbiota modulation. Adding fermented foods to the diet is advantageous due to their low-cost and easy applicability. However, since the data on fermented foods other than dairy products have been obtained using preclinical models, future research is needed to evaluate the effectiveness and safety of fermented foods in CRC treatment.

Table 1. Effects of fermented foods on colorectal cancer or adenomas in animal models

Study	Models and groups used	Type of fermented food	Fermentation method	Dose	Time	Mechanism of action
Han et al. (41), 2020	AOM/DSS colitis cancer mouse models (fermented kimchi-non-fermented kimchi) (6 groups*10 pieces)	Fermented kimchi	Obtained by fermentation that involves the production of *Lactobacilli,* such as *L. plantarum*	1.7 g/kg/day ve 5.0 g/kg/day	11 weeks	- Decreasing TNF-α, iNOS, Cox-2, γ-IFN and IL-6 (mRNA levels) - Suppression of NF-κB, particularly NF-κB p65 - Increasing caspase-3 and PARP cleavage or decreasing Bcl-2 expression - Proliferation-related β-catenin nuclear translocation and inhibition of c-Jun
Lim et al. (42), 2023	AOM/DSS colitis cancer mouse models -Normal group; water only (n=8) -Control group; AOM/DSS (n=8) -Positive control group; AOM/DSS group treated with AOM/DSS and 5-aminosalicylic acid -AOM/DSS group treated with fermented soy	Fermented soybeans (Cheonggukjang)	Produced using the traditional method of Kangjin-gun (Jeollanam-do, Republic of Korea)	100 mg/kg/day	-	-Alleviated pathological symptoms such as colonic shortening and increased spleen weight -Modulation of proinflammatory and anti-inflammatory cytokine levels by suppressing NF-κB and inflammatory mediator signaling pathways (decrease in TNF-α, IFN-γ, IL-1β and IL-6 levels and increase in IL-4 and IL-10 levels in soya group compared to the control group) -Phospho-p65 inhibited NF-κB, iNOS, and Cox-2 expression -By regulating mucin-related and tight junction proteins (increased MUC-2, occludin, and ZO-1 levels) improved intestinal integrity -Suppressed tumor growth by regulating apoptosis and proliferation
Chang et al. (43), 2019	CT26 orthotopic colon cancer mouse model (n=30)	NTU 101 Fermented skim milk	*Lactobacillus paracasei* subsp. *Paracasei* NTU 101	1.0 g/kg	5 weeks	NTU 101FM+chemotherapy combined treatment compared to chemotherapy alone; -Improved anorexia -Significantly suppressed tumor growth and metastasis by regulating VEGF, MM-9, and TIMP-1 levels -Controlled proinflammatory cytokines and oxidative stress in tumor, intestine, and serum (increased SOD activity) -Suppressed increases in spleen weight and factors associated with chemotherapy-induced inflammation
Kumar et al. (44), 2022	AOM/DSS male mouse germ-free model -Rice bran group (n=20) -Fermented rice bran group (n=20) -Control group (n=20)	Fermented rice bran	*Bifidobacterium longum*	-	15 weeks	-The incidence of high-grade dysplasia was found to be relatively higher in the fermented group -A significant increase in both the number and size of goblet cells was found in both rice bran groups compared to the control -CD-44 expression decreased in both rice bran groups -Occludins and claudins (tight junction proteins) and zonula occludin increased in both rice bran groups -Cox-2 and NF-κB/p65 decreased in both rice bran groups -Fermentation of rice bran plays an important role in intestinal microbiota metabolism

L. plantarum: Lactobacillus plantarum, AOM/DSS: Azoxymethane-induced/dextran sulfate sodium, NTU 101FM: NTU 101-fermented skim milk, NTU 101: *Lactobacillus paracasei* subsp. paracasei NTU 101, VEGF: Vascular endothelial growth factor, MM-9: Matrix metallopeptidase-9, TIMP-1: Tissue inhibitor of matrix metalloproteinase-1, SOD: Superoxidase dismutase, NO: Nitric oxide, iNOS: Inducible nitric oxide synthase, IL: Interleukin, TNF-α: Tumor necrosis factor alpha, NF-κB: Nuclear factor kappa-B, SOD: Superoxide dismutase, Cox-2: Cyclooxygenase-2, MUC-2: Mucin-2, CD-44: Cluster of differentiation-44, IFN: Interferon

Table 2. Effects of fermented foods in colorectal cancer cell models

Study	Model used	Type of fermented food	Fermentation method	Time	Dose	Mechanism of action
Al-Madboly et al. (45), 2023	HCT-116	Fermented juice of Kidachi aloe leaf	-	-	-	-Cell arrest in G1 phase; promotion of apoptosis -TNF-α decrease and IFN-γ increase; anti-inflammatory and/or immunomodulatory effect -Antimicrobial effect against opportunistic pathogens
Divisekera et al. (46), 2019	HCT-116 and HT-29 cells	LAB isolated from fermented millet flour	-	-	-	-Potential bactericidal activity against drug-sensitive pathogens (anti-bacterial activity)
Lizardo et al. (47), 2020	SW480	Fermented cherry silver fruit (Elaeagnus multiflora Thunb.)	*L. plantarum* KCTC 33131 and *L. casei* KCTC 13086	-	25 to 50 µg/mL	-Inhibited cell proliferation and reduced SW480 cell viability -Was able to suppress the proliferation of SW480 cells by inducing cell cycle arrest in S and G2/M phases by downregulating the expression of cyclin A, E, and B and cyclin-dependent kinases (CDKs) CDK1, CDK2, and CDC2 -Upregulated p53 expression -Tumor suppressive effect by inhibiting the chemotactic motility and invasiveness of SW480 cells, downregulating matrix MM-9, and PI3K/AKT/mTOR pathways, and upregulating TIMP-9 and E-cadherin
Jaiswal et al. (48), 2023	HT-29 and SW480	Fermented rice (Bhaati jaanr)	Traditional fermentation with a mixed starter culture called Marcha	-	50-100 µg	-Reduced the viability of both cancer cells -Suppressed LPS-induced inflammation through reduction of NO production and expression of the iNOS gene -Anti-proliferative, antioxidant and anti-inflammatory effects
Iga-Buitrón et al. (49), 2023	Caco-2, HT-29 and HT-116	Fermented broccoli	*Levilactobacillus brevis* (3M1) and *Lactococcus lactis* (3M8)		600 µg/mL	-Cellular antioxidant activity in Caco-2 cells -Anti-proliferative activity in HT-116 and HT-29 cells -Anti-inflammatory effect by reducing IL-8 production in HT-29 cells stimulated with TNF-α
Kim et al. (50), 2021	Drug-resistant human HT-29 cells	Kefir	*Lactobacillus kefiranofaciens, Lactobacillus kefiri, Streptococcus* spp., *Enterococcus* spp., Candida kefyr, Saccharomyces cerevisiae, Kluyveromyces marxianus	24 h	5% (h/h)	-Weakened multidrug resistance -Improved the anticancer effect of DOX chemotherapy -Intracellular ROS levels increased significantly up to 3.8 times in the 10% (v/v) kefir treatment group -HT-29 improves drug resistance of cells -Shows that it can modulate ERK1/2 and JNK signaling pathways -Increased nuclear translocation of NF-κB p65 was down-regulated by kefir treatments in a concentration-dependent manner

L. plantarum: Lactobacillus plantarum, MM-9: Matrix metallopeptidase-9, HCT-116: Human colorectal carcinoma cells, HT-29: Human colon colorectal adenocarcinoma cells, SW480: Human colorectal adenocarcinoma cell line, NO: Nitric oxide, iNOS: Inducible nitric oxide synthase, Caco-2: Human epithelial colorectal adenocarcinoma cell line, DOX: Doxorubicin, LPS: Lipopolysaccharide, IL: Interleukin, TNF-α: Tumor necrosis factor alpha, NF-κB: Nuclear factor kappa-B, JNK: Jun N-terminal kinase, TIMP-9: Tissue inhibitor of matrix metalloproteinase-9, ROS: Reactive oxygen species, IFN: Interferon

Footnotes

Authorship Contributions

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

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

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Assessment of autoimmune thyroiditis in Turkish children with celiac disease

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ABSTRACT

Aims: It has been reported that there is a link between celiac disease and other autoimmune diseases in children. We aimed to compare the presence of autoimmune thyroid disease in children with celiac disease and the ultrasonographic evaluations of these patients with healthy controls.

Methods: This cross-sectional, case-control study enrolled pediatric patients diagnosed with celiac disease and healthy children as controls. All patients and controls were tested for celiac antibodies (anti-tissue transglutaminase immunoglobulin A), thyroid function tests (thyroid-stimulating hormone, free thyroxine, free triiodothyronine, thyroid peroxidase antibody, and anti-thyroglobulin antibody), and thyroid ultrasonography. The primary endpoint was the difference in the frequency of autoimmune thyroiditis between patients and controls.

Results: The study included 50 children with celiac disease [mean±standard deviation (SD) age: 10.98±3.84, 59% girls] and 50 healthy controls (mean±SD age: 11.36±4.17 years, 65% girls). Five patients (10%) with celiac disease and none of the controls were diagnosed with autoimmune thyroiditis at the time of enrolment (p=0.022). No relationship was identified between the severity of small bowel pathology and autoimmune thyroiditis in patients with celiac disease. Additionally, no significant differences were observed in the ultrasonographic evaluation between celiac patients and controls.

Conclusions: In this low-sample study, patients with celiac disease were more likely to have autoimmune thyroiditis than the controls. However, the severity of small bowel damage in celiac disease may not be associated with autoimmune thyroiditis.

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Introduction

Celiac disease is an immune-mediated systemic condition causing pathology in the small intestine mucosa of genetically predisposed individuals, leading to lifelong intolerance to dietary gluten intake (1). Studies have shown that the prevalence of celiac disease in Europe is approximately 0.6-1% (2). Today, it is well-known that celiac disease affects not only the gastrointestinal system but also the extraintestinal systems and it can present with highly variable clinical symptoms (3).

There is a close association between celiac disease, diabetes mellitus, and pubertal disorders. One of the extraintestinal organs affected by celiac disease is the thyroid gland. In patients with celiac disease, the rates of thyroid gland dysfunction, papillary thyroid carcinoma, and autoimmune thyroiditis, including Hashimoto's thyroiditis, and Graves' disease, are higher than in healthy individuals. Therefore, it is recommended to screen patients with celiac disease at certain intervals for thyroid gland pathologies, regardless of their compliance with a gluten-free diet (4).

In this study, we sought to assess autoimmune thyroid disease in children with celiac disease and compare the ultrasonographic assessments of these patients with those of healthy controls.

Methods

Study design setting and sample

This cross-sectional, case-control study was conducted between November 2021 and November 2022 at our tertiary hospital's pediatric gastroenterology and general pediatric outpatient clinics. The study included pediatric patients diagnosed with celiac disease based on biopsy reports according to the European Society of Pediatric Gastroenterology Hepatology and Nutrition criteria (3). Patients diagnosed with autoimmune thyroiditis who presented for investigation of celiac disease were not included in the study. The control group consisted of healthy children who visited the pediatrics outpatient clinic annually for routine growth assessment. They had no known chronic illnesses, tested negative for the anti-tissue transglutaminase immunoglobulin A (anti-tTG IgA) marker, and had normal IgA levels for their age. Figure 1 shows the flow chart of the study sample selection.

Instruments and data collection

We measured the anti-tTG IgA antibody titer during the initial screening using the enzyme-linked immunosorbent assay (ELISA) method. The upper standard limit considered was 10 U/mL. When total serum IgA levels are low, we measured the anti-tTG IgG antibody using the ELISA method, with normal levels defined as <10 U/mL. The participants' thyroid function was evaluated using thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), and by measuring thyroid autoantibodies such as anti-thyroid peroxidase antibodies (Anti-TPO) and anti-Tg antibody with the ELISA method. TSH level was used as the primary indicator of thyroid dysfunction. Subclinical hypothyroidism was defined as TSH levels higher than the normal range, while fT4 levels remained within the normal limits for age. Autoimmune thyroid disease was diagnosed using the electrochemiluminescence method when the anti-TPO levels were >9 IU/mL and/or the anti-Tg levels were >4 IU/mL.

Histopathologic evaluation

Patients underwent at least four biopsies from the distal duodenum and at least one biopsy from the bulb while on a diet containing gluten. An experienced pathologist evaluated biopsies. The degree of histopathologic damage in the small intestine was identified based on the modified Marsh classification, which involves assessing the elevation of intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy (5,6). An increased number of intraepithelial lymphocytes with normal villi morphology characterizes type 1. In addition to the characteristics of type 1, type 2 includes hyperplasia of glandular structures. Type 3 is classified into three groups: type 3a includes mild villous atrophy, type 3b includes moderate villous atrophy; and type 3c includes total villous atrophy.

Ultrasonographic assessment

An experienced nuclear medicine specialist, blinded to the participants' group allocations and laboratory results, performed the thyroid ultrasonography in both the patient and control groups using a GE Logiq 5 (GE, California, USA), equipped with a 7-11 MHz linear transducer, which utilized continuous, real-time visualization. The echotexture of the thyroid gland was characterized as either homogeneous or heterogeneous compared to the surrounding muscular structures. Thyroid nodules were identified by solid and cystic (fluid-filled) components their size, margins, echogenicity, calcifications, central compartment, and cervical lymph nodes (7). The color Doppler characteristics of the thyroid gland and nodules were also recorded.

Ethical approval

University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Scientific Research Ethics Committee reviewed and approved this study protocol (decision number: 2021-395, date: 25.11.2021). It was conducted according to the principles outlined in the Helsinki Declaration. All participants and their parents signed the informed consent form.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corporation, Armonk, NY, USA).

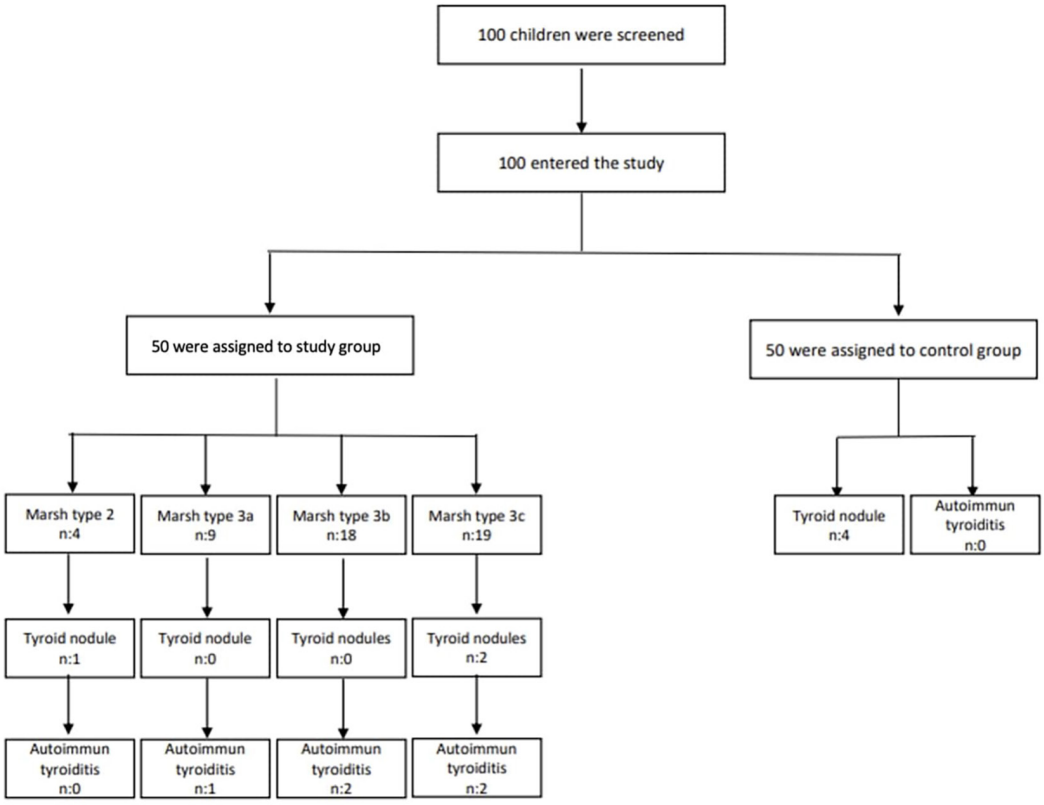


Figure 1. Flowchart of the study sample selection

Continuous variables are reported as mean±standard deviation or median [minimum-maximum (min.-max.)], while categorical variables are presented as frequency and percentage values. The normality of continuous variables was assessed using the Kolmogorov-Smirnov goodness-of-fit test. We used the independent-sample t-test for normally distributed data to compare continuous variables between two groups and the Mann-Whitney U test for non-normally distributed data. When necessary, categorical variables were compared using the chi-squared test, Fisher's exact test, or the likelihood ratio. The level of statistical significance was set at $p<0.05$.

Results

Socio-demographic and clinical characteristics

The study included 100 children, divided equally into 50 patients and 50 controls. The mean age at diagnosis for the patient and control groups was 10.98±3.84 and 11.36±4.17 years, respectively. There was no significant difference in mean ages between the two groups (p=0.637). The demographic composition of the study population was further characterized by a gender distribution of 63% girls and 37% boys. The socio-demographic characteristics of the patients in both groups are provided in Table 1. The most common presenting symptoms in patients with celiac disease were abdominal pain (34%) and failure to thrive (32%). Surprisingly, two patients visited the hospital, thinking they were overweight. Based on the pathological examination results of the patient group, 8% (n=4) were classified as Marsh type 2, 18% (n=9) as Marsh type 3a, 36% (n=18) as Marsh type 3b, and 38% (n=19) as Marsh type 3c.

Laboratory findings

Based on blood tests and ultrasound examinations, 10% of patients diagnosed with celiac disease (n=5) were found to have autoimmune thyroiditis. In contrast, there was no autoimmune thyroiditis among the control group participants (p=0.022). It's worth noting that all the patients with autoimmune thyroiditis were female. Among these five patients examined, two exhibited a condition described as "slightly heterogeneous echogenicity" of the thyroid gland, while three presented with "heterogeneous echogenicity" as observed through ultrasonography. Additionally, elevated levels of TSH, anti-Tg, and/or anti-TPO antibodies were detected in all individuals. The mean TSH, anti-TPO, and anti-Tg values for these patients were 7.65 mIU/L (min.: 5.02 mIU/L, max.: 9.75 mIU/L), 350.02 IU/mL (min.: 28.1 IU/mL, max.: 675 IU/mL), and 11.38 IU/mL (min.: 7.1 IU/mL, max.: 33 IU/mL), respectively. Additionally, the fT4 and fT3 levels in all these five

patients were within the normal range for their age; hence, these patients were considered to have subclinical hypothyroidism.

Ultrasonographic findings

In the patient group, there were no significant differences in the rates of autoimmune thyroiditis and thyroid nodules based on the Marsh scores of the patients. Thyroid nodules were detected in one patient with Marsh type 2, and two patients with Marsh type 3c in the patient group, as well as in a total of four patients from the control group. There was no significant difference between the groups in terms of the presence of nodules (p=0.695), nodule structure (p=1.000), nodule heterogeneity (p=0.956), and the number of nodules (p=0.956) (Table 1). In both groups, there was no significant difference between the volumes of the right and left lobes of the thyroid gland (p=0.934 and p=0.812, respectively). Likewise, the two groups had no notable difference in the thyroid function test results (p=0.495) or thyroid antibodies (p=0.495).

All identified nodules in the patient and control groups had clear margins. All participants had normal free T3 and T4 values. In both groups, none of the participants had microcalcifications, macrocalcifications, central compartment lymph nodes (levels 6-7), or lateral cervical lymph nodes (levels 1-5) (Table 2).

Discussion

It is well-established that the frequency of celiac disease is higher in patients with autoimmune thyroiditis (1). Conversely, it is believed that the frequency of autoimmune thyroiditis is also higher in patients with celiac disease. Therefore, patients with celiac disease should be monitored for thyroid diseases (4). In our study, we found no significant difference in the prevalence of hyperthyroidism between the patient group and the control group, which aligns with some previous research (4). However, we did observe that five patients with celiac disease had elevated levels of TSH and thyroid autoantibodies, suggesting a potential case of autoimmune thyroiditis. Midhagen et al. (8) reported a prevalence of thyroid dysfunctions in patients with celiac disease at 5.8%, while Volta et al. (9) documented it as 5.7%. In a study by Elfström et al. (10), which examined 15,439 patients with celiac disease from 1964 to 2003, the overall prevalence of thyroid disorders was found to be 3.7%. Additionally, research by Metso et al. (11) compared the rates of autoimmune thyroiditis in patients with celiac disease at diagnosis and one year later against those in a control group. The findings revealed that the patient group had significantly higher rates of autoimmune thyroiditis at both time points than the control group (11). A meta-analysis conducted by Sun et al. (12) found that the prevalence of hyperthyroidism in patients with celiac disease

Table 1. Socio-demographic, clinical and laboratory characteristics of the groups

	Celiac patients (n=50)	Controls (n=50)	p
Age, years, mean±SD	10.98±3.84	11.36±4.17	0.637*
Age of diagnosis, years, mean±SD	9.04±3.55	-	-
Sex, female, n (%)	34 (68.0)	29 (58.0)	0.300***
Autoimmune thyroiditis, n (%)	5 (10.0)	0 (0.0)	**0.022*** **
Nodule present, n (%)	47 (94.0)	46 (92.0)	0.695***
Number of nodules, median (min.-max.)	5 (4-8)	2.5 (1-6)	0.629**
Nodule heterogeneity, n (%)			
Homogenous	35 (70.0)	36 (72.0)	0.956***
Slightly heterogenous	7 (14.0)	6 (12.0)	
Heterogenous	8 (16.0)	8 (16.0)	
Structure of the nodule, n (%)			
Cystic	3 (100.0)	3 (75.0)	1.000***a
Solid	0 (0.0)	1 (25.0)	

*Independent samples t-test, **Mann-Whitney U test, ***Chi-square test (aFisher's exact test, likelihood ratio)
min.-max.: Minimum-maximum, SD: Standard deviation

Table 2. Diagnoses of autoimmune thyroiditis and thyroid nodule across Marsh score groups among patients with celiac disease

	Marsh score				p
	2	3A	3B	3C	
Autoimmune thyroiditis, n (%)	0	1 (11.1)	2 (11.1)	2 (10.5)	0.922*
Thyroid nodule, n (%)	1 (25.0)	0	0	2 (10.5)	0.174*

*Chi-square test

was similar to that in control groups. However, the prevalence of hypothyroidism was significantly higher in patients with celiac disease. Although autoimmune thyroid disease is known to be more common in adult patients with celiac disease, no significant difference was found between patients and controls in the prevalence of hypothyroidism and hyperthyroidism on thyroid function tests (13). There has been increase in the frequency of celiac disease among patients diagnosed with autoimmune thyroiditis (1). However, there is a lack of data on the frequency of autoimmune thyroiditis in patients with celiac disease. A study of Italian children revealed that 32% of those diagnosed with celiac disease also had autoimmune thyroiditis at the time of their celiac disease diagnosis. Furthermore, 68% of patients were diagnosed with autoimmune thyroiditis after the initiation of a gluten-free diet (14). Another study by Diamanti et al. (15) reported that autoimmune thyroiditis was not more prevalent in children with celiac disease on a gluten-free diet than healthy control groups.

The histopathological assessments of patients with celiac disease are currently predominantly performed based on the Marsh classification (6). A literature review revealed no studies that have examined the relationship between autoimmune thyroiditis and intestinal histopathology. In addition, the relationship between Marsh scores and the prevalence of autoimmune thyroiditis was investigated. The findings indicated no significant relationship between the degree of intestinal injury and the severity of thyroid issues. This finding suggests that autoimmune thyroiditis or thyroid pathology cases are not secondary to celiac disease but are associated with it through common genetic factors.

The comorbidity of different autoimmune diseases is a well-known clinical phenomenon. The genetic characteristics of human leukocyte antigen (HLA) DQ2 and DQ8 have been identified as risk factors for celiac disease, with approximately 2-5% of individuals with autoimmune thyroid disease also exhibiting symptoms of celiac disease (16). Furthermore, studies have identified specific HLA antigen alleles, such as HLA-DR 4/5 for autoimmune thyroiditis and HLA-DR3 for Graves disease, associated with autoimmune thyroid disease (17). The observed relationship between celiac disease and autoimmune thyroid diseases may be attributed to a genetic predisposition. A review of the extant literature revealed a paucity of studies in both English and Turkish that examined the prevalence of thyroid nodules and thyroid function among pediatric patients with celiac disease. However, a study by Collin et al. (18) revealed that 25 of the 53 patients with autoimmune thyroid disease presented with solitary nodules; though, only 1 of these patients (4%) was also diagnosed with celiac disease. In contrast, our study identified thyroid nodules in three patients with celiac disease and four participants in the control group. Subsequent analysis revealed no statistically significant differences among the groups concerning nodule structures, heterogeneity, or echogenicity. Moreover, between the patient and control groups, a lack of statistically significant variation was observed in the number and size of nodules, as well as the volume of the right and left thyroid lobes. A previous publication on adult patients with celiac disease noted that the thyroid gland volumes of the patients gradually decreased during their one-year follow-up after they started gluten-free diets (13). This observation suggests that thyroid gland pathologies may manifest in adulthood rather than childhood, emphasizing the need to monitor these patients' thyroid functions closely. Furthermore, as indicated by ultrasound findings, a higher prevalence of heterogeneous echogenicity of the thyroid parenchyma has been observed in patients with celiac disease compared to the healthy population (14). The prevalence of pediatric thyroid carcinomas among all childhood malignancies was reported as approximately 1.4% (19). The ultrasonography assessment of participants in both the patient and control groups revealed no micro-macrocalcifications indicative of precancerous conditions, despite the increasing incidence of malignancies.

While there has been no significant increase in the prevalence of hyperthyroidism or hypothyroidism among patients diagnosed with celiac disease in childhood, the prevalence of autoimmune thyroiditis in this population is high, similar to that observed in adult patients with celiac disease. While there appear to be no issues related to pathologies and malignancies at an early age, it is imperative to address the long-term follow-up of patients. No significant relationship is observed between the degree of intestinal injury assessed by histopathological examinations and the presence of autoimmune thyroiditis. There is no significant relationship between the presence of pediatric celiac disease and the presence of thyroid nodules or thyroid volume. The potential risk factors for thyroid carcinomas in pediatric patients with celiac disease remain to be elucidated, and their long-term follow-ups are of crucial importance.

Due to the low incidence of celiac disease in the region, the study population was small, which significantly constrained the study's execution. Moreover, the study's design, which included data analysis from a single pathologist, constitutes a potential limitation. Prospective studies, re-evaluations, and longitudinal studies with a larger number of patients are necessary following the initiation of a gluten-free diet.

Conclusion

In conclusion, the present study suggests that autoimmune thyroiditis may be more prevalent in pediatric patients with celiac disease, than healthy controls, though no significant ultrasonographic differences were observed. Further investigation with a more substantial sample size is necessary to ascertain whether pediatric patients are predisposed to autoimmune thyroiditis.

Ethics

Ethics Committee Approval: University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Scientific Research Ethics Committee reviewed and approved this study protocol (decision number: 2021-395, date: 25.11.2021).

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.F.Ö., M.A., E.G.B., S.İ., S.O.G., N.B., Concept: C.F.Ö., N.B., Design: C.F.Ö., N.B., Data Collection or Processing: C.F.Ö., M.A., E.G.B., S.İ., S.O.G., Analysis or Interpretation: C.F.Ö., S.İ., S.O.G., N.B., Literature Search: C.F.Ö., M.A., E.G.B., S.İ., S.O.G., N.B., Writing: C.F.Ö., M.A., E.G.B., S.İ., S.O.G., N.B.

Conflict of Interest: The authors declared no conflict of interest.

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Stump complications leading to stump revision surgery and related factors in individuals with trauma-related lower limb amputation: a 7-year retrospective cohort study

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Keywords: Amputation stump, complication, surgery, lower limb

ABSTRACT

Aims: Stump complications (SCs) are common in individuals with lower extremity amputations due to trauma, and these complications may require revision surgeries. This study aimed to describe SCs leading to revision surgery and to determine the factors associated with these complications.

Methods: This retrospective cohort study included individuals with traumatic lower extremity amputation who underwent stump revision surgery due to SCs and were admitted to a tertiary rehabilitation hospital between January 2016 and November 2023. Demographic, clinical and amputation data were recorded.

Results: The study included 84 patients (age, mean±standard deviation: 39.4±10.5 years; 100% male). The reason for the first revision was infection in 30 patients (35.7%), neuroma in 22 patients (26.2%), bone spur formation in 21 patients (25%), and stump socket incompatibility in 11 patients (13.1%). The time from amputation to the first revision and the duration of prosthesis use before the operation were significantly longer in patients who underwent revision surgery due to neuroma (p=0.016 and p=0.018, respectively). In patients who had revision surgery due to infection, these times were significantly shorter (p=0.028 and p=0.015, respectively).

Conclusions: This study demonstrated that stump infection was the leading cause of revision surgery in trauma-related lower limb amputations, followed by neuroma. While neuroma-related surgeries were associated with longer amputation and prosthesis use durations, infection-related revisions occurred earlier in the post-amputation period.

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Introduction

Stump complications (SCs) are common in individuals with trauma-related amputations (1). Delayed wound healing, stump scar, or infection, residual limb pain, painful bone spur, neuroma, and skin and circulatory problems are among SCs (2). Despite the developments in amputation surgery and prosthesis technology, these complications negatively affect the rehabilitation process and make it difficult to wear a prosthesis (3,4).

Stump revision surgery should be considered in selected cases where recovery cannot be achieved with comprehensive rehabilitation management (2). It has been reported in the literature that the most common cause of hospitalization after traumatic lower extremity amputations is SCs (5), and the stump revision surgery rate is 61% due to the complications (6). Since stump revisions will cause recurrent surgeries, repeated hospitalizations, difficulty in returning to social life, and increased costs, it is essential to analyze the causes of stump revisions and determine the associated factors.

Our current understanding of the causes and associated factors of stump revision surgery after traumatic lower limb amputation is limited. Only a small number of studies has been conducted on the reasons for stump revision surgery (3,7), but some of these also include non-traumatic amputations. This study aimed to share the demographic and clinical data of individuals with traumatic lower extremity amputation, who underwent stump revision surgery, to describe the SCs that lead to the revision, and to determine the factors associated with these complications.

Methods

Study design and participants

This study designed as a retrospective cohort trial. The study cohort consisted of 1031 lower limb amputees. These patients were identified by scanning patients with International Classification of Diseases diagnosis codes S78, S78.0, S78.1, S78.9, S88, S88.0, S88.1, S88.9, S98.0, T13.6, T05.4, T05.6, T05.8, T05.9 who were admitted to a tertiary rehabilitation hospital between January 2016 and November 2023. Among these, patients with traumatic lower extremity amputation who were between the ages of 18-65 and underwent stump revision surgery due to SCs were included in the study. Patients who had amputation due to a reason other than trauma, who did not undergo revision surgery, and whose amputation and revision data were missing were excluded from the study.

The Clinical Research Ethics Committee No. 1 of Ankara Bilkent City Hospital approved the study (decision number: E1-23-4070, date: 04.10.2023). The study was carried out in accordance with the principles of the Declaration of Helsinki.

Assessments

Demographic data (age, gender, occupation, body mass index, marital status) and clinical data (comorbidities, knowledge of amputation and stump revision surgery) of the patients were collected. “Stump revision number 1” was used to indicate the total number of stump revision surgeries of the amputee, and “Stump revision number 2” was used to indicate that the revision operation was performed one or more times. Etiology of traumatic amputation, amputation duration, amputation level (transfemoral, knee disarticulation, transtibial, Syme, Chopart), and amputation side (right/left/bilateral) were noted.

Prosthesis use duration before revision, type of prosthesis used, concomitant pathology of the operated limb and non-operated limb, number of revisions, time from primary amputation to stump revision (month), revision etiology (bone spur, infection, neuroma, and stump socket incompatibility), and type of revision operation were recorded. In individuals with bilateral amputation, the amputation level and prosthesis type of the side on which the revision operation was performed were noted.

Activity level was assessed with the Amputee Mobility Predictor Scale. It is a valid and reliable scale developed to help assign activity level in individuals with lower limb amputation, and is considered nearly the gold standard. It scores 21 activities, including transfers, static and dynamic sitting and standing balance, walking, climbing stairs, and using assistive devices, on a total scale of 0-47. Higher scores indicate better activity level. This scale can be used with and without prostheses (8,9).

Outcomes

The primary outcome of this study is to identify the most common SCs leading to revision surgery in individuals with trauma-related lower limb amputations. Secondary outcomes include the factors associated with each type of complication.

Statistical Analysis

The research data were analyzed using the Statistical Package for the Social Sciences for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was performed to confirm whether the data were normally distributed. Categorical data were expressed as frequencies (percentages). Continuous data were presented as mean and standard deviation, median (interquartile range), or minimum-maximum values. The chi-square test was used for comparisons of categorical variables. The Mann-Whitney U test or Student’s t-test was performed to compare continuous variables for abnormally or normally distributed data, respectively. Statistical significance was determined as $p<0.05$.

Results

Demographic and clinical data

Eighty-four patients who met the inclusion criteria were included in the study. The mean age of the patients was 39.4±10.5 years and all of the patients were men. The mean time since amputation was 179.5±131.9 months, and the mean time from primary amputation to stump revision was 87.8±103.5 months. A total of 48 patients (57.1%) were employed. Twenty (23.8%) of the patients had at least one comorbid disease, 3 (3.6%) had concomitant pathology in the operated extremity, and 28 (33.3%) had concomitant pathology in the non-operated extremity. In 54 (64.1%) patients, the amputation level was transtibial, and the amputation side was right in 38 (45.2%) of these patients.

Table 1. Demographics and clinics of the individuals with lower limb amputation (n=84)

Demographic and clinical characteristics	Value
Age (years), mean±SD	39.4±10.5
Body mass index (kg/m²), mean±SD	25.8±3.4
Occupation, n (%)	
Employed	48 (57.1)
Unemployed	36 (42.9)
Marital status, n (%)	
Married	49 (58.3)
Single	35 (41.7)
Comorbidity, n (%)	
None	64 (76.2)
Present	20 (23.8)
Hypertension	4 (4.8)
Diabetes mellitus	8 (9.5)
Hyperlipidemia	1(1.2)
Coronary artery disease	1(1.2)
Other	6 (7.1)
Time since amputation (month), mean±SD	179.5±131.9
Amputation etiology, n (%)	
Mine	44 (52.4)
Explosives	19 (22.6)
Gunshot	17 (20.2)
Earthquake	2 (2.4)
Car accident	1 (1.2)
Electric shock	1 (1.2)
Amputation side, n (%)	
Right	38 (45.2)
Left	30 (35.7)
Bilateral	16 (19)
Amputation level, n (%)	
Transfemoral	15 (17.9)
Knee disarticulation	6 (7.1)
Transtibial	54 (64.1)
Syme	4 (4.8)
Chopart	5 (6)
Concomitant pathology of the operated limb, n (%)	
None	81 (96.4)
Fracture	1 (1.2)
Peripheral nerve injury	1 (1.2)
Vascular injury	1 (1.2)
Concomitant pathology of the non-operated limb, n (%)	
None	56 (66.7)
Fracture	4 (4.8)
Peripheral nerve injury	4 (4.8)
Others	4 (4.8)
Amputation	16 (19)
Prosthesis use period before revision (month), mean±SD	83.1±101.6
Activity level before revision, n (%)	
K2	3 (3.6)
K3	17 (20.2)
K4	64 (76.2)
Type of prosthesis, n (%)	
Microprocessor-controlled knee prosthesis	18 (21.4)
Hydraulic controlled knee prosthesis	1 (1.2)
Active vacuum system modular prosthesis	45 (53.6)
Passive vacuum system modular prosthesis	7 (8.3)
Pin lock system modular prosthesis	3 (3.6)
Syme prosthesis	3 (3.6)
Chopart prosthesis	4 (4.8)
None	3 (3.6)

SD: Standard deviation

Demographic and clinical data including prosthesis use period before revision, activity level, and type of prosthesis are presented in detail in Table 1.

Stump revision data

More than one revision operation was performed in 32 (38.1%) of the patients. The first revision of SCs was due to infection in 30 (35.7%) of the patients, neuroma in 22 (26.2%), bone spur formation in 21 (25%), and stump socket incompatibility in 11 (13.1%). The types of revision operation were spur excision (21, 25%), soft tissue revision (42, 50%), and reamputation (21, 25%) (Table 2).

Relationship between demographic and clinical characteristics and stump complications

The relationship between demographic and clinical characteristics and SCs was shown in Tables 3 and 4. In patients who underwent revision surgery due to neuroma, the time from amputation to the first revision and the duration of prosthesis use before the operation were significantly longer than in patients who underwent surgery for reasons other than neuroma (p=0.016 and p=0.018, respectively). The time from amputation to the first revision and the duration of prosthesis use were significantly shorter in patients operated on because of infection than in those operated on because of other complications (p=0.028 and p=0.015, respectively) (Table 4).

Discussion

Continuity of prosthesis use is necessary for the social integration of amputated individuals. Stump revision operations interrupt the prosthesis usage and negatively affect the success of rehabilitation. This study shared epidemiological data on individuals with traumatic lower extremity amputation who underwent stump revision surgery, examined the SCs that lead to stump revision, and defined the factors associated with these complications. The most common complication that led to stump revision operation was infection in the stump area followed by neuroma. It seems that the time from amputation to the first revision, and the duration of prosthesis use before the operation, are related to revision operations due to neuroma. It appears that stump operations due to infection are needed earlier after amputation than those due to other reasons.

In this study, individuals with traumatic lower extremity amputation who underwent stump revision surgery were mostly young, with a mean age of 39 years, and more than half were employed. The main causes of the trauma were mines, explosives and gunshot. The most common level of amputation was transtibial, and the average time from amputation to revision was 88 months. Three-quarters of the individuals were at the K4 activity level. In this respect, the study population is mostly active individuals for whom continuity of prosthesis use is important.

Table 2. Stump revision data (n=84)

Stump revision parameters	**Value**
Number of stump revision 1, mean±SD	1.7±1.3
Number of stump revision 2, n (%)	
Single	52 (61.9)
Multiple	32 (38.1)
Time from amputation to stump revision (month), mean±SD	87.8±103.5
Stump revision etiology, n (%)	
Neuroma	22 (26.2)
Infection	30 (35.7)
Bone spur	21 (25)
Stump socket incompatibility	11 (13.1)
Revision operation, n (%)	
Spur excision	21 (25)
Soft tissue revision	42 (50)
Reamputation	21 (25)

SD: Standard deviation

There are limited data in the literature regarding the frequency of SCs requiring its revision. In a study conducted by Kumar et al. (3), poor initial stump (38%) was the most common reason for revision operation, followed by infection (25%), recurrent ulceration (19%), abscess (6%), neuroma (6%), and necrosis (6%) in individuals with both traumatic and non-traumatic amputations. In the study of Liu et al. (7), in which 80 stump revisions were examined, 53% of the patients with above-ankle traumatic amputation had severe scarring, 48% had neuroma, 30% had excessively soft tissues, and 18% had ulcers. SCs leading to revision in this study were infection in approximately 36% of patients, neuroma in 26%, bone spur formation in 25%, and stump socket incompatibility in 13%. These results suggested that the rate of neuroma leading to stump revision was higher in studies that included only traumatic amputees. However, in the study of Kumar et al. (3), which included amputees due to vascular, infectious, and malignant causes other than trauma, the frequency of neuroma caused by revision surgery seems to be low. In a study, it was determined that approximately half of the individuals with residual stump pain who were amputated due to traumatic reasons had neuroma (10). It is known that neuroma is a non-neoplastic proliferation at the end of the injured nerve (11,12) and its size is directly related to the number of damaged axons (13). For this reason, neuroma formation is more common in traumatic amputations and may be due to the injuries caused to the nerve by the trauma itself, as well as the trauma due to amputation surgery. However, a previous study has reported that the incidence of neuroma was not significantly different in patients who underwent amputation for traumatic indications and those with non-traumatic indications (14). More studies are needed to investigate the frequency and formation mechanism of neuromas in traumatic and non-traumatic amputees to fully understand this relationship.

In this study, excess soft tissue in the stump, scar formation, poor stump condition, and inconvenient shape were evaluated as socket-stump incompatibility. Compared to the other two studies, the frequency of stump incompatibility, requiring stump revision, was lower in this study. We believe this situation may depend on developments in amputation surgery and post-amputation rehabilitation.

The relationship between demographic and clinical factors and the four complications, which we determined as causes of revision operation in this study cohort, was examined. However,

Table 3. The relationship between demographic and clinical characteristics and stump complications

Variables	Neuroma			Bone spur			Infection			Stump socket incompatibility		
	Yes	No	p	Yes	No	p	Yes	No	p	Yes	No	p
Occupation			0.086			0.611			0.148			0.401
Employed	16 (72.7)	32 (51.6)		13 (61.9)	35 (55.6)		14 (46.7)	34 (63)		5 (45.5)	43 (58.9)	
Unemployed	6 (27.3)	30 (48.4)		8 (38.1)	28 (44.4)		16 (53.3)	20 (37)		6 (54.5)	30 (41.1)	
Marital status			0.557			0.523			0.817			0.702
Married	14 (63.6)	35 (56.5)		11 (52.4)	38 (60.3)		17 (56.7)	32 (59.3)		7 (63.6)	42 (57.5)	
Single	8 (36.4)	27 (43.5)		10 (47.6)	25 (39.7)		13 (43.3)	22 (40.7)		4 (36.4)	31 (42.5)	
Comorbidity			0.161			0.805			0.708			0.825
None	16 (72.7)	48 (77.4)		17 (81)	47 (74.6)		21 (70)	43 (79.6)		10 (90.9)	54 (74)	
Hypertension	2 (9.1)	2 (3.2)		0	4 (6.3)		2 (6.7)	2 (3.7)		0	4 (5.5)	
Diabetes mellitus	1 (4.5)	7 (11.3)		2 (9.5)	6 (9.5)		4 (13.3)	4 (7.4)		1 (9.1)	7 (9.6)	
Hyperlipidemia	1 (4.5)			0	1 (1.6)			1 (1.9)		0	1 (1.4)	
Coronary artery disease	1 (4.5)			0	1 (1.6)			1 (1.9)		0	1 (1.4)	
Other	1 (4.5)	5 (8.1)		2 (9.5)	4 (6.3)		3 (10)	3 (5.6)		0	6 (8.2)	
Trauma etiology			0.909			0.839			0.429			0.544
Mine	12 (54.5)	32 (51.6)		10 (47.6)	34 (54)		16 (53.3)	28 (51.9)		6 (54.5)	38 (52.1)	
Explosives	5 (22.7)	14 (22.6)		6 (28.6)	13 (20.6)		7 (23.3)	12 (22.2)		1 (9.1)	18 (24.7)	
Gunshot	5 (22.7)	12 (19.4)		5 (23.8)	12 (19)		4 (13.3)	13 (24.1)		3 (27.3)	14 (19.2)	
Earthquake	0	2 (3.2)		0	2 (3.2)		1 (3.3)	1 (1.9)		1 (9.1)	1 (1.4)	
Car accident	0	1 (1.6)		0	1 (1.6)		1 (3.3)			0	1 (1.4)	
Electric shock	0	1 (1.6)		0	1 (1.6)		1 (3.3)			0	1 (1.4)	
Amputation level			0.472			0.699			0.127			0.058
Transfemoral	6 (27.3)	9 (14.5)		5 (23.8)	10 (15.9)		3 (10)	12 (22.2)		1 (9.1)	14 (19.2)	
Knee disarticulation	1 (145)	5 (8.1)		2 (9.5)	4 (6.3)		0	6 (11.1)		3 (27.3)	3 (4.1)	
Transtibial	14 (63.6)	40 (64.5)		13 (61.9)	41 (65.1)		22 (73.3)	32 (59.3)		5 (45.5)	49 (67.1)	
Foot amputations	1 (4.5)	8 (12.9)		1 (4.8)	8 (12.6)		5 (16.7)	4 (7.4)		2 (18.2)	7 (9.6)	
Amputation side			0.992			0.413			0.161			0.637
Right	10 (45.5)	28 (45.2)		10 (47.6)	28 (44.4)		12 (40)	26 (48.1)		6 (54.5)	32 (43.8)	
Left	8 (36.4)	22 (35.5)		9 (42.9)	21 (33.3)		9 (30)	21 (38.9)		4 (36.4)	26 (35.6)	
Bilateral	4 (18.2)	12 (19.4)		2 (9.5)	14 (22.2)		9 (30)	7 (13)		1 (9.1)	15 (20.5)	
Activity level			0.655			0.199			0.870			0.138
K2	1 (4.5)	2 (3.2)		1 (4.8)	2 (3.2)		1 (3.3)	2 (3.7)		0	3 (4.1)	
K3	3 (13.6)	14 (22.6)		7 (33.3)	10 (15.9)		7 (23.3)	10 (18.5)		0	17 (23.3)	
K4	18 (81.8)	46 (74.2)		13 (61.9)	51 (81)		22 (73.3)	42 (77.8)		11	53 (72.6)	

Table 3. Continued

Variables	Neuroma			Bone spur			Infection			Stump socket incompatibility		
	Yes	No	p	Yes	No	p	Yes	No	p	Yes	No	p
Concomitant pathology of the amputated limb			0.317			0.299			0.405			0.926
None	21 (95.5)	60 (96.8)		20 (95.2)	61 (96.8)		29 (96.7)	52 (96.3)		11 (100)	70 (95.9)	
Fracture	0	1 (1.6)		1 (4.8)	0		0	1 (1.9)		0	1 (1.4)	
Peripheral nerve injury	0	1 (1.6)		0	1 (1.6)		1 (3.3)	0		0	1 (1.4)	
Others	1 (4.5)	0		0	1 (1.6)		0	1 (1.9)		0	1 (1.4)	
Concomitant pathology of the non-amputated limb			0.624			0.357			0.228			0.151
None	13 (59.1)	43 (69.4)		16 (76.2)	40 (63.5)		19 (63.3)	37 (68.5)		8 (72.7)	48 (65.8)	
Fracture	2 (9.1)	2 (3.2)		1 (4.8)	3 (4.8)		1 (3.3)	3 (5.6)		0	4 (5.5)	
Peripheral nerve injury	2 (9.1)	2 (3.2)		0	4 (6.3)		0	4 (7.4)		2 (18.2)	2 (2.7)	
Amputation	4 (18.2)	12 (19.4)		2 (9.5)	14 (22.2)		9 (30)	7 (13)		1 (9.1)	15 (20.5)	
Others	1 (4.5)	3 (4.8)		2 (9.5)	2 (3.2)		1 (3.3)	3 (5.6)		0	4 (5.5)	
Type of prosthesis			0.885			0.391			0.104			0.890
Microprocessor-controlled knee prosthesis	6 (27.3)	12 (19.4)		7 (33.3)	11 (17.5)		2 (6.7)	16 (29.6)		3	15 (20.5)	
Hydraulic controlled knee prosthesis	0	1 (1.6)		0	1 (1.6)		1 (3.3)	0		0	1 (1.4)	
Active vacuum system modular prosthesis	12 (54.5)	33 (53.2)		8 (38.1)	37 (58.7)		19 (63.3)	26 (48.1)		6	39 (53.4)	
Passive vacuum system modular prosthesis	1 (4.5)	6 (9.7)		2 (9.5)	5 (7.9)		3 (10)	4 (7.4)		1	6 (8.2)	
Pin lock system modular prosthesis	1 (4.5)	2 (3.2)		2 (9.5)	1 (1.6)		0	3 (5.6)		0	3 (4.1)	
Syme prosthesis	1 (4.5)	2 (3.2)		0	3 (4.8)		1 (3.3)	2 (3.7)		1	2 (2.7)	
Partial foot prosthesis	0	4 (6.5)		1 (4.8)	3 (4.8)		3 (10)	1 (1.9)		0	4 (5.5)	
None	1 (4.5)	2 (3.2)		1 (4.8)	2 (3.2)		1 (3.3)	2 (3.7)		0	3 (4.1)	
Number of stump revision 2			0.480			0.604			0.461			0.428
Single	15 (68.2)	37 (59.7)		12 (57.1)	40 (63.5)		17 (56.7)	35 (64.8)		8	44 (60.3)	
Multiple	7 (31.8)	25 (40.3)		9 (42.9)	23 (36.5)		13 (43.3)	19 (35.2)		3	29 (39.7)	

Data are presented as n (%)

no relationship was found between SCs and age, body mass index, active employment, amputation side, amputation level, amputation duration, trauma etiology, activity level, and type of prosthesis used. Additionally, there was no relationship between SCs and accompanying comorbid diseases, the presence of other pathologies on the side where the revision surgery was performed, or the presence of other pathologies on the other side.

In a systematic review by Huang et al. (15), including 1329 patients and 13 studies, symptomatic neuromas were diagnosed more frequently when the follow-up period was longer than 3 years and were observed less frequently in studies with short follow-up periods. In this study, the average time from amputation to first revision in patients who had revision surgery due to neuroma was 122 months, and this period was significantly longer in patients who underwent stump revision operation due to neuroma than in those revised for other reasons. This result may support the notion that neuromas continue to enlarge over time (16) and may remain asymptomatic for long periods (17).

Neuromas that occur after amputation of a limb or complete transection of a nerve are known as terminal neuromas. All neuroma formations, including terminal neuromas, result from nerve damage followed by inappropriate internal nerve repair (18). Nerve damage can occur due to chronic irritation, pressure, ischemia, stretch, transection, and iatrogenic causes (19). We did not come across any studies in the literature investigating whether wearing a prosthesis has an effect on neuroma formation. In this study,

Table 4. The relationship between demographic and clinical characteristics and stump complications

Variables	Neuroma			Bone spur			Infection			Stump socket incompatibility		
	Yes	No	p	Yes	No	p	Yes	No	p	Yes	No	p
Age, median (IQR)	45.5 (34.0-50.5)	37.0 (28.8-48.0)	0.103	37.0 (27.0-46.5)	41.0 (31.0-50.0)	0.198	38.0 (31.0-47.5)	38.5 (29.0-48.3)	0.769	38.0 (26.0-51.0)	39.0 (31.0-48.0)	0.958
BMI (kg/cm^2), median (IQR)	26.4 (24.9-29.01)	24.81 (22.9-27.3)	0.072	23.9 (22.4-27.9)	25.6 (23.9-28.4)	0.131	25.2 (23.5-26.5)	25.4 (23.5-28.8)	0.634	24.2 (23.4-31.0)	25.2 (23.5-28.4)	0.791
Time since amputation (month), median (IQR)	221.5 (72.5-321.0)	162.0 (37.5-312.0)	0.16	204 (56.5-312)	168 (46-312)	0.934	162.0 (26.5-300.0)	197.0 (56.7-315.0)	0.207	78.0 (27.0-360.0)	168.0 (49.5-312.0)	0.905
Time since first revision (month), median (IQR)	72.5 (27.8-219)	30.0 (5.8-108.3)	**0.016**	42.0 (9.0-114.0)	36.0 (8.0-144.0)	0.856	16.0 (1.8-108.3)	41.5 (12.8-186.0)	**0.028**	17.0 (6.0-324.0)	40.0 (9.0-132.0)	0.801
Prosthesis use period before revision (month), median (IQR)	60.0 (24.5-200.0)	25.0 (0-104.75)	**0.018**	42.0 (7.5-165.0)	32.0 (0-120.0)	0.492	5.0 (0-100.8)	45.0 (8-200)	**0.015**	14.0 (0-300.0)	35.0 (3.5-120.0)	0.626

BMI: Body mass index, IQR: Interquartile range, Significant difference between groups p<0.05 demostrated with bold

the duration of prosthesis use before the operation was higher in patients who had revision surgery due to neuroma than in those who had revision surgery for other reasons. This result may raise the question of whether prosthesis use causes pressure and ischemia to the nerve and contributes to neuroma formation over time. This situation can be further clarified by comparing neuroma formation in amputees who use and do not use prostheses. However, in this study, the long duration of prosthesis use may also be a natural consequence of the long period between amputation and revision in patients operated on due to neuroma.

Stump infections are still among the leading causes of stump revision surgery. The most common reason for revision surgery in this study cohort was stump infections. In the study of Kumar et al. (3), it was observed that a significant portion of those with infected stumps and abscesses had a disease that suppresses the immune system, such as diabetes. However, in this study, there was no significant difference in terms of comorbidities between those who were operated on due to infection and those who were operated on for other reasons. On the other hand, the time from amputation to revision was significantly shorter in patients who underwent revision surgery due to stump infection. Stump revisions due to infection appear to be needed earlier than revisions due to other reasons in the post-amputation process.

The limitation of the study is missing data, such as, alcohol and cigarette use, which may be associated with SCs. Another limitation is that patients included in the study were only male, which may prevent the results from being generalized to the entire population.

Conclusion

The majority of individuals with traumatic lower extremity amputation who underwent stump revision surgery were young and active patients for whom continued use of the prosthesis in daily life was important. The most common SC leading to stump revision surgery was infection, followed by neuroma. Although most of the demographic and clinical factors evaluated had no relationship with SCs, it appears that the time from amputation to the revision and the duration of prosthesis use before the operation are related to neuroma- and infection-related revision operations. It would be useful to investigate the presence of other factors that may be associated with SCs, leading to recurrent operations in this population already having undergone a major operation.

Ethics

Ethics Committee Approval: The Clinical Research Ethics Committee No. 1 of Ankara Bilkent City Hospital approved the study (decision number: E1-23-4070, date: 04.10.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.K., İ.Ç.G., G.K.K., Y.D., K.A., Concept: N.K., Design: N.K., G.K.K., Data Collection or Processing: İ.Ç.G., H.C., G.K.K., Analysis or Interpretation: N.K., H.C., Y.D., Literature Search: N.K., İ.Ç.G., K.A., Writing: N.K.

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Knowledge, attitude and practice of long-acting reversible contraception among healthcare workers in Kelantan, Malaysia

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Keywords: Knowledge, attitude, long-acting reversible contraception, healthcare worker

ABSTRACT

Aims: Long-acting reversible contraception (LARC) offers numerous advantages in preventing unintended pregnancies; however, its usage in Malaysia remains low. This study aimed to determine the knowledge, attitude, and practice (KAP) levels regarding LARC provision among primary healthcare workers (HCWs) and identify their associated factors.

Methods: A cross-sectional study involving doctors and nurses with at least one year of experience in maternal and child health (MCH) services at health clinics in Kelantan, Malaysia, was conducted between July and September 2023. The level of KAPs towards LARC provision was assessed using a self-administered questionnaire, which was developed and validated by the research team.

Results: A total of 190 doctors and nurses were involved in the study [mean (standard deviation) age: 38.36 (7.05) years; female: 86.3%]. The mean percentage scores for KAP were 69.1%, 48.1%, and 64.1%. Knowledge of LARC provision was associated with being a doctor [adjusted b=8.40; 95% confidence interval (CI): 3.76, 13.05; p<0.001], having formal LARC training (adjusted b=7.47; 95% CI: 2.81, 12.12; p=0.002), and awareness of LARC insertion services in their healthcare facility (adjusted b=8.92; 95% CI: 0.82, 17.02; p=0.031). Additionally, HCWs with more years of experience in MCH service exhibited more favorable attitudes (adjusted b=0.36; 95% CI: 0.23, 0.50; p<0.001) and practices (adjusted b=0.74; 95% CI: 0.43, 1.04; p<0.001) towards LARC provision.

Conclusions: HCWs demonstrated relatively high knowledge and practice levels but a less favorable attitude towards LARC provision, with these levels being associated with the categories of HCWs, formal training, awareness of LARC services, and years of experience in MCH.

Introduction

The unmet need for family planning, where fecund women wish to delay or cease childbearing but do not use contraception, is a significant public health concern issue. Malaysia faces a notably high unmet need at 26.7%, surpassing other Asian countries (1). This statistic correlates with the alarming prevalence of unplanned pregnancies among Malaysian women, reported at 33.0% (1). Unplanned pregnancies not only pose significant risks to maternal and child health (MCH), but also have detrimental societal repercussions, including poorer educational achievement, reduced labor force participation and economic instability (2,3).

Long-acting reversible contraceptive (LARC) methods, including the intrauterine contraceptive device (IUCD) and implant, are effective, safe, and long-lasting contraceptive methods. They can be recommended as first-line contraception

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from adolescence to perimenopause, to prevent unintended pregnancies (4). Nonetheless, the utilization of LARC in Malaysia remains low. Out of 42.8% of women who use contraception, merely 6.5% opted for IUCD, and 5.5% for implant, respectively (1).

Healthcare workers (HCWs) serve as clients' first point of contact and main source of information when seeking family planning services. However, their outdated knowledge regarding LARC leads to the dissemination of inaccurate information to clients, which can prevent clients from making informed decisions about contraception (5,6). Moreover, HCWs may sometimes impose additional barriers and restrictions on providing LARC to specific clients based on factors such as the patient's medical condition, parity, or marital status. However, these restrictions often do not align with established clinical guidelines. For instance, a study in the United States revealed that over one-fifth of HCWs deemed IUCD inappropriate for nulliparous women or those with a history of pelvic inflammatory disease (PID) or ectopic pregnancies (7). This contradicts the medical eligibility criteria for contraceptive use established by the World Health Organization (WHO) in 2015 (8). HCWs can also act as barriers by not offering LARC methods to clients, consequently restricting clients' choices. A study revealed that one-third of HCWs in the United States of America (USA) never discuss implants with their clients (5).

Evaluating HCWs' knowledge, attitudes, and practice (KAP) can provide insights into the extent of misconceptions and challenges in LARC provision. Furthermore, understanding the factors influencing HCWs KAP helps tailor interventions to specific HCWs' characteristics. Although numerous global studies have examined HCWs' KAP regarding LARC, limited information is available on the validity and reliability of the questionnaires used. Additionally, while extensive research has focused on IUCD, studies assessing implants remain scarce. A bibliometric analysis supports this, showing that research on HCWs and IUCDs outnumbers research on implants by a three-to-one ratio (9). A study in Malaysia assessed KAP with regard to IUCD provision among doctors (10). However, the questionnaire used in that study only underwent content validity and reliability testing and did not assess KAP on implants. Furthermore, the study focused exclusively on doctors, even though nurses play a significant role in providing contraceptive services.

Therefore, this study aimed to determine the level of KAP towards LARC (IUCD and implant) provision among doctors and nurses, and their associated factors at government-based health facilities in Kelantan, Malaysia. The study was conducted using a questionnaire that was developed and validated by the research team.

Methods

Study design and settings

This cross-sectional study was conducted between July and September 2023 and included doctors and nurses from 16 government-based health clinics in Kelantan, Malaysia. The study was conducted in accordance with the Declaration of Helsinki and the good clinical practice guidelines. Ethical approval was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia [ID-22-01463-WYY (IIR)], and the Research Ethics Committee (Human), University Sains Malaysia (JEPeM Code: USM/JEPeM/22060427, date: 08.08.2022). Additionally, permission to conduct research in government health clinics was obtained from the Director of the Kelantan State Health Department.

Inclusion and exclusion criteria

Inclusion criteria required participants to have at least one year of experience in MCH services at their current healthcare facility and be able to understand the Malay language. Individuals who were unavailable during the study period or declined participation were excluded.

Participants selection

Four districts-Bachok, Jeli, Pasir Puteh, and Tanah Merah-were randomly selected from the ten districts in Kelantan. These districts were chosen based on their similar socio-economic background. Only four districts were chosen to make data collection feasible without compromising the study's outcomes. From each district, four health clinics were randomly selected, resulting in a total of 16 clinics. The required number of HCWs at each clinic was determined using a stratified proportionate sampling method. Participants from each clinic were then selected through simple random sampling, based on a list of eligible HCWs provided by the clinic's person in charge. All random sampling procedures were carried out using the simple random sampling generator in Excel, developed by Najib (11).

The minimum required sample size of 135 participants was determined using a single mean formula, considering a 95% confidence level, a 10% non-response rate, and a precision of 0.5, based on a standard deviation (SD) of 2.8 from a previous study (10). For multiple linear regression analysis, G*Power version 3.1.9.7 software calculated a sample size of 190 participants, considering an effect size of 0.15, a margin of error of 0.05, 15 expected factors at 90% power and a 10% non-response rate. The final sample size for the study was set at 190 participants, based on the largest sample size calculation.

Assessment tool: development, validity, reliability, and scoring

This study utilized the knowledge, attitudes, perceptions, and practices (KAPP)-LARC questionnaire, which was developed and validated by the research team. The questionnaire was written in Malay and consisted of 39 items categorized into three sections: 15 items on knowledge, 13 on attitude, and 11 on practice. The knowledge section covered the general knowledge and side effects of LARC. The attitude section comprised factors named as "client-related", "method-related resources" and "method-related limitations" on LARC provision. The practice section emphasized counselling, clinical evaluation, and insertion of LARC.

The development process included a comprehensive literature review, field discussions with HCWs, and expert consultations. For validity assessment, the item content validation index and item face validation index, values were reported as greater than 0.83 (12). The knowledge section underwent item response theory analysis, where the difficulty and discrimination values were within or close to the acceptable range (13). In the exploratory factor analysis of the attitude and practice sections, all items loaded above 0.32, with acceptable Cronbach's alpha values ranging from 0.666 to 0.840, indicating good internal consistency (14). The confirmatory factor analysis fit indices were acceptable for both the attitude and practice sections, with satisfactory Raykov's rho values ranging from 0.642 to 0.825 (15).

In the knowledge section, response options were "true", "false", and "don't know". Correct responses were scored as one, whereas incorrect or "don't know" responses were scored as zero. A five-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree) was used in the attitude section. Similarly, a five-point scale from 1 (never) to 5 (always) was used in the practice section. Reverse-worded items were reverse-coded before analysis.

Definitions and study terms

LARC specifically refers to Implanon and the copper IUCD. These two methods were chosen because they are available options in the government health clinics in Kelantan. The MCH services encompass a range of healthcare offerings, including family planning, child health, antenatal, and postnatal services. The term "formal LARC training" is defined as training about LARC received within the last five years through continuous medical education, presentations, workshops, conferences, or courses. The term "average number of clients" refers to the estimated average number of MCH clients seen daily.

Data collection

The study was conducted face-to-face, in which the researchers approached and distributed the self-administered questionnaires to participants who met the study criteria. Detailed explanations were provided before the study commenced, and any questions raised were clarified. Written informed consent was obtained from all participants. The approximate time for completion was 20 minutes.

Outcomes

The primary outcome was the level of KAP regarding LARC provision among primary HCWs. The secondary outcomes were the factors associated with the KAP levels.

Statistical Analysis

The data were analyzed using SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Numerical data were presented as mean (SD) while categorical data were presented as number (n) and percentage (%). The scores for the knowledge section were transformed into percentage scores by dividing the participant scores by the maximum score of 15 marks and multiplying by 100. The Likert scale ratings employed in the attitude and practice sections generate ordinal scores. Therefore, the scores for each factor and the total score for each section were converted to percentage scores using the recommended formula by Hasson and Arnetz (16) as depicted below. The higher the percentage score, the more favorable the attitude and practice of LARC provision among HCWs.

$$Percentage\ score = \frac{(obtained\ score - minimum\ score)}{(maximum\ score - minimum\ score)} \times 100$$

Linear regression analysis was performed to determine the associated factors influencing each KAP score. The independent variables were age, sex, ethnicity, marital status, education, monthly income, category of HCW (doctors or nurses), years working as an HCW, years working in MCH, formal LARC training (yes or no), number of clients, personal or partner's use of LARC (yes or no), number of children, clinic with or without family medicine specialist (FMS), and awareness of the availability of LARC insertion service in the clinic (yes or no). The dependent variables were the KAP percentage scores.

Only variables demonstrating a p-value of less than 0.25 in the simple regression were incorporated into the multiple linear regression analysis. Stepwise, backward, and forward variable selection methods were used to assess all independent variables, and variables with a p-value <0.05 were retained in the model. Subsequently, interaction and multicollinearity were examined. Model assumptions of normality, linearity, and homoscedasticity were checked. The final model was presented with crude and adjusted regression coefficients, 95% confidence intervals (CI), and p-values.

Results

Characteristics of the study participants

A total of 190 participants were involved in the study [mean (SD) age: 38.36 (7.05) years; female: 86.3%]. Table 1 presents the detailed characteristics of the participants, highlighting that the majority were Malay (99.5%) and nurses (54.7%). Notably, 24.7% of HCWs or their partners have utilized LARC, making it the most popular modern contraceptive method, followed by pills (11.6%), depot medroxyprogesterone acetate injections (9.5%), and condoms (7.4%).

Table 1. Characteristics of the study participants (n=190)

Variables	Value
Age (years), mean (SD)	38.36 (7.05)
Sex, n (%)	
Male	26 (13.7)
Female	164 (86.3)
Ethnicity, n (%)	
Malay	189 (99.5)
Non-Malay	1 (0.5)
Marital status, n (%)	
Married	171 (90.0)
Non-married	13 (10.0)
Education, n (%)	
Certificate	48 (25.3)
Diploma	54 (28.4)
Degree and higher	88 (46.3)
Category of HCW, n (%)	
Nurse	104 (54.7)
Doctor	86 (45.3)
Monthly income (RM), mean (SD)	4545.26 (1679.08)
Years working as HCW, mean (SD)	13.34 (7.59)
Years working in MCH, mean (SD)	9.71 (7.58)
Average number of clients, mean (SD)	12.78 (5.57)
Formal LARC training, n (%)	
No	113 (59.5)
Yes	77 (40.5)
Personal/partner's use of LARC, n (%)	
No	143 (75.3)
Yes	47 (24.7)
Number of children, mean (SD)	2.49 (1.64)
Clinic with FMS, n (%)	
No	78 (41.1)
Yes	112 (58.9)
Awareness of LARC insertion service, n (%)	
No	17 (8.9)
Yes	173 (91.1)

SD: Standard deviation, HCW: Healthcare workers, MCH: Maternal and child health, LARC: Long-acting reversible contraception, FMS: Family medicine specialist, RM: Ringgit Malaysia

Knowledge, attitude and practice on long-acting reversible contraception provision among healthcare workers

Table 2, Table 3, and Table 4 display the descriptive analysis of the KAP sections of the KAPP-LARC questionnaire. The respective mean percentage scores for the KAP sections were 69.1%, 48.1%, and 64.1%. In the knowledge section, the mean (SD) of the raw score was 10.37 (2.53) and the mean (SD) of the percentage score was 69.1 (16.9). Most participants provided correct responses to the majority of questions. However, most participants answered incorrectly regarding whether the IUCD can be inserted even when a client is not menstruating (item K9), whether it causes cramping pain during the early stages of insertion (item K14), and whether it can be inserted 24 hours after delivery (item K10). Besides, half of the participants answered incorrectly regarding the length of efficacy of Implanon (item K2). It is crucial to recognize that Implanon is effective in preventing pregnancy for up to three years, not five years (17).

In the attitude section, among the three factors, the "client-related" factor had the lowest mean percentage score of 33.1% (Table 3). More than 70% of participants exhibited a misunderstanding, as they disagreed or strongly disagreed with the statement that LARC is suitable for nulliparous women, unmarried women, or women with a history of PID or ectopic pregnancy (items A2 to A5). Furthermore, around one-third of the participants disagreed or strongly disagreed that many doctors have the necessary skills to insert LARC (items A6 and A7). In the practice section, the study revealed that HCWs provided more frequent counselling and recommendations for IUCD, compared to Implanon (Table 4). Additionally, nearly one-third of doctors never perform IUCD insertion and Implanon insertion (items P10 and P11).

Factors associated with knowledge, attitude and practice of long-acting reversible contraception provision among healthcare workers

The simple linear regression was carried out for each section. The multiple linear regression analysis of KAP sections is shown in Table 5. In the univariable analysis in the knowledge section, the p-value of <0.25 was observed for ten independent variables, which include age, education, monthly income, category of HCW, years working as HCW, years working in MCH, number of clients, formal LARC training, clinic with or without FMS, and awareness of LARC insertion service. These variables were incorporated into the multiple linear regression. The multiple linear regression analysis showed the category of HCW, formal LARC training, and awareness of LARC insertion service had a significant linear relationship with the percentage score for the knowledge section, after controlling for other confounders.

Table 2. Descriptive statistics of items in the knowledge section (n=190)

No	Item	Answer response, n (%)			Response, n (%)	
		True	False	Don't know	Correct	Incorrect
K1	Implanon makes cervical mucus thicker	137 (72.1)	35 (18.4)	18 (9.5)	137 (72.1)	53 (27.9)
K2	Implanon is effective in preventing pregnancy for up to 5 years*	109 (57.4)	79 (41.5)	2 (1.1)	81 (42.6)	109 (57.4)
K3	Implanon releases a low dose of the hormone progestin	139 (73.2)	34 (17.9)	17 (8.9)	139 (73.2)	51 (26.8)
K4	Implanon can be inserted regardless of the menstrual cycle time, provided that the client is not pregnant	176 (92.6)	11 (5.8)	3 (1.6)	176 (92.6)	14 (7.4)
K5	Fertility returns immediately after the removal of Implanon	137 (72.1)	38 (20.0)	15 (7.9)	137 (72.1)	53 (27.9)
K6	Implanon can cause the clients to have no period (amenorrhea)	148 (77.9)	35 (18.4)	7 (3.7)	148 (77.9)	42 (22.1)
K7	Implanon can cause irregular menstrual cycles	159 (83.7)	24 (12.6)	7 (3.7)	159 (83.7)	31 (16.3)
K8	Implanon is safe for use by clients who are breastfeeding	185 (97.4)	3 (1.6)	2 (1.1)	185 (97.4)	5 (2.6)
K9	IUCD can be inserted when the client is not menstruating	93 (48.9)	94 (49.5)	3 (1.6)	93 (48.9)	97 (51.1)
K10	IUCD can be inserted within 24 hours after delivery	43 (22.6)	127 (66.8)	20 (10.5)	43 (22.6)	147 (77.4)
K11	Fertility returns immediately after the removal of IUCD	163 (85.8)	13 (6.8)	14 (7.4)	163 (85.8)	27 (14.2)
K12	IUCD can cause heavier menstrual bleeding	123 (64.7)	61 (32.1)	6 (3.2)	123 (64.7)	67 (35.3)
K13	IUCD can cause prolonged menstrual bleeding	117 (61.6)	64 (33.7)	9 (4.7)	117 (61.6)	73 (38.4)
K14	IUCD can cause cramping pain during the early phase of insertion	94 (49.5)	76 (40.0)	20 (10.5)	94 (49.5)	96 (50.5)
K15	The effectiveness of LARC in preventing pregnancy is over 99%	177 (93.2)	7 (3.7)	6 (3.2)	177 (93.2)	13 (6.8)

*Negative statement. IUCD: Intrauterine contraceptive device, LARC: Long-acting reversible contraception

Table 3. Descriptive statistics of items in the attitude section (n=190)

No	Item	Answer response, n (%)					Mean (SD)[a]	Mean % (SD)[b]
		Strongly disagree	Disagree	Neutral	Agree	Strongly agree		
	Client-related						**11.62 (2.18)**	**33.1 (10.9)**
A1	I think IUCD is suitable for clients who are having sexually transmitted diseases*	95 (50.0)	71 (37.4)	9 (4.7)	8 (4.2)	7 (3.7)	1.74 (0.99)	
A2	I think IUCD is suitable for clients with a history of pelvic inflammatory disease	87 (45.8)	74 (38.9)	12 (6.3)	12 (6.3)	5 (2.6)	1.81 (0.99)	
A3	I think IUCD is suitable for clients with a history of ectopic pregnancy	67 (35.3)	73 (38.4)	16 (8.4)	29 (15.3)	5 (2.6)	2.12 (1.13)	
A4	I think LARC is suitable for clients who have never been pregnant (nulliparous)	78 (41.1)	86 (45.3)	16 (8.4)	8 (4.2)	2 (1.1)	1.79 (0.85)	
A5	I think LARC is suitable for unmarried clients	101 (53.2)	63 (33.2)	20 (10.5)	4 (2.1)	2 (1.1)	1.65 (0.83)	

Table 3. Continued

No	Item	Answer response, n (%)					Mean (SD)[a]	Mean % (SD)[b]
		Strongly disagree	Disagree	Neutral	Agree	Strongly agree		
	Method-related resources						**12.24 (3.00)**	**51.5 (18.7)**
A6	I think many doctors have the skill to insert Implanon	2 (1.1)	50 (26.3)	52 (27.4)	69 (36.3)	17 (8.9)	3.26 (0.98)	
A7	I think many doctors have the skill to insert IUCD	2 (1.1)	58 (30.5)	54 (28.4)	59 (31.1)	17 (8.9)	3.16 (1.00)	
A8	I think the LARC training is sufficient	11 (5.8)	87 (45.8)	42 (22.1)	42 (22.1)	8 (4.2)	2.73 (1.01)	
A9	I think the LARC insertion procedure is easy	7 (3.7)	49 (25.8)	63 (33.2)	62 (32.6)	9 (4.7)	3.09 (0.96)	
	Method-related limitations						**13.98 (2.12)**	**62.4 (13.3)**
A10	I think LARC counselling takes a long time*	4 (2.1)	86 (45.3)	59 (31.1)	36 (18.9)	5 (2.6)	2.75 (0.88)	
A11	I think LARC can cause severe side effects*	24 (12.6)	119 (62.6)	31 (16.3)	15 (7.9)	1 (0.5)	2.21 (0.78)	
A12	I feel worried about being blamed if a complication occurs after LARC insertion*	7 (3.7)	74 (38.9)	56 (29.5)	49 (25.8)	4 (2.1)	2.84 (0.93)	
A13	I will not recommend LARC to clients because it is expensive*	33 (17.4)	105 (55.3)	30 (15.8)	21 (11.1)	1 (0.5)	2.22 (0.88)	
	Total score						**38.00 (3.99)**	**48.1 (7.7)**

*Negative statement, [a]Mean of raw score, [b]Mean of percentage score.
SD: Standard deviation, IUCD: Intrauterine contraceptive device, LARC: Long-acting reversible contraception

Table 4. Descriptive statistics of items in the practice section (n=190)

No	Item	Answer response, n (%)					Mean (SD)[a]	Mean % (SD)[b]
		Never	Rarely	Sometimes	Often	Always		
	Counselling						**23.97 (5.24)**	**60.6 (18.7)**
P1	I provide counselling regarding IUCD to clients	3 (1.6)	22 (11.6)	45 (23.7)	77 (40.5)	43 (22.6)	3.71 (1.00)	
P2	I provide counselling regarding Implanon to clients	4 (2.1)	28 (14.7)	62 (32.6)	67 (35.3)	29 (15.3)	3.47 (0.99)	
P3	I explain the advantages of LARC during counselling	8 (4.2)	20 (10.5)	38 (20.0)	81 (42.6)	43 (22.6)	3.69 (1.07)	
P4	I use visual aids (for example, flipcharts and pictures) while providing counselling regarding LARC	27 (14.2)	32 (16.8)	53 (27.9)	52 (27.4)	26 (13.7)	3.09 (1.25)	
P5	I explain LARC to clients who are planning to use other contraception	11 (5.8)	27 (14.2)	58 (30.5)	68 (35.8)	26 (13.7)	3.37 (1.07)	
P6	I recommend IUCD to clients	4 (2.1)	28 (14.7)	63 (33.2)	69 (36.3)	26 (13.7)	3.45 (0.97)	
P7	I recommend Implanon to clients	4 (2.1)	38 (20.0)	83 (43.7)	49 (25.8)	16 (8.4)	3.18 (0.92)	
	Clinical evaluation						**8.13 (1.80)**	**76.6 (22.5)**
P8	I assess sexually transmitted disease risk before IUCD insertion	12 (6.3)	14 (7.4)	35 (18.4)	64 (33.7)	65 (34.2)	3.82 (1.17)	
P9	I check blood pressure readings before Implanon insertion	7 (3.7)	3 (1.6)	14 (7.4)	66 (34.7)	100 (52.6)	4.31 (0.95)	

Table 4. Continued

No	Item	Answer response, n (%)					Mean (SD)[a]	Mean % (SD)[b]
		Never	Rarely	Sometimes	Often	Always		
	Total score						**32.07 (6.10)**	**64.1 (17.0)**
	Insertion (for doctors only, n=86)							
P10	I perform IUCD insertion	28 (32.6)	22 (25.6)	23 (26.7)	6 (7.0)	6 (7.0)	2.29 (1.20)	
P11	I perform Implanon insertion	25 (29.1)	13 (15.1)	26 (30.2)	12 (14.0)	9 (10.5)	2.62 (1.32)	

[a]Mean of raw score, [b]Mean of percentage score.
SD: Standard deviation, IUCD: Intrauterine contraceptive device, LARC: Long-acting reversible contraception

Table 5. Factors associated with knowledge, attitude and practice of LARC provision (n=190)

Variables	Multiple linear regression					
	Knowledge		Attitude		Practice	
	Adjusted b[a] (95% CI)	p-value	Adjusted b[a] (95% CI)	p-value	Adjusted b[a] (95% CI)	p-value
Provider type						
Nurse	Ref.	**<0.001**	-	-	-	-
Doctor	8.40 (3.76, 13.05)					
Formal LARC training						
No	Ref.	**0.002**	-	-	-	-
Yes	7.47 (2.81, 12.12)					
Awareness of LARC insertion service						
No	Ref.	**0.031**	-	-	-	-
Yes	8.92 (0.82, 17.02)					
Years working as HCW	-	-	0.36 (0.23, 0.50)	**<0.001**	0.74 (0.43, 1.04)	**<0.001**

[a]Adjusted regression coefficient. Forward, backward and stepwise methods were applied. No interaction between independent variables and no multicollinearity problem.
Only significant variables in multiple linear regression were included in the table.
LARC: Long-acting reversible contraception, HCW: Healthcare worker, CI: Confidence interval

Doctors demonstrated a higher knowledge score of 8.40 (95% CI: 3.76, 13.05; p<0.001) compared to nurses when adjusted for other variables. HCWs with formal LARC training had knowledge scores 7.47 higher (95% CI: 2.81, 12.12; p=0.002) than those without such training when adjusted for other variables. Additionally, those who were aware of LARC insertion services at their healthcare facilities had higher knowledge scores by 8.92 (95% CI: 0.82, 17.02; p=0.031) than those who were not, when adjusted for other variables.

In the attitude section, eight variables demonstrated a p-value of <0.25 in univariable analysis (age, marital status, education, category of HCW, years working as HCW, years working in MCH, number of clients, and clinic with or without FMS). These variables were included in the multivariate analysis. Multiple linear regression showed that only years of experience in MCH had a significant association with attitude percentage scores towards LARC provision. With each additional year of experience in MCH, attitude scores increased by 0.36 percentage points (95% CI: 0.23, 0.50; p<0.001).

In the practice section, eleven variables exhibited a p-value of <0.25 in univariable analysis, namely age, sex, marital status, education, category of HCWs, years working as HCWs, years working in MCH, number of clients, formal LARC training, number of children, and clinic with or without FMS. These eleven variables were subsequently included in the multivariate analysis. Similar to the attitude section, the sole significant factor associated with the percentage score in the practice section was the number of years of experience in MCH. An extra year of MCH experience increased practice percentage scores by 0.74 (95% CI: 0.43, 1.04; p<0.001).

Discussion

This study evaluated the KAP of LARC provision among HCWs in Kelantan, Malaysia, and explored their associated factors using a locally validated questionnaire. The findings revealed that while HCWs demonstrated relatively high knowledge and practice levels regarding LARC provision, their attitudes toward it were less favorable. Higher knowledge levels were observed among doctors, those with formal LARC training, and those aware of LARC insertion services at their healthcare facilities. Additionally, longer experience in MCH services was associated with more positive attitudes and better practices towards LARC provision.

The majority of the participants were female, which can be attributed that all nurses were female, and most doctors in the MCH Unit were also women. This female dominance is consistent with a similar study conducted among HCWs in MCH in Selangor, Malaysia (18). Additionally, in this study, LARC was the most favored contraceptive method among HCWs, in contrast to the general population, who preferred short-acting methods such as pills, injections, and condoms (19). This preference among HCWs for LARC may be due to their being more up-to-date with the evidence supporting LARC, making them more comfortable using the method themselves (20).

The overall knowledge score in this study was similar to that found in other research on IUCD knowledge in Malaysia and Nepal, with scores of 68% and 61.4%, respectively (10,21). In contrast, the average baseline knowledge score among Canadian HCWs regarding IUCD was 82.8% (22). However, a direct comparison of the scores between these settings is challenging because the survey questions and target participants were different.

The present study revealed participants' confusion regarding Implanon's efficacy duration, possibly due to confusion with IUCD, which is effective for up to five years. This misinformation might lead HCWs to provide clients with inaccurate information, influencing their contraceptive decisions (23). Furthermore, a significant portion of the participants lacked awareness regarding the potential cramping pain during the early stages of LARC insertion. Awareness of such side effects is essential, enabling HCWs to implement preventive measures that alleviate clients' discomfort and prevent this issue from discouraging others from choosing this method. Additionally, providing clients with accurate and detailed information about side effects when initiating a method has been shown to increase continuation rates (24).

In this study, only half of the participants were aware that an IUCD can be inserted at any phase of the menstrual cycle, which is not consistent with the WHO's recommendation (17). Research has also shown that there is no significant difference in pain scores or ease of IUCD insertion whether it is performed during or outside of menstruation (25). Furthermore, awareness of immediate post-partum IUCD insertion was low in this study, in contrast to higher levels of awareness reported in France (26) and Nepal (21).This misunderstanding may hamper timely LARC insertion, particularly for clients experiencing barriers to accessing contraception, such as those who reside in rural areas (27).

The overall attitude score was low, largely influenced by a particularly poor performance in the "client-related" factor. This score was lower than a study conducted among pediatricians and nurses in New York City, where the score was 63.3% (28). In the present study, the majority of HCWs perceived the LARC as unsuitable for specific groups of women, such as those who are nulliparous, unmarried, or have a history of PID or ectopic pregnancy. These findings are consistent with previous studies, which demonstrated the common misconception about LARC eligibility for certain clients (29,30). This attitude contradicts the guidelines outlined by the WHO in the "Medical eligibility criteria for contraceptive use" and "Family planning: a global handbook for providers", which report that LARC is safe and suitable for these groups of women (8,17). Such attitudes can limit women's access to a wide range of contraceptive choices, restricting their ability to make well-informed decisions. To address this, HCWs are encouraged to use the Medical Eligibility Criteria mobile application, developed by the WHO, for contraceptive use (31). This tool provides easy access to updated information on the medical eligibility of LARC, which can help reduce misconceptions, ensure adherence to guidelines, and ultimately foster confidence in providing evidence-based care.

Furthermore, a smaller proportion of the respondents in this study agreed that LARC counselling is time-consuming, than in another study, which found that two-thirds of HCWs believed they needed more time to counsel about LARC compared to other contraceptive options (28). Therefore, the HCWs in our study demonstrated a more favorable attitude towards LARC provision, suggesting that they did not perceive time as a significant barrier. Despite the government covering the expense of LARC through subsidy, a minority of HCWs remained hesitant to recommend LARC, citing concerns about its perceived high-cost. It is noteworthy that while LARC methods have a higher upfront cost, they become cost-saving within the initial two years of use (32).

Overall, the high total percentage for the practice section suggested a favorable attitude towards the provision of LARC provision. Notably, counselling and recommendations for IUCD were more frequent than for Implanon. This trend is in line with the higher prevalence of IUCD usage in Malaysia compared to that of Implanon (1) implying that HCWs might be more accustomed to IUCD.

Almost one-third of doctors never perform IUCD insertion or Implanon insertion. This aligns with a similar proportion of participants who thought that many doctors lacked competence in LARC insertion, and who found the procedure difficult. These observations resonate with the fact that more than half of HCWs have not undergone formal LARC training in the past five years. The issue of incompetency in LARC insertion could limit LARC insertion services and prevent timely insertions.

This study revealed that doctors have exhibited higher knowledge scores regarding LARC than nurses. This aligns with findings from an Australian study, which reported that general practitioners had greater knowledge about implants compared to practical nurses (33). A Malaysian study also highlighted that doctors had better contraceptive knowledge scores compared to nurses (34). This disparity can be attributed to the more

advanced and extensive medical training among doctors compared to nurses. The present study also demonstrated that HCWs who were aware of the LARC insertion service in their healthcare facilities had higher knowledge scores compared to those who were not. This may be due to their direct exposure and familiarity with the LARC procedure.

The present study found that HCWs who received formal LARC training demonstrated higher knowledge scores compared to those without such training. Similarly, a case-control study in China showed that HCWs who underwent LARC training via mobile videos had higher knowledge scores compared to the control group (30). Furthermore, a study in Nepal indicated that more recent training was associated with higher overall knowledge scores on IUCD (21). While previous studies suggested that training could enhance attitude and practice scores (30,35), this present study found no significant association between formal LARC training and attitude or practice scores. A study in Nepal showed that even though a three-day training improved the HCWs' attitude towards client selection, biases persisted towards certain groups of clients at 6 and 24 months after the intervention (27). It suggests that ongoing training would be more effective in reducing biases among HCWs, as opposed to one-time training sessions.

This study discovered that HCWs with more years of experience in MCH exhibited more favorable attitudes and practices towards LARC provision. This corresponds with another study conducted in Selangor, Malaysia, indicating a significant association between the duration of working in MCH and the confidence of providing contraceptive counselling (34). Another study found that HCWs with greater experience, measured by the number of IUCDs inserted, demonstrated better attitudes towards LARC eligibility (36).

This finding was also consistent with the Dreyfus Model of Skill Acquisition, which describes the progression from novice to expert in any skill domain (37). The experience provides exposure to a diverse range of cases and scenarios, enabling HCWs to make well-informed decisions. Experienced HCWs can apply their knowledge to real-world clinical settings, even in complex situations (37). Therefore, intervention should focus on skill enhancement for less experienced HCWs, especially those who are new to MCH services. Mentorship programs can be adopted where experienced HCWs act as role models by sharing their experiences with the new ones to improve the attitudes and practices of HCWs (5).

Rather than blaming HCWs for their misconceptions, biases, or incompetence, the focus should be on supporting them through a comprehensive intervention aimed at improving LARC provision (38). It should incorporate both theoretical and practical training, complemented by a mentorship program to improve KAP of HCWs. An outstanding example is the maternal and child survival program, which implemented a modular LARC training encompassing theoretical knowledge, client eligibility assessment, counselling techniques, and insertion procedures (39). Certified experienced HCWs specializing in LARC provision mentored a group of mentees, providing continuous support. Once mentees were confident in providing LARC services, they could then be assessed and certified. In Kenya and Zambia, the mentorship program had successfully expanded choices of methods.

The strength of this study lies in employing a valid, reliable, and culturally appropriate questionnaire in the Malay language to assess KAP on LARC provision among local HCWs. Unlike other studies, which used inadequately validated questionnaires, our instrument ensures effective measurement of KAP, enhancing the likelihood of deriving meaningful conclusions. Additionally, the study established a baseline for KAP of implant among Malaysian HCWs and represents the first study on the KAP of LARC provision among nurses. This distinguishes our study from the previous local study, which focused solely on the KAP of IUCD among doctors.

However, the study, which was carried out in the northeastern region of Malaysia, may not capture unique cultural aspects distinct from other regions, posing a limitation in generalizing the findings to the entire country. Despite this, it is noteworthy that HCWs frequently relocate between states throughout their careers, exposing them to various cultures in Malaysia. In addition, this study specifically focused on primary HCWs within the public sector, omitting those in private primary healthcare sectors and family planning providers in hospital settings. However, the majority of clients in Malaysia received family planning services from the public primary healthcare facilities.

Conclusion

The current study explored the KAP of LARC provision among HCWs using the locally validated KAPP-LARC questionnaire. While the overall knowledge level among HCWs was relatively high, the study revealed some misinformation regarding fundamental LARC knowledge. A significant association was identified between LARC knowledge and both formal LARC training and the HCW category. Thus, it is recommended to develop targeted training programs with a particular focus on nurses, covering both fundamental and updated knowledge of LARC. The study also revealed a markedly low attitude score. Although practice scores were relatively high, there was a lack of counselling and recommendations for Implanon, compared to IUCD. Additionally, the study demonstrated that HCWs with more years of experience in MCH tended to have more favorable attitudes and practices in LARC provision. An ongoing mentorship program could enhance HCWs' attitudes and practices by facilitating the transfer of values and skills from more experienced HCWs to those newer to the field.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and the good clinical practice guidelines. Ethical approval was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia [ID-22-01463-WYY (IIR)], and the Research Ethics Committee (Human), University Sains Malaysia (JEPeM Code: USM/JEPeM/22060427, date: 08.08.2022).

Informed Consent: Written informed consent was obtained from all participants.

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Footnotes

Authorship Contributions

Concept: N.N.J., T.A.T.I., S.M.H., Design: N.N.J., T.A.T.I., S.M.H., Data Collection or Processing: N.N.J., Analysis or Interpretation: N.N.J., T.A.T.I., S.M.H., Literature Search: N.N.J., Writing: N.N.J., T.A.T.I., S.M.H.

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Diabetic foot resulting from post-earthquake care deficiencies

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ABSTRACT

Aims: After natural disasters such as earthquakes, which affect many people, there can be an increase in flare-ups of chronic diseases because of the chaos, destruction, and insufficient resources resulting from the disaster. The aim of this study was to evaluate cases of diabetic foot that developed due to lack of care after an earthquake in Türkiye.

Methods: This descriptive research was conducted in the diabetic foot clinic of a training and research hospital between March and September 2023. Socio-demographic and diabetic foot-related data were recorded. In addition, in-depth face-to-face interviews were conducted individually with each patient using semi-structured questions based on qualitative descriptive methods. Diabetes education given during the wound healing process was also evaluated.

Results: The study included nine diabetic foot patients (mean age: 58.11±12.05 years, all male), with a mean diabetes duration of 17.33±8.7 years. Three main themes emerged from the analysis results. There are challenges related to diabetic foot care in the earthquake region. Firstly, with or without awareness, diabetic foot ulcers can develop because of the difficult living conditions. Secondly, diabetic foot patients injured in the earthquake experience problems accessing interventions and care from healthcare teams in the region. Lastly, there is a lack of information on the prevention, protection, care, and treatment of diabetic foot in earthquake victims.

Conclusions: The findings of this study demonstrated that after an earthquake, diabetic patients were late to notice foot ulcers, experienced delays in accessing healthcare personnel and services, and needed information and guidance about diabetic foot.

Introduction

Among the most recent disasters this century, 2 earthquakes occurred consecutively in Türkiye on 6 February 2023, almost completely destroying 11 large cities. More than 50,000 lives were lost and more than 100,000 people were injured in earthquakes with magnitudes of 7.7 and 7.8 on the Richter scale, in the town of Pazarcık in Kahramanmaraş province at the epicentre of the quake (1). Although the negative effects of earthquakes are directly related to the severity of the quake, insufficient precautions and efforts to reduce these effects are influenced by factors such as the proximity of residential areas to the epicenter, the number of vulnerable groups (children, the elderly, the disabled) in densely populated communities, and other disasters that can be triggered by the earthquake (2).

In addition to causing mass deaths and injuries, earthquakes prevent the effective control, treatment, and care of chronic diseases of survivors (3). The chaotic conditions, severe stress, insufficient resources, and destruction resulting from the

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disaster cause disease flare-ups, especially in individuals with a chronic disease. This can then cause an increase in disability and mortality rates (4).

Previous studies have reported that the patients most often affected are those with diabetes, heart disease, hypertension, stroke, and chronic lung diseases (5). In the period after an earthquake, damage to healthcare centres, disruptions to transport networks, and negative environmental conditions result in restrictions to medical supplies for patients with chronic diseases and disrupt access to healthcare and a healthy, balanced diet. Just as for other chronic diseases, this leads to glycemic dysregulation in diabetic patients (6-10).

Diabetes is a disease that requires lifelong adherence to medical treatment and healthy nutrition (9). In the weeks following an earthquake, the diabetes adherence process is negatively affected for reasons such as lack of shelter, staying warm, stress, and participating in search and rescue operations. The inability to provide suitable conditions after an earthquake, reduced hygiene facilities, and failure to meet short-term needs could be preparatory factors for the formation of diabetic foot. Psychological stress also has negative effects on diabetes control (11). In previous literature, being under severe stress has been associated with increased glycated hemoglobin A1c (HbA1c) and poor glycemic control in the early period after an earthquake (12). The deaths of family members in the earthquake, material losses, and the fear of experiencing another earthquake can cause prolonged psychological stress (9,13). In a study by Inui et al. (14), of the effect of the Kobe (Japan) earthquake on stress and glycemic control, it was reported that HbA1c levels reached a peak in the 3rd and 4th months after the earthquake, and there was a relationship between life-threatening stress and worsening metabolic control in diabetic patients. In addition, the development of diabetes complications is caused by reasons such as dietary changes, missed medications, poor glycemic control, and disruptions to healthcare services (15). Of the acute complications after an earthquake, diabetic foot infections are one of the most important complications that increase hospitalisation rates in diabetes (16). The presence of these restrictions can be a significant determinant of the development of diabetic foot.

Therefore, the aim of this study was to investigate the reasons for the development of diabetic foot in patients who presented at a tertiary-level diabetic foot centre and were diagnosed with diabetic foot at risk of or with the recommendation of below-the-knee amputation due to care deficiencies after the earthquake in which they were injured, through qualitative examination of access to healthcare, and the diabetic foot care and treatment conditions, and the quantitative examination of nursing care and education after discharge.

Methods

Study design and participants

This research was conducted in a diabetic foot clinic of a training and research hospital between March and September 2023. This study was designed as descriptive research using both qualitative and quantitative methods. When considering the nature of life experiences after the earthquake, qualitative methodology was used. The study population comprised patients who presented at a tertiary-level diabetic foot centre and were diagnosed with diabetic foot.

The study sample consisted of nine patients diagnosed with diabetic foot who were injured during the earthquake and were either recommended for or at risk of below-the-knee amputation due to deficiencies in post-earthquake care. All were transferred to our center, located 595 km from Kahramanmaraş, the epicenter of the earthquake, after the disaster. Individuals who did not speak Turkish, were under 18 years old, or were unwilling to participate were excluded from the study.

The study protocol was in accordance with the ethical principles of the Declaration of Helsinki and was approved by the University of Health Sciences Türkiye, Gülhane Scientific Research Ethics Committee (desicion no.: 2023-284).

Data collection

The data were collected from patients hospitalised for treatment at a tertiary-level diabetic foot centre within 7 months after the earthquake. The participants were informed about the study and all provided written informed consent. After explaining the purpose of the study, the patients were questioned about socio-demographic characteristics. A record was also made of the diabetic history of the patients and information about the diabetic foot characteristics at the time of presentation, treatment, and care approaches. In-depth face-to-face interviews were then held separately with each patient using semi-structured questions. Care was taken to ensure that the interview rooms were quiet to allow uninterrupted discussion. The questions used in the research were prepared based on qualitative descriptive methods (17).

Descriptive, open-ended questions about the diabetic foot and coping methods were asked in respect of “diabetic foot wounds due to deficiencies in care after the earthquake, which were not earthquake injuries”. The open-ended questions included, “How did the wound on your foot form?”, “What did you do when you first noticed the wound on your foot?”, “What kind of care method did you follow for the wound on your foot?”, “Have you had difficulties related to the dressing?”, “What did you do to cope with the difficulties you experienced with the dressing and care?”. Each interview lasted approximately 30-40 minutes. In this study, data saturation was reached after 9 face-to-face interviews.

While the patients were hospitalised and receiving care, they also received diabetic foot education. The diabetic foot education was prepared with reference to the "Diagnosis, Treatment, and Prevention of Diabetic Foot Wounds and Infection: National Consensus Report" (18), and was evaluated during outpatient visits for wound care and follow-up in an average 3-month period following discharge. The education was organized under the headings of glycemic regulation, foot care, off loading, exercise, nutrition, and wound care.

Statistical Analysis

Quantitative parameters were analyzed using SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were stated as the mean±standard deviation values for numerical variables and as number (n) and percentage (%) for categorical variables. In the analysis of the responses given by the patients using interview forms, the inductive method and content analysis were used. The data analysis was performed based on the content analysis explained by Graneheim and Lundman (19).

The qualitative research data obtained in the study were analyzed in four stages: First, the transcribed data were confirmed. The interview notes were written in full, and the transcripts were reviewed several times by the researchers to obtain a general understanding. In the second stage, researchers attempted to find the conceptual meaning of the statements given by the patients. Coding was then performed according to the concepts found within the aim and conceptual framework of the study. In the third stage, significant units were considered in an abstract way, and labelled with codes. The codes were categorised through comparisons of similarities and differences. From the starting point of the codes, themes were identified that could be gathered under certain categories at a general level. When forming the themes, attention was paid to whether or not a significant whole was formed or not, and similar concepts were gathered under the same theme. Finally, in the fourth stage, the data were organized according to the codes and themes, and definitions were formulated. At this stage, quotes were taken from the statements which best emphasized the opinions of the patients without any commentary or opinions from the researchers. To confirm the data, comments from colleagues, and handwriting analyses of the participants were used. The findings were given to specialists in two subjects for examination, and when the same result was reached and reported, consistency and reliability of the data were confirmed. Repeatability of the study was ensured through detailed explanations of the data. The emerging themes, along with descriptive patient information and data on the diabetic foot status, were interpreted and discussed by the researchers.

Results

The study included nine diabetic foot patients (mean age: 58.11±12.05 years, all male), with a mean diabetes duration of 17.33±8.7 years. The mean time to epithelialization of the diabetic foot in the long-term follow-up of the patients was 103.67±32.61 days. The characteristics of the study participants are shown in Table 1.

As a result of the analysis of qualitative data, three main themes were established:

1. The awareness of ulcers on the foot of diabetic individuals in the earthquake region

Hospitals in Kahramanmaraş, which was the epicentre of the earthquakes, tried to provide healthcare services in field hospitals, family health centres, tent cities, and mobile healthcare teams. After the earthquake, some patients and the injured were treated as far as possible, and attempts were made to normalize their conditions.

After experiencing these major earthquakes, those affected first rushed to save themselves and their families and to help other people. Although the person was a diabetic patient, no attention was given to their foot health or care. Thus, the development of diabetic foot wounds was inevitable.

In earthquake victims who were diagnosed with type II diabetes mellitus, diabetic foot ulcers developed, either noticed or unnoticed, because of the difficult living conditions. The statements of patients who experienced this are given below:

"I rushed outside after the earthquake. It was cold and raining. My children suggested that we take our shoes from home. There was a piece of glass inside my shoe, and I walked around for 4-5 days on this piece of glass. The glass had gotten into my shoe from broken windows at the time of the earthquake. I didn't take my shoes off for four days. When I noticed the wound, I went to the hospital four days after the earthquake" (Patient 1).

"The wound on my foot developed within two days. The weather was cold, with snow and rain falling, and we didn't have enough clothes. We were outside. We were trying to rescue people from under the rubble. When my wife took my socks off, she noticed that there were blisters on both sides of my foot" (Patient 2).

"After the earthquake, my foot was in a shoe and a sock the entire time for 10 days. There was nowhere to change the medical dressing for 10 days. You could not go into your home, the hospitals were not working, and everywhere was destroyed, completely razed to the ground (Figures 1, 2)" (Patient 3).

2. Problems of access to healthcare personnel for individuals with diabetic foot

Many diabetic patients were living on the streets, in vehicles, or in containers after the earthquake, and could not control their blood sugar because of the difficult living conditions. Diabetic

Table 1. Demographic and clinical data of patients with diabetic foot linked to post-earthquake care deficiencies (n=9)

Demographic and clinical characteristics	
Age (years), mean ± SD	58.11±12.05
Gender, n (%)	
Male	9 (100.0)
Marital status, n (%)	
Married	8 (88.9)
Single	1 (11.1)
Educational level, n (%)	
Primary school (5 years)	5 (55.6)
Middle school (3 years)	3 (33.3)
University and above (4 years and above)	1 (11.1)
Diabetes mellitus duration (years since diagnosis), mean ± SD	17.33±8.7
Employment status, n (%)	
Employed	2 (22.2)
Unemployed/retired	7 (77.8)
Living condition, n (%)	
Alone	1 (11.1)
With family	8 (88.9)
City of living, n (%)	
Gaziantep	1 (11.1)
Hatay	3 (33.3)
Kahramanmaraş	5 (55.6)
Diabetes mellitus type, n (%)	
Type 1	1 (11.1)
Type 2	8 (88.9)
Diabetes mellitus treatment, n (%)	
OAD	1 (11.1)
Insulin	3 (33.3)
OAD+insulin	5 (55.6)
Diabetes mellitus family history, n (%)	
Yes	8 (88.9)
No	1 (11.1)
Other chronic diseases, n (%)	
Yes	7 (77.8)
No	2 (22.2)
Allergy, n (%)	
Yes	3 (33.3)
No	6 (66.7)
WAGNER grade, n (%)	
W 2	3 (33.3)
W 3	4 (44.4)
W 4	2 (22.2)
PEDIS grade, n (%)	
P 2	7 (77.8)
P 3	2 (22.2)
Wound care and treatment methods, n (%)	
Surgical debridement and intralesional epidermal growth factor (i-EGF)	2 (22.2)
Enzymatic debridement	4 (44.4)
Minor amputation	1 (11.1)
Minor amputation and i-EGF	2 (22.2)
Mean time from the wound formation to presentation at hospital (days), mean ± SD	14.22±12.46
Epithelialisation duration, mean ± SD	103.67±32.61

SD: Standard deviation, OAD: Oral antidiabetic, i-EGF: Intralesional epidermal growth factor

control was negatively affected in the acute period because of problems seeking shelter, discontinuation of treatment, because drugs were lost, and psychological stress. Earthquake victims who were diabetic patients needed interventions and care from regional healthcare teams due to wounds developing on their feet, but confusion and chaos caused problems in accessing healthcare services. The statements of the patients in this context are given below:

"For 1 week to 10 days, I didn't take my shoes off, and I could not care for my feet. The wound became inflamed, and then became bigger. After 10 days, I noticed the wound when I took my socks off. There were no dressing materials. There were a few staff working in the hospital. They were changing dressings outside because the hospital was about to be overwhelmed" (Patient 4).

"You couldn't go into your home, and the hospital wasn't operational, so I couldn't change the dressing. I had no means of going to the hospital. I couldn't receive any dressing or care for my foot. I had to wait there for 10 days. When I came here after 10 days, treatment and care were started" (Patient 5).

"The time from the wound's formation to hospital admission was 20 days. I couldn't come. There was a wound on my foot and blisters on my toes. I stayed out in the cold with only slippers on my feet. I couldn't protect my foot. When I first noticed it, I burst the blisters with a needle to let out the water; then the skin on my foot ruptured, and the wound got bigger. I wrapped gauze around it. I couldn't clean the wound. For 20 days, I washed the wound on my foot with water, wiped it, and then wrapped it in gauze. There was no cloth, so I cut up a sock to make a pad, then wrapped it around the pad. There were no materials" (Patient 6).

3. Information needs of earthquake victims with diabetic foot

Diabetes is a chronic disease that can affect the individual in many aspects and therefore, there is a great deal of information that patients must learn and apply. However, the current study participants had a tendency to neglect foot care recommendations. In addition, the experience of the earthquake



Figure 1. Diabetic foot patient post-earthquake and treatment process



Figure 2. Foot protective care and epithelialization

by diabetic patients created more difficult conditions associated with the development of diabetic foot. Another reason for the greater exposure to diabetic foot development was the patients' lack of knowledge about the prevention, protection, care, and treatment. The statements of the patients in this context are given below:

"I applied no dressing for 6 days. The wounds were getting bigger, and up to that time I applied no dressing. I didn't know that there would be a wound like that, so I didn't apply a dressing. Subsequently, they sent me here, saying that I needed an operation. There were things falling all over, and due to the earthquake, I struck my ankle somewhere when I was running" (Patient 2).

"I couldn't tend to my foot during the earthquake conditions. We came here, and my wife did it. It was painful for a week and I couldn't touch it. We got dressing materials from the pharmacy and my wife applied the dressing. The first days were difficult, but we came to the hyperbaric unit for treatment. A family friend said that I had diabetes and that I should come here and I could be treated with ozone therapy. I have had no education about regulating blood sugar" (Patient 7).

"I kept warm in the open air with the heat of the stove; one night I slept in a tent. When I got up in the morning, I saw that my feet were blistered" (Patient 5).

"On the day of the earthquake, I burned my foot. There was a fire outside, and everybody was gathered around it. When I was sitting, I stretched out my feet in sandals to the fire, and my wife realized, but I didn't notice that I had burned my foot. Blisters had formed in the shape of balloons. I didn't do anything. I thought that if I burst the blister, there would be a wound, and it would be worse, so I did nothing. I put my sock on over it, I did nothing to care for my foot. At that time, I was just experiencing turmoil about life" (Patient 8).

"My children said to take our shoes from home. There was some glass inside my shoe and I walked around for 4-5 days on this piece of glass. The glass had gone into my shoe from broken

windows at the time of the earthquake. I didn't take my shoes off for 4 days. I wore my shoes without socks" (Patient 9).

"I burned my foot in the fire outside. I stretched out my feet to the fire, and they burned" (Patient 10).

The data related to the hospitalisation of the patients who developed diabetic foot, including glycemic regulation, foot care, exercise, protection from weight-bearing, nutrition education, and post-discharge applications is shown in Table 2. The effects of the education given to the patients on HbA1c measurements 3 months later are presented in Table 3.

Table 2. Data on education provided during hospitalization and applications after discharge in diabetic foot patients linked to post-earthquake care deficiencies (n=9)

Glycemic regulation	n (%)
Fasting and post-prandial glycemia monitoring	
Yes	6 (66.7)
No	3 (33.3)
Glycemic measurement <180 mg/dL	
Yes	6 (66.7)
No	3 (33.3)
Regular use of antidiabetic drugs	
Yes	6 (66.7)
No	3 (33.3)
Regular physician check-ups	
Yes	6 (66.7)
No	3 (33.3)
Foot care	
Daily washing	
Yes	8 (88.9)
No	1 (11.1)
Moisturising	
Yes	6 (66.7)
No	3 (33.3)
Weekly foot checks	
Yes	5 (55.6)
No	4 (44.4)
Selecting suitable socks	
Yes	6 (66.7)
No	3 (33.3)
Exercise and prevention from weight-bearing	
Exercise management in bed	
Yes	6 (66.7)
No	3 (33.3)
Adherence to off loading	
Yes	6 (66.7)
No	3 (33.3)
Nutrition	
Protein-rich diet	
Yes	8 (88.9)
No	1 (11.1)
Daily fluid intake	
Yes	8 (88.9)
No	1 (11.1)
Prevention from high glycemic index foods	
Yes	5 (55.6)
No	4 (44.4)

Discussion

This study demonstrated that diabetic foot ulcers can develop in earthquake victims due to challenging living conditions, limited healthcare access, and insufficient knowledge about prevention and care.

The destruction of ecological balance and social order, high loss of life, and lack of water, energy sources, and transport services in living areas are said to constitute a disaster. Disasters cause destruction that exceeds the capacity of local people to cope. The destruction may cause social order to deteriorate to such an extent that external assistance is required. Patients with long-term chronic diseases and diabetic patients, even if not injured at the time of the earthquake, constitute a high-risk group after an earthquake because of the high risk of morbidity and mortality due to "deaths associated with the interruption from healthcare services". Healthcare personnel providing service in the region and those planning healthcare services are responsible for the triage of patients to appropriate centres at risk of morbidity and mortality due to diabetic foot. Therefore, there is a need for the education and training of healthcare personnel in disaster conditions (4,20).

Due to the interruption of healthcare services for patients transferred to or presenting at our centre, the rescue plans after an earthquake include triageing to centres that are far from the affected area, where they can receive first-line treatment before the risk to life and limb loss develops. When the triage of these patients is delayed, the resulting limb loss and risk of mortality require high-cost treatments.

Based on the findings the qualitative interview data of this study, three main themes were discussed. Although all the patients in the study were long-term diabetic patients, it was

Table 3. HbA1c levels at admission and three months after education

Patient number	Admission (%)	3-months (%)
1.	10.6	7.7
2.	11.8	8.6
3.	11.0	10.0
4.	9.3	6.2
5.	9.7	7.8
6.	9.2	7.0
7.	7.2	6.2
8.	9.1	8.0
9.	8.9	7.5

HbA1c: Glycated hemoglobin

understood that they lacked information in respect of exposure to the development of diabetic foot, problems experienced in accessing healthcare services, protection of diabetic foot, and preventative care because of the many negative factors following an earthquake. Therefore, importance must be given to the development of appropriate and specific interventions for diabetic patients in extraordinary circumstances, the protection of diabetic foot in an earthquake, the elimination of knowledge deficiencies on the subjects of treatment and care if diabetic foot develops, and the management of diabetic foot in tertiary-level centres. There is also a need to increase the knowledge and awareness of nurses, in particular, on managing diabetic foot patients who are at risk of limb loss.

Previous studies have shown that disasters worsen diseases such as diabetes and its complications (16). HbA1c values are important in the evaluation of diabetes compliance and glycemic control (21). Following the Kumamoto earthquake, the HbA1c values of 557 diabetic patients increased in the 3rd-4th months after the earthquake, and this was reported to be associated with a lack of antidiabetic drugs, insufficient availability of food, destruction, and patients being unable to manage their condition independently. Anxiety and stress can also lead to a deterioration in glycemic control (22). After the North Osaka earthquake in 2018, HbA1c levels in diabetic patients were determined to be significantly higher compared to the years before the earthquake, and the rate of deterioration in HbA1c was higher in the regions where the earthquake occurred (6,22). This can increase the predisposition to diabetic foot. High HbA1c levels have also been reported to increase Wagner/PEDIS grades in diabetic foot, worsen disease severity, and contribute to tissue loss (23). When there are such conditions, the ongoing problems of shelter in the days and weeks after an earthquake, psychological stress, the need to keep warm, and participation in search and rescue efforts negatively affect diabetes adherence. This occurs due to issues such as not paying attention to foot care, insufficient food availability, and lack of antidiabetic drugs, and these factors can strongly contribute to the development of diabetic foot.

Considering diabetic foot patients who are earthquake victims experience problems in accessing healthcare teams in the region, there is need to rethink the healthcare system's disaster approach and plan effective strategies that will provide access to medical and care services for patients in natural disasters (24). Statistics has shown an increase in hospital admissions of patients with at least one chronic disease during disasters. For example, during the Sichuan earthquake, patients with diabetes constituted the highest proportion, accounting for 24% of presentations at city hospitals (25). In unexpected disasters, preparation to provide care to a vulnerable population is extremely important. The time from the development of diabetic foot to presentation at our tertiary-level diabetic foot centre was a mean of two weeks for the patients in the current study. Disruption in access to healthcare services can cause the development of diabetic foot and worsen prognosis.

Self-care management for diabetic patients is extremely important. In this way, patients with diabetes can continue a normal life. Nurses contribute to the self-care of diabetic patients through their roles as education and learning facilitators (26). Foot evaluation plays an important role in protecting against diabetic foot by teaching correct and regular foot care skills and forming these habits (27,28).

Unfortunately, many patients are not given adequate education about diabetes after being diagnosed. These deficiencies are partially due to inadequate education methodologies used by healthcare providers, and partially to a lack of standards and institutional education programs for patients (29).

From the statements of the current study participants, it was understood that they had not previously received any education about diabetes and did not have information about the development of diabetic foot. This demonstrates the need to establish guidelines for both patients and healthcare service providers with the aim not only of maintaining a normal life but also of meeting their needs in extraordinary disaster situations. As Türkiye is located in an earthquake zone, lessons about diabetes, and diabetic foot management in a period of disaster can be added to the diabetes school education. The role of nurses in diabetes disaster teams, who work in close collaboration with patients in the clinic environment, is of critical importance in addressing the needs related to diabetes and diabetic foot care (10). During normal periods, nurses should educate diabetic patients (30). Therapeutic patient education should be a comprehensive, planned, structured program, meeting clinical and psychological needs while taking the educational and cultural background of the individual into consideration. The healthcare professionals providing this education should check the information needs and whether the patient translates diabetic education into action (31).

It is recommended that wound healing and efforts to preserve the limb are undertaken by a multidisciplinary team. Nurses are indispensable components of this team. Evaluation of the data on practices after discharge and the education given during hospitalisation of patients who developed diabetic foot due to the earthquake shows that nursing education is expected to provide a positive contribution to the epithelialisation period and patient education.

This study was conducted with a small sample of diabetic foot patients in Türkiye, which may be a limitation in terms of generalizability. However, generalization is not the primary aim of qualitative research. Participants were selected through purposive sampling, which may introduce selection bias by favoring individuals with specific knowledge or experiences. In qualitative research, such bias is intentionally used to enrich theoretical

understanding and provide a detailed, accurate depiction of experiences. Despite the small sample size, it was considered sufficient to capture variation and maintain analytical depth.

Conclusion

This study demonstrated that diabetic foot ulcers can develop in earthquake victims due to challenging living conditions, limited healthcare access, and insufficient knowledge about prevention and care. In the training within the scope of disaster preparedness for nurses and healthcare personnel, the necessary information should be given about the care and management of individuals with diabetes after a disaster. In this way, diabetes and diabetic foot management can be successfully maintained in the event of a disaster.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Gülhane Scientific Research Ethics Committee (decision no.: 2023-284).

Informed Consent: The participants were informed about the study and all provided written informed consent.

Footnotes

Authorship Contributions

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

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Efficacy of intraoperative periarticular Ranawat solution in reducing hidden blood loss and transfusion requirements in hip fracture hemiarthroplasty: a randomized controlled trial

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Keywords: Hip fracture, hemiarthroplasty, periarticular injection, hidden blood loss, blood transfusion

ABSTRACT

Aims: This randomized controlled trial evaluated the efficacy of intraoperative periarticular Ranawat solution injection in reducing total and hidden blood loss (HBL), as well as allogeneic blood transfusion (ABT) rates, in elderly patients undergoing bipolar hemiarthroplasty for intra-articular hip fractures.

Methods: In this single-center trial (NCT06701695), 84 patients (aged 65-95) undergoing bipolar hemiarthroplasty between May 2020 and February 2022 were randomized to receive either the Ranawat solution injection or no injection. Primary outcomes were total blood loss (TBL), HBL, and ABT rate. Secondary outcomes included intraoperative blood loss (IBL), postoperative drainage volume, and hospital stay duration.

Results: The injection group included 41 patients (14 males, 34.1%; mean age 82.6±6.96 years), whereas the control group comprised 43 patients (18 males, 41.8%; mean age 81.5±8.47 years).The injection group showed significantly lower HBL (327.4±148.8 mL vs. 442.2±168.9 mL, p=0.013) and TBL (1100.2±423.4 mL vs. 1330.3±434.2 mL, p=0.049) compared to controls. ABT was required in 34.1% of the injection group versus 58.1% in controls (p=0.043). Ranawat solution reduced HBL by 26% and TBL by 17.2%. No significant differences were found in IBL or drainage volume, and no injection-related adverse effects were observed.

Conclusions: Intraoperative periarticular Ranawat solution injection effectively reduces perioperative blood loss and transfusion requirements in elderly patients undergoing hemiarthroplasty for hip fractures, supporting its use to enhance outcomes and safety in this population.

Introduction

Hip fractures among elderly individuals represent a significant global public health issue due to the high morbidity, mortality, and healthcare costs associated with their management. With the global increase in life expectancy, the incidence of fragility-related hip fractures continues to rise markedly. Recent epidemiological projections estimate that fragility-related hip fractures could surpass six million cases annually worldwide by the year 2050, highlighting an urgent need for effective clinical strategies to improve outcomes in this vulnerable population (1).

Surgical intervention for hip fractures, such as hemiarthroplasty, is associated with considerable perioperative blood loss. Postoperative anemia following hip fracture surgery has been linked to delayed functional recovery, increased morbidity, prolonged hospital stays, and elevated mortality rates (2). Moreover, a substantial proportion of patients who

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suffer from hip fractures require allogeneic blood transfusions (ABT), with reported rates ranging from 26.2% to 39.5% (3,4). Unfortunately, ABT may elevate the risk of surgical site infections, increase healthcare expenses, and extend hospital stays for this vulnerable population. On the other hand, a significant yet often overlooked aspect of perioperative blood loss in hip fracture surgery is "hidden blood loss (HBL)," referring to the blood lost into tissue compartments and not directly measurable intraoperatively. Foss and Kehlet (5) reported HBL to be up to six times greater than visible intraoperative loss, posing substantial risks for patient recovery.

Numerous strategies have been employed to mitigate perioperative blood loss, including topical epinephrine (EP) infusion, controlled hypotensive anesthesia, periarticular cocktail injections, and the application of cold saline (6-8). Periarticular cocktail injections have garnered attention due to their localized effects, directly targeting tissues surrounding the surgical site and thus minimizing systemic exposure and side effects (9,10). Despite this growing interest, the efficacy of specific cocktail formulations such as the Ranawat solution, comprising bupivacaine, dexamethasone, EP, and cefuroxime, has not been extensively evaluated for HBL reduction in hip fracture surgeries.

Therefore, this study aimed to evaluate the effectiveness of intraoperative periarticular Ranawat solution injections, in reducing total and HBL, and, consequently, the need for ABT in elderly patients undergoing hemiarthroplasty for intra-articular hip fractures. We hypothesized that this technique would significantly reduce perioperative blood loss and thus decrease ABT needs compared to standard procedures without periarticular injection.

Methods

Study design

This study was a single-center randomized controlled trial at our tertiary trauma center. The study protocol and design were approved by the Ankara City Hospital, No. 1 Clinical Research Ethics Committee (decision no.: E1-19-3292, date: 22.02.2019). Additionally, the study was registered in the ClinicalTrials.gov Protocol Registration System (trial number NCT06701695). All researchers involved in the study have agreed to the most recent version of the Helsinki Declaration. Patients enrolled in the study provided their consent after receiving comprehensive information included in the consent forms. The reporting procedures adhered to the guidelines outlined in the Consolidated Standards of Reporting Trials (11).

Inclusion and exclusion criteria

One hundred thirteen consecutive patients with intra-articular hip fracture (femoral neck fracture) (age range sixty-five to ninety-five) who were admitted to our institution and underwent bipolar hemiarthroplasty from May 2020 to February 2022, were initially assessed for eligibility, and 84 patients eligible for inclusion were randomized to either receive intraoperative periarticular Ranawat solution injections or not receive any injection at this institution. The exclusion criteria included: 1) extra-articular hip fractures (pertrochanteric fractures), 2) patients receiving any form of anti-aggregant, anticoagulant, or anti-thrombotic therapy prior to sustaining a hip fracture, 3) pathological fractures, periprosthetic fractures, or revision procedures, 4) presence of intolerance or allergy to any of the drugs utilized in the study, and 5) refusal to participate in this study (Figure 1).

Randomization

Upon obtaining informed consent, random numbers generated by statistical software were used to allocate patients based on their order of admission. Subsequently, patients were assigned to either the intraoperative periarticular Ranawat solution injection group or the control group (which did not receive intraoperative injections) in a 1:1 ratio using these random numbers. The randomization numbers were securely enclosed in opaque, sequentially numbered envelopes. These sealed envelopes were accessed by an independent researcher solely during the patient's anesthesia. During the trial, patients were kept unaware of their group assignments, ensuring they remained blinded to the study parameters. While the surgeon possessed knowledge of the group allocations, he was not directly involved in patient data analysis.

Description of cohort

In the study, patients were divided into two distinct groups: the "injection group", comprising those who received an intraoperative periarticular Ranawat solution injection, and the "non-injection group", comprising those who did not receive such injections. The periarticular injection solution used in our study was designed by adopting the cocktail sample used by Ranawat Orthopedic Center after knee and hip surgery (12). This regimen has been variously utilized in patients undergoing arthroplasty and has demonstrated its efficacy in reducing postoperative morbidity (12-14). Patients in the injection group were administered a 100 mL periarticular solution comprising 200 mg of bupivacaine (40 mL), 8 mg of dexamethasone (2 mL), 2 mg of 1:1000 EP (2 mL), 750 mg of cefuroxime (7.5 mL), and standard saline solution (48.5 mL). This solution was prepared in two 50 mL syringes. The first syringe containing 50 mL of the cocktail was injected into the capsule and gluteal muscles prior to femoral stem insertion. Following joint capsule closure, the second syringe containing 50 mL of the periarticular Ranawat solution injection was injected into the fascia lata muscle, subcutaneous tissue, and wound layers.

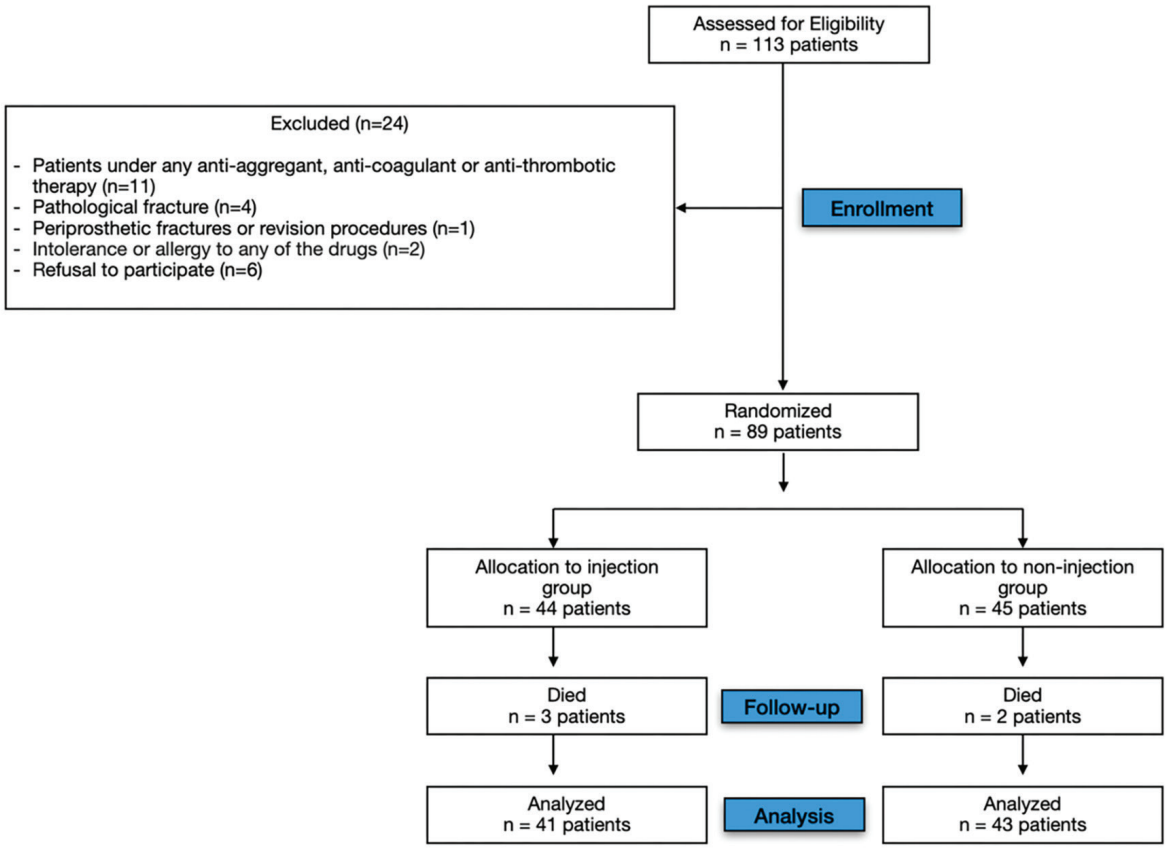


Figure 1. Flowchart of the study

Surgical procedures and postoperative rehabilitation

All surgical procedures were performed by the same surgeon using an anterolateral (Watson-Jones) approach and a cementless bipolar hemiarthroplasty prosthesis (Echo® Femoral Hip System-Zimmer-Biomet, Warsaw, IN). All patients underwent the same perioperative procedure. Elastic above-the-knee stockings are initiated at the diagnosis of hip fracture and continue to be worn for at least three more weeks postoperatively. Upon admission to our emergency services, the appropriate dosage of enoxaparin sodium, adjusted for patient weight, was promptly administered to all individuals presenting with hip fractures. This regimen was systematically maintained until the patients were discharged. All patients have been prescribed oral aspirin or enoxaparin sodium. The medical staff followed the patients' postoperative suction drains. Postoperative daily hemoglobin (Hb) values of the patients were examined. According to our clinical approach, 300 cc erythrocyte suspension was transfused to patients with Hb values <7-8 g/dL or with anemia symptoms such as dizziness, headache, weakness, and palpitations. On the 1st postoperative day, the patients were mobilized to full weight bearing, and the standard rehabilitation process was applied.

Data collection

Age, sex, body mass index (BMI) (kg/m^2), preoperative and postoperative first three days' hematocrit (Hct) and Hb (g/dL) values, intraoperative blood loss (IBL), postoperative drainage volume, number of ABT, length of stay were collected prospectively by an investigator and entered into a database with all clinical information.

Calculation of blood loss

IBL was determined through anesthesia recordings during the operation, which included the measurement of blood suction bottles and the weight of surgical swabs.

The calculation of total blood volume (TBV) was conducted using the Nadler method (8,15) in the following manner:

$TBV=k_1xH_3 + k_2xW + k_3$

For males, $k_1=0.3669$, $k_2=0.03219$, and $k_3=0.1833$; for females, $k_1=0.3561$, k2=0.03308, and $k_3=0.1833$.

H=height (m) and W=weight (kg).

The calculation of total blood loss (TBL) was conducted using the Gross formula (16) method as follows:

TBL=TBV × (preoperative Hct-postoperative 3-day Hct) / Mean Hct

Each erythrocyte suspension volume containing 300 mL administered to the patient, was introduced to TBL separately. The total HBL was determined by deducting the visible blood loss from the TBL volume (15).

Statistical Analysis

To demonstrate the robustness of this study, we performed a post-hoc power analysis using G*Power version 3.1.9.4. This analysis is intended to assess the sufficiency of our sample size. Remarkably, the results indicated that our study achieved a power of 99%, with an alpha level (α) set at 0.05. The substantial level of statistical power reinforces the reliability and validity of our findings, indicating that the sample size was adequately large to identify significant effects. The statistical analysis was conducted SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). To evaluate the normality of distribution, the Kolmogorov-Smirnov test was utilized. Categorical variables were presented as counts and percentages and compared using either the chi-squared test or Fisher's exact test, as appropriate. Continuous variables were described as means and standard deviations. Normally distributed continuous variables were compared using independent samples Student's t-test, while non-normally distributed continuous variables were compared using the Wilcoxon-Mann-Whitney U test. A two-sided p-value less than 0.05 was considered statistically significant.

Results

Of the 84 (52 female and 32 male) eligible for this study, 41 patients were randomized to the injection group and 43 patients were randomized to the non-injection group. The average age of the cohort was 81.5±7.69, ranging from 65 to 95 years. There was no statistically significant difference between groups regarding age, sex, BMI, and length of stay (p=0.548, p=0.222, p=0.801, p=0.071, respectively) (Table 1).

Blood loss

A detailed statistical analysis is illustrated in Figure 2. The mean TBL for the non-injection group was recorded at 1330.3±430.4 mL; while the injection group had a mean TBL of 1100.2±420.3 mL. The measured HBL was 442.2±168.9 in the non-injection group and 327.4±148.8 in the injection group. A total of 14 patients (34.1%) in the injection group and 25 patients (58.1%) in the non-injection group received at least one allogenic blood transfusion. These findings indicate that HBL and TBL values were significantly higher in the non-injection group (p=0.013, p=0.049, respectively). Hence, indirectly, ABT rates were lower in our injection group (p=0.043). Furthermore, our findings showed that patients who received intraoperative periarticular Ranawat solution injections had a 26% decrease in HBL and a 17.2% decrease in TBL compared to the non-injection group. However, there was no statistically significant difference between groups regarding IBL and postoperative drainage volume (p=0.745 and p=0.705, respectively). Detailed analysis is provided in Table 2. This study recorded no adverse effects or postoperative complications associated with periarticular injections of Ranawat solution.

Discussion

The principal finding of our study was that intraoperative periarticular Ranawat solution injections significantly reduced HBL by approximately 26%, and TBL by 17.2%, thereby reducing postoperative ABT requirements in elderly patients undergoing hemiarthroplasty for hip fractures.

HBL has several causes, including procedural factors such as hemolysis (17), infiltration into tissues during surgery (18), incision length (19), operation duration, and trauma-to-surgery interval (20), as well as patient-related factors like BMI and age. Our findings, aligning with previous studies, confirm that HBL constitutes a significant portion of TBL, highlighting the clinical importance of controlling hidden perioperative bleeding. Foss and Kehlet (5) reported that HBL could represent up to 75% of total perioperative blood loss in hip fractures, while Lei et al. (21) emphasized substantial HBL following hip surgery. Our study demonstrated a 26% reduction in HBL with intraoperative periarticular Ranawat solution injections, strongly supporting its effectiveness.

Table 1. Demographic data of the patients in the study age, BMI, length of stay, and sex

		Mean	SD	Min.	Max.	p-value*
Age	Group I (n=41)	82.6	6.96	65	93	0.548
	Group II (n=43)	81.5	8.47	65	95	
BMI (kg/m^2)	Group I (n=41)	28.2	4.12	18.4	35	0.801
	Group II (n=43)	28.1	4.99	19.4	45.2	
Length of stay (day)	Group I (n=41)	6.7	3.12	2	15	0.071
	Group II (n=43)	11.2	10.13	3	56	

Table 1. Continued

		Mean	SD	Min.	Max.	p-value*
				Number	Percent (%)	p-value*
Sex	Group I (n=41)		Male	14	34.1	0.222
			Female	27	65.9	
			Total	41	100	
	Group II (n=43)		Male	18	41.8	
			Female	25	58.2	
			Total	43	100	

*: p<0.05 was considered statistically significant
SD: Standard deviation, Min.: Minimum, Max.: Maximum, BMI: Body mass index

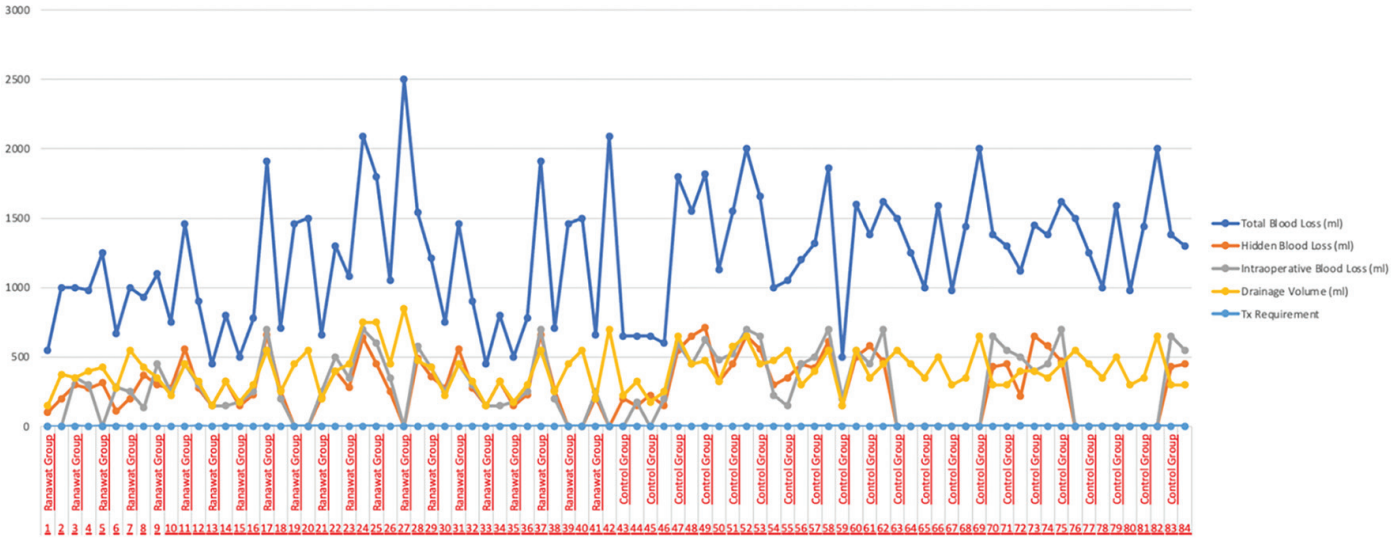


Figure 2. Statistical analysis of the variables for both the study and control groups. Total blood loss (mL), hidden blood loss (mL), intraoperative blood loss (mL), drainage volume (mL), and Transfusion (Tx) requirement

Table 2. Comparison of groups in terms of perioperative blood loss and blood transfusion requirements. HBL, TBL, and IBL

		Mean	SD	Min.	Max.	p-value*
HBL (mL)	Group I	327.4	148.8	100	660	0.013*
	Group II	442.2	168.9	150	710	
TBL (mL)	Group I	1100.2	423.4	450	2085	0.049*
	Group II	1330.3	434.2	500	2090	
IBL (mL)	Group I	447	200.7	250	750	0.745
	Group II	474.1	221.8	175	750	
Postoperative drainage volume (mL)	Group I	400	158.5	150	750	0.705
	Group II	424.2	143.2	150	700	
Transfusion requirement (Unit)	Group I	0.48	0.5	0	1	0.043*
	Group II	1	0.89	0	4	

*: p< 0.05 was considered statistically significant
SD: Standard deviation, Min.: Minimum, Max.: Maximum, HBL: Hidden blood loss, TBL: Total blood loss, IBL: Intraoperative blood loss

The observed efficacy of the Ranawat solution can primarily be explained by the pharmacologic effects of its constituents. EP is commonly used in periarticular injections. It is a sympathomimetic catecholamine that affects alpha- and beta-adrenergic receptors. Its effect on α_1 receptors produces increased vascular smooth muscle contraction (22). Moreover, EP is a platelet-stimulating agent since it causes aggregation of human platelets through α_2-adrenoceptors (23). These actions may explain the efficacy of this drug in reducing blood loss during perioperative (due to contraction of peripheral vessels) and postoperative (due to hemostatic effect) periods. On the other hand, dexamethasone, a glucocorticosteroid (GCS), also leads to decreased production of prostaglandins with their vasodilatory effects and a subsequent diminution in blood loss (24,25). Two recent randomized controlled trials assessed blood loss in patients who received GCS during periarticular infiltration, revealing a non-significant reduction in blood loss for the GCS group (25).

Perioperative blood loss is a key criterion for evaluating the efficacy of periarticular injections. Recent studies support using EP-based periarticular infiltration to decrease postoperative blood loss without increasing deep-vein thrombosis risk (26,27). Lombardi et al. (28) retrospectively reported significantly lower blood loss after total knee arthroplasty with a cocktail injection of morphine, EP, and bupivacaine compared to controls ($p<0.0001$). Similarly, Gasparini et al. (22) in a prospective randomized trial observed significant reductions in TBL with nor-EP lavage (821 vs. 1,270 mL; $p<0.0001$). Our results align with these findings, demonstrating significantly reduced TBL in the injection group.

IBL and drainage volumes serve as crucial metrics for assessing the effectiveness of EP in managing postoperative bleeding. Nevertheless, the injection group did not show a significant decrease in IBL and postoperative drainage volume when compared to the control group. Our results are consistent with recent research conducted by Teng et al. (27) and Villate et al. (29). The result may be related to the time of EP administration and the methods of EP application during the procedure. Although the platelets of the spleen are immediately released after the administration of EP, the peak of the coagulation factor cannot be reached until more than 20 minutes after administration (30). Thus, the relatively short operation time of total joint arthroplasty may alter the effects of EP.

Transfusion rates indirectly indicate the efficacy of EP. Our study showed significantly lower transfusion rates in the Ranawat solution group (34.1%) compared to controls (58.1%), which aligns with prior studies on periarticular injections containing EP (9,31). However, conflicting findings exist. Gao et al. (32) found no significant transfusion differences in hip arthroplasty patients treated with tranexamic acid plus diluted EP, and Villatte et al. (29) reported similar transfusion requirements between EP infiltration and control groups ($p=0.92$). These discrepancies might reflect inconsistent transfusion criteria, often influenced by subjective patient factors alongside Hb levels.

As expected, female patients predominated in our study, though the female-to-male ratio was lower in previous reports. Recent global analyses show a decreasing female-to-male ratio for hip fractures, emphasizing the growing importance of diagnosing and treating osteoporosis in males (33,34). Enhancing physician education on osteoporosis management in men should be a priority.

We acknowledge some possible limitations in this study's scope. First, it's notable that this research is constrained by being conducted at a single-center with a relatively small sample size. Notably, the small sample size was primarily due to the COVID-19 pandemic, which made it challenging to identify eligible patients who were not on anticoagulant treatments during specific periods of our study. Second, we could not analyze how the intraoperative injection of the Ranawat solution, affects perioperative blood loss in patients who are on different anticoagulant regimens. However, in the context of ensuring standardization, recent studies investigating HBL excluded individuals receiving anticoagulant therapy before experiencing a hip fracture (7,21). This approach aligns with established reference studies and is intended to reduce potential bias in the findings. Lastly, it is important to note that an independent anesthesiologist documented the IBL, while a separate observer conducted the calculation of postoperative blood loss. This methodological distinction may introduce bias into the study.

Conclusion

Our study shows that intraoperative periarticular injection of Ranawat solution effectively reduces hidden and TBL in elderly patients undergoing bipolar hemiarthroplasty for intra-articular hip fractures. This reduction in blood loss may facilitate faster recovery, fewer transfusion-related complications, and potentially shorter hospital stays, benefiting this vulnerable patient group. However, multicenter comparative studies are necessary to validate our findings and evaluate alternative treatment strategies.

Ethics

Ethics Committee Approval: The study was approved by the Ankara City Hospital, No. 1 Clinical Research Ethics Committee (decision no.: E1-19-3292, date: 22.02.2019), which was performed in accordance with the ethical standards of the Declaration of Helsinki.

Informed Consent: Patients gave written informed consent prior to participation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.B., E.K., G.Ö., Concept: T.K., O.B., E.K., G.Ö., Design: T.K., O.B., E.K., G.Ö., Data Collection or Processing: T.K., Ö.H.K., A.D., Analysis or Interpretation: T.K., Ö.H.K., A.D., Literature Search: T.K., Ö.H.K., A.D., Writing: T.K., O.B.

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Bleeding disorders in patients with hemoperitoneum due to corpus luteum cyst rupture: a retrospective analysis and screening considerations

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Keywords: Bleeding disorder, bleeding assessment tool, corpus luteum cyst rupture, hemoperitoneum

ABSTRACT

Aims: Hemoperitoneum due to corpus luteum cyst rupture (CLCR) can be a life-threatening condition, especially in patients with underlying bleeding disorders (BDs). Identifying the prevalence of BDs in such cases may aid in early diagnosis and management. This study aims to evaluate and determine the prevalence and role of congenital and acquired BDs in patients presenting with hemoperitoneum secondary to CLCR.

Methods: A retrospective case-control study was conducted on 81 patients with hemoperitoneum caused by CLCR, managed at our tertiary care center. The presence of BDs was assessed using the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT).

Results: Among the 81 patients, 76.5% (n=62) had an ISTH-BAT score <6, while 23.5% (n=19) had a score ≥6. Among those with an ISTH-BAT score ≥6, 7 patients (36.9%) were diagnosed with congenital or acquired BDs, with 6 having a prior diagnosis, and 1 being newly diagnosed. Compared to the ISTH-BAT <6 group, patients with a score ≥6 had lower initial hemoglobin levels (p=0.02) and higher activated partial thromboplastin time levels (p<0.001). Surgical intervention was significantly more frequent in patients with ISTH-BAT ≥6 (47.4%) than in those with a lower score (8.1%) (p<0.001), particularly among individuals with BDs.

Conclusions: This study highlights the clinical significance of the association between BDs and hemoperitoneum due to CLCR, emphasizing the importance of considering BD screening in the management of affected patients.

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Introduction

Hemorrhagic corpus luteum (HCL) is a rare ovarian cyst that develops due to spontaneous bleeding within the corpus luteum after ovulation (1). The physiological rupture of follicular cysts during the menstrual cycle is generally an asymptomatic event. However, the formation of a hemorrhagic cystic lesion, resulting from bleeding within the cyst, leads to distension, increased intraluminal pressure, and potential rupture. While typically asymptomatic in healthy women, HCL can cause serious complications such as hemoperitoneum, which may require emergency medical or surgical intervention (1,2).

Corpus luteum cyst rupture (CLCR) is one of the differential diagnoses for acute abdominal pain in women of reproductive age. CLCR must be differentiated from hemorrhagic ovarian cysts, ruptured ovarian cysts, and adnexal torsion. Accurate diagnosis relies on clinical findings, test results, and careful differential diagnosis. A ruptured ectopic pregnancy must be excluded. Diagnostic evaluation includes ultrasonography, complete blood count (CBC), coagulation tests, and inflammatory markers (2).

In the evaluation of HCL, ultrasonography serves as the primary diagnostic tool. Typical sonographic findings include a round cyst with smooth, thin borders and an average diameter of 3.0-3.5 cm. The clot usually begins as an initial fibrin framework and progressively transforms into a reticular formation. Hemorrhagic effusions can be observed in the Douglas and Morrison pouches. Computed tomography (CT) is less sensitive than ultrasonography for diagnosis (2).

In women with bleeding disorders (BDs) or those undergoing anticoagulant therapy, the risk associated with HCL increases. These women may experience more severe clinical outcomes, as HCL can become more complicated and difficult to manage in such cases (3-5).

Several studies have reported an increased incidence of HCL in women with BDs such as von Willebrand disease (vWD). In one study, the incidence of ovarian cysts in women with vWD was found to be 52%, compared to 22% in the control group ($p<0.0001$) (4). Furthermore, heavy menstrual bleeding (HMB) is a common symptom among women with BDs, with prevalence ranging from 32% to 100% in women with vWD (6). HCL, however, is considered a rare but more specific finding associated with HMB. In Silwer's report, 6.8% of 136 women with vWD experienced HCL (7).

These findings highlight the clinical significance of HCL in women with BDs, emphasizing the need for accurate diagnosis of underlying conditions in such patients. The relationship between HCL and hemoperitoneum may open new avenues for management strategies. This study aims to examine the incidence of bleeding disorders in individuals presenting with hemoperitoneum due to CLCR and to provide insights that may support the improvement of early diagnostic and therapeutic approaches in this patient group.

Methods

Study design

This retrospective case-control study was conducted at the University of Health Sciences Türkiye, Gülhane Training and Research Hospital, between January 2019 and March 2023. The study included 165 patients who presented to the emergency department with abdominal pain and were subsequently diagnosed with hemoperitoneum resulting from CLCR.

Ethics committee approval

This study, was conducted following approval by the University of Health Sciences Türkiye, Gülhane Training and Research Hospital of Local Ethics Committee (approval no.: 2022/28, date: 02.03.2022). The study protocol complied with the ethical guidelines outlined in the 1975 Declaration of Helsinki and its revisions (most recently in 2013).

Informed consent

All participants provided written informed consent before enrollment. They were informed that their data would be used exclusively for research purposes, and strict confidentiality was maintained throughout the study. Names and personal identifiers were not recorded. Every stage of the study was carried out in adherence to relevant ethical guidelines and regulations.

Data collection

Clinical parameters were retrospectively extracted from the patients' medical records. These parameters included demographic data such as age, parity, symptom onset, past medical history, the laterality of the ovarian cyst, and management strategies. Most patients were admitted with an acute onset of lower abdominal pain accompanied by symptoms such as nausea, vomiting, and dizziness. On arrival at the emergency department, vital parameters-including blood pressure, heart rate, body temperature, and oxygen saturation were recorded. Additionally, comprehensive medical and surgical histories, including menstrual history, were documented. Physical examinations were conducted by a gynecologist. Laboratory tests, including CBC, activated partial thromboplastin time (aPTT), international normalized ratio (INR), platelet count, and blood group, were recorded for all patients.

Diagnostic imaging was performed through ultrasonography or abdominal-pelvic CT scans. The size and location of the ovarian cyst, as well as the volume of fluid within the pelvic cavity, were assessed using transvaginal or abdominal ultrasonography. The amount of intraperitoneal fluid varied from small collections to extensive bleeding. The diagnosis of hemoperitoneum secondary to CLCR was established through

the combination of clinical presentation, physical examination, and imaging modalities such as ultrasonography, or CT (8).

Of the initial 165 patients with hemoperitoneum attributed to CLCR, 81 patients with complete clinical and laboratory data were included in the final analysis. Patients who declined participation, those with incomplete laboratory results, or those with a posterior cul-de-sac fluid collection depth of less than 2 cm or with hemoperitoneum attributed to alternative causes (e.g., endometriosis, bleeding post-ovum retrieval for in vitro fertilization, ectopic pregnancy rupture, or suspected ovarian cyst torsion) were excluded from the study. To ensure accuracy, all diagnoses were retrospectively confirmed by a specialist gynecologist.

The management decisions were primarily based on clinical examination findings, the presence of hemodynamic instability, and the ongoing nature of the bleeding.

Bleeding scores

Informed consent was obtained from all participants through telephonic communication. A standardized telephone interview was specifically developed for this study to systematically assess the patients' medical and medication history. Participants were questioned regarding existing comorbidities, any known BDs, and the use of medications that may impact platelet function or coagulation. These medications included non-steroidal anti-inflammatory drugs, aspirin, antiplatelet agents, heparin, oral anticoagulants (both vitamin K antagonists and non-vitamin K oral anticoagulants), corticosteroids, antiepileptics, and antidepressants.

To ensure a comprehensive evaluation of BDs, the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT) was employed (9). Developed in 2010, ISTH-BAT provides a standardized approach to assessing bleeding symptoms and has been validated as a screening tool for conditions such as vWD, hemophilia, qualitative platelet disorders, and other rare BDs. The ISTH-BAT assigns a severity score ranging from 0 (absence of symptoms) to 4 (symptoms requiring medical intervention) across 14 clinically significant bleeding sites. The scoring system incorporates age- and gender-specific reference ranges, with abnormal scores defined as ≥ 6 in adult females (10).

In this study, ISTH-BAT forms were completed for all 81 participants following informed consent. The bleeding scores were calculated by a hematologist. For female participants, a total ISTH-BAT score of ≥6 was considered indicative of a potential BD.

Menstrual and obstetric histories were meticulously recorded to evaluate the presence of HMB. Patients were asked about their age at menarche, menstrual cycle patterns, duration of menstruation exceeding 8 days, prior use of iron supplementation for iron deficiency, and a history of menorrhagia. Obstetric history included details of pregnancies and incidents of postpartum hemorrhage.

To further assess HMB severity, the specific ISTH-BAT score for HMB was calculated separately. A score of 2 was indicative of moderate bleeding, necessitating medical management such as antifibrinolytic therapy, hormonal treatment, or iron supplementation. Additionally, scores of ≥2 for HMB were classified as abnormal and suggestive of clinically significant bleeding (10,11).

Laboratory assays

Laboratory evaluations are a crucial component in the screening process for BDs. However, a universally accepted screening panel for the exclusion of BDs in women presenting with abnormal bleeding, such as menorrhagia, postpartum hemorrhage, or HMB, has not yet been established. Current guidelines suggest that initial laboratory tests should include a CBC to evaluate hemoglobin levels and rule out thrombocytopenia (12).

Baseline coagulation studies, including prothrombin time and aPTT, are commonly recommended, even though these tests lack sensitivity and specificity for diagnosing BDs. Additional assays, such as thrombin clotting time for qualitative fibrinogen defects and clottable fibrinogen levels for quantitative defects, can provide further insights into fibrinogen abnormalities.

For vWD screening, specific tests include von Willebrand factor antigen (vWF:Ag), Ristocetin Cofactor activity (vWF:RCo), and Factor VIII activity (FVIII:C) (13). In this study, these assays were performed for participants with ISTH-BAT scores ≥6. Results for FVIII:C, vWF:Ag, and vWF:RCo levels, as well as fibrinogen levels, were documented for this subset of patients.

The diagnosis of vWD was established based on reduced levels of vWF:Ag, vWF:RCo, and FVIII:C. The diagnostic threshold was defined as vWF:Ag and vWF:RCo levels below 0.50 IU/mL, in accordance with established criteria (12,13).

Statistical Analysis

We used IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA) to perform statistical analyses. Descriptive data were summarized as frequency, percentage, mean ± standard deviation, and range (minimum-maximum), depending on the variable type. To assess whether the data followed a normal distribution, the Kolmogorov-Smirnov and Shapiro-Wilk tests were applied. For normally distributed variables, differences between two independent groups were analyzed using the Student's t-test. The Mann-Whitney U test was applied for non-normally distributed continuous variables, whereas categorical data were examined with the chi-square test. A p-value below 0.05 was accepted as indicating statistical significance.

Results

This study included 81 women diagnosed with hemoperitoneum due to CLCR. Of these, 19 (23.5%) were in the ISTH-BAT score ≥6 group, and 62 (76.5%) were in the ISTH-BAT score <6 group. The mean age was 28.79±7.26 years (range: 15-45), and the mean parity was 0.58±0.49 (range: 0-1). No significant differences in age or parity were found between the groups (p=0.345 and p=0.605, respectively). Ovarian cysts were more common in the left ovary than the right in both ISTH-BAT <6 and ≥6 groups [15 (78.9%) vs. 33 (53.2%), p=0.049]. Clinical characteristics are summarized in Table 1.

The most frequently reported symptoms were recurrent skin and oral mucosal bleeding, menorrhagia, and recurrent epistaxis, listed in order of frequency. These symptoms were observed both in the general population and in the group with BDs. However, in patients with ISTH-BAT scores ≥6, nasal and skin bleeding were reported at a higher frequency. In patients diagnosed with BDs, nasal and skin bleeding (scores ranging from 1-4) was reported in all cases.

Two patients had a history of epilepsy, while one had Takayasu arteritis, and another had immune thrombocytopenia. All of these patients had ISTH-BAT scores <6 and were managed conservatively.

In terms of HMB-specific scores, 12 (63.1%) women in the ISTH-BAT ≥6 group had scores ≥2, compared to none (0%) in the ISTH-BAT <6 group (p<0.001) (Table 1). The most commonly reported symptom was heavy and prolonged menstrual bleeding.

Table 2 presents laboratory findings for the ISTH-BAT ≥6 and ISTH-BAT <6 groups. The aPTT level was significantly higher in the ISTH-BAT group ≥6 (30.7±7.96 vs. 25.9±2.91, p<0.001), while hemoglobin levels were lower in this group (11.1±2.22 vs. 12.1±1.39, p=0.02). No statistically significant differences were found for INR or platelet count.

In the ISTH-BAT <6 group, 5 patients (8.1%) underwent surgery, while, in the ISTH-BAT ≥6 group, 9 patients (47.4%) underwent surgery (p<0.001). Of the 81 patients, 14 (17.3%) underwent laparoscopic surgery for ovarian cysts (Table 1). Two patients had a history of previous surgical interventions due to ruptured ovarian cysts (Cases 2 and 3). Both cases, including the most recent episode of hemoperitoneum, were managed conservatively (Table 3). All surgeries preserved the ovaries. Additionally, one patient required surgery for a suspected case of acute appendicitis.

Of the 19 patients in the ISTH-BAT ≥6 group, 13, without a diagnosed BD, were referred for further testing. Four of these 13 women missed their follow-up visits. vWD analysis and fibrinogen testing were performed on 9 patients (Cases 7-15). Fibrinogen levels were within the normal range in all cases, and no evidence of dysfibrinogenemia was found (Table 4). One patient showed low levels of vWF:Ag, vWF:RCo, and FVIII:C, leading to a diagnosis of vWD (Table 4).

Six patients reported a previous history of BDs (Cases 1-6; Table 3). Two of these patients were known to have vWD; one was a cardiac surgery patient on chronic coumadin therapy with a prosthetic valve; one had been diagnosed with Glanzmann thrombasthenia (GT) in childhood; one had a history of congenital Factor V deficiency; and one was in the pancytopenic phase following acute myeloid leukemia chemotherapy. Treatments used to manage these bleeding episodes included tranexamic acid, hormonal therapy, platelet transfusion, vWF-containing plasma-derived FVIII concentrate, and fresh frozen plasma (FFP) (Table 3).

Table 1. Demographic and clinical characteristics of the patient in both groups.

Variables		ISTH-BAT score <6 n=62, (76.5%)	ISTH-BAT score ≥6 n=19 (23.5%)	p
Age (years) (mean ± SD)		28.41±6.78	30.00±8.72	0.345
Parity, n (%)	**Nulliparous n(%)**	27 (43.5)	7 (36.8)	0.605
	Multiparous, n(%)	35 (56.5)	12 (63.2)	
Site of ovarian cyst	**Right, n (%)**	33 (53.2)	15 (78.9)	**0.049**
	Left, n (%)	29 (46.8)	4 (21.1)	
HMB-specific scores	**0**	48 (77.4)	4 (21.1)	**<0.001**
	1	14 (22.6)	3 (15.8)	
	>2*	0	12 (63.1)	
Management	**Conservatively**	57 (91.9)	10 (52.6)	**<0.001**
	Surgery	5 (8.1)	9 (47.4)	

*The difference is due to this line with asterisk, p-values < 0.05 are shown in bold
% frequency; ISTH-BAT: International Society on Thrombosis and Haemostasis Bleeding Assessment Tool HMB: Heavy menstrual bleeding

Table 2. Laboratory testing in both groups

Laboratory test	All case (n=81)		ISTH-BAT score <6 (n=62)		ISTH-BAT score ≥6 (n=19)		P
	Mean ± SD	Min-Max	Mean ± SD	Min - Max	Mean ± SD	Min-Max	
Hemoglobin, g/DL	11.8±1.66	5.2-14.8	12.1±1.39	8.4-14.4	11.1±2.22	5.2-14.8	**0.02***
Platelet, 10^3/µL	246.1±69.90	107-435	243.7±1.53	107-435	254.1±52.22	170-359	0.58*
INR	1.1±0.34	0.9-4	1.0±0.01	0.9-1.5	1.2±0.68	0.9-4	0.21**
aPTT (sec)	27.0±4.99	20.6-55.4	25.9±2.91	20.6-33.3	30.7±7.96	21.3-55.4	**0.001****

*:T test applied, **: Mann-Whitney U Test applied.
ISTH-BAT: International Society on Thrombosis and Haemostasis Bleeding Assessment Tool, aPTT: Activated partial thromboplastin time, INR: International normalized ratio

Table 3. Characteristics of 19 cases with ISTH-BAT score ≥6

Case no.	Bleeding disorder	Age	ISTH-BAT score	HMB-specific scores	Blood group	Platelet (/mm³)	aPTT (sec)	Site of ovarian cyst	Treatment	Medication used to controlled bleeding event
1	Coumadin Therapy	30	6	0	A^+	250	55.4	Right	Conservative	FFP
2	vWD	36	9	2	A^-	267	21.8	Right	Conservative (Past LS)	VWF-containing plasma-derived FVIII concentrate
3	GT	41	25	1	B^+	170	32	Right	Conservative (Past LS)	Platelet transfusion
4	VWD	29	16	2	B^-	359	25	Right	LS	VWF-containing plasma-derived FVIII concentrate
5	Factor V Deficiency	18	15	3	A^+	217	31	Right	LS	FFP
6	AML	25	8	1	0^+	276	46	Right	Conservative	Platelet transfusion
7	VWD*	31	8	0	A^+	294	33.8	Right	LS	
8		18	6	0	A^+	227	29.9	Left	Conservative	
9		19	6	2	B^+	185	30.6	Right	Conservative	
10		43	6	2	0+	274	29	Right	Conservative	
11		24	7	2	B^+	243	29.7	Left	Conservative	
12		30	13	1	B^-	196	23.8	Left	LS	
13		22	10	2	AB^+	303	28.7	Right	Conservative	
14		31	10	2	A^+	248	26	Left	Conservative	
15		33	6	2	A^+	214	30	Right	LS	
16	N/A	45	7	4	0-	289	21.3	Right	Conservative	
17	N/A	43	6	0	0^+	319	30.6	Right	LS	
18	N/A	20	6	2	0^+	313	29.3	Right	Conservative	
19	N/A	32	6	2	B^+	183	29	Right	LS	

*:New case
ISTH-BAT: International Society on Thrombosis and Hemostasis, HMB: Heavy menstrual bleeding score, aPTT: Activated partial thromboplastin time, vWD: von Willebrand disease, GT: Glanzmann thrombasthenia, AML: Acute myeloid leukemia, GT: Glanzmann thrombasthenia, FFP: Fresh frozen plasma, LS: Laparoscopy, N/A: Not applicable

Table 4. Further laboratory results of patients with an ISTH-BAT score ≥6 without a diagnosed bleeding disorder (n=9)

Laboratory test (case 7-15)	Mean ± SD	Min-Max
Hemoglobin, g/dL	12.00±1.88	9.00-14.80
Platelet, 10^3/μL	242.66±41.61	185.00-303.00
INR	1.05±0.07	0.90-1.10
aPTT (sec)	29.00±2.76	23.80-33.30
Factor VIII level	81.88±13.92	64.00-104.00
vWF Ag	99.55±24.64	67.00-136.00
vWF Rco	140.16±177.48	50.00-607.00
Fibrinogen (mg/dL)	293.55±109.37	174.00-558.00

ISTH-BAT: International Society on Thrombosis and Haemostasis Bleeding Assessment Tool, INR: International normalized ratio, aPTT: Activated partial thromboplastin time, vWF Ag: von Willebrand factor antigen, vWF Rco: von Willebrand factor ristocetin cofactor

Discussion

This study investigates the prevalence and clinical impact of BDs in women presenting with hemoperitoneum due to CLCR. Congenital or acquired BDs are known to lead to significant gynecological complications in women of reproductive age, including HMB, miscarriages, and postpartum hemorrhage. However, the role of hemostasis in reproductive hemorrhages is often overlooked, which can delay diagnosis and treatment. The primary aim of this study was to evaluate the prevalence of genetic and acquired BDs in women who developed hemoperitoneum due to CLCR and to assess the potential utility of the ISTH-BAT as a diagnostic screening tool.

Gynecologists often encounter bleeding disorder symptoms in adolescents, yet awareness of these disorders remains insufficient. A study involving 75 women with vWD found that the most frequently reported symptom was menorrhagia (84%), and the average time from the onset of the first symptom to diagnosis was 16 years (14). In a survey, 77% of obstetricians and gynecologists considered BDs a potential cause of menorrhagia in adolescents, whereas only 38.8% did so in reproductive-aged women (15). This underscores the insufficient investigation of BDs and the lack of hematologic referrals, emphasizing the need for systematic screening to facilitate early diagnosis and management.

Although the true incidence of ruptured ovarian cysts remains unclear, this condition is common, particularly among young women, and more frequent in BDs (16). A study of 102 women with vWD reported ovarian cysts in 52%, compared to 22% in controls (8). vWD, the most prevalent inherited BD in reproductive-aged women, affects 1 in 100 individuals (17,18). Thus, vWD should be considered in cyst rupture cases, especially with abnormal bleeding. In our study, 3 of 81 patients had vWD, aligning with the reported prevalence (0.44-1%) in Türkiye, though findings should be interpreted cautiously due to the small sample size (19).

In women of reproductive age, benign etiologies such as ovulation, retrograde menstrual flow, and endometriosis are among the frequent causes of hemoperitoneum. These bleeding events often resolve spontaneously without the need for intervention. However, when hemoperitoneum is persistent or severe, a broader differential diagnosis should be considered, and potentially life-threatening etiologies should be taken into account. The literature on gynecological cases of hemoperitoneum suggests that most of these cases occur in patients with BDs and are related to ovarian cyst rupture. Hemorrhagic ovarian cysts are associated with various coagulopathies, including different types of vWD (types 1, 2A, 3), afibrinogenemia, GT, hemophilia A, hemophilia B, and deficiencies in factor X and factor XIII. Furthermore, cases of hemoperitoneum have been reported in patients receiving anticoagulant therapy due to antiphospholipid antibody syndrome (2). Our findings support the potential link between BDs and hemoperitoneum caused by CLCR; 23.5% of patients in our study had an ISTH-BAT score indicating an increased likelihood of a BD (≥6). Moreover, 36.9% of patients in this subgroup were diagnosed with genetic or acquired BDs, highlighting the importance of considering these conditions in the clinical management of hemoperitoneum associated with CLCR.

Jarvis and Olsen (20) reported on cases of type I vWD presenting with recurrent hemorrhagic ovarian cysts and recommended that coagulation studies be conducted even in the absence of menorrhagia or a known history of BDs. However, systematic screening for potential BDs is not a common practice in gynecological settings. Structured history-taking and screening processes to evaluate underlying BDs could prevent unnecessary surgical interventions in patients with undiagnosed BDs and provide an opportunity for appropriate treatment.

The necessity of routine BD screening in hemoperitoneum due to CLCR remains debated. Evaluating suspected BDs is challenging and requires a detailed bleeding history and a BAT assessment. A high BAT score indicates an increased BD likelihood, supported by the literature (21,22). In our study, 36.9% of patients with ISTH-BAT ≥6 were diagnosed with a BD, highlighting the importance of screening in those with abnormal bleeding histories.

Coordinated management involving hematology can facilitate effective medical treatment and prevent recurrent cyst ruptures in patients with BDs. Our study demonstrated that patients with an ISTH-BAT score ≥6 or a diagnosed BD exhibited higher incidences of severe hemoperitoneum and hemodynamic instability, necessitating more extensive surgical interventions and blood transfusions. However, those receiving multidisciplinary care, including tranexamic acid, factor replacement, cryoprecipitate, and FFP, frequently achieved resolution of hemorrhagic events without the need for surgical

intervention. Surgical intervention should be reserved as a last resort, only when hemostatic therapy proves inadequate, and with sufficient perioperative support to minimize potential complications (1,2,23).

The retrospective nature and small sample size of this study limit its generalizability. Although ISTH-BAT is a useful screening tool, further confirmatory tests, such as vWF levels and coagulation assays, are needed. Larger prospective studies with more extensive cohorts are required to confirm the role of routine BD screening in the management of CLCR-related hemoperitoneum and to explore the potential for early intervention in high-risk populations.

This study has several limitations. First, its retrospective design limits causal inference and may introduce bias. Second, the relatively small sample size reduces statistical power. Third, the study being conducted in a single tertiary center may restrict the generalizability of the findings. Despite these limitations, the study provides valuable insights into the association between BDs and hemoperitoneum due to CLCR.

Conclusion

In conclusion, this study supports the hypothesis that BDs may play a significant role in the pathogenesis and management of hemoperitoneum caused by CLCR. The findings highlight the potential value of routine BD screening in patients with unexplained hemoperitoneum, especially those with abnormal bleeding histories or high bleeding scores. Early detection and appropriate management of these disorders could improve patient outcomes and prevent the need for invasive interventions.

Ethics

Ethics Committee Approval: University of Health Sciences Türkiye, Gülhane Training and Research Hospital of Local Ethics Committee (approval no.: 2022/28, date: 02.03.2022).

Informed Consent: Written informed consent was obtained from all participants included in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.T.A., M.Y., G.E.Y.C., Ö.Ö., K.E.K., Concept: A.T.A., M.Y., Design: A.T.A., M.Y., Y.E.B., Data Collection or Processing: A.T.A., M.Y., G.E.Y.C., Analysis or Interpretation: A.T.A., Y.E.B., Literature Search: A.Y.A., Ö.Ö.., K.E.K., Writing: A.T.A.

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Wernicke's encephalopathy rapidly progressed to Korsakoff syndrome after laparoscopic sleeve gastrectomy

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ABSTRACT

We report the case of a 26-year-old woman who developed Wernicke's encephalopathy following a sleeve gastrectomy for obesity. Despite receiving supplemental thiamine therapy, her condition deteriorated into severe Korsakoff syndrome, characterized by significant memory impairment and confabulation. This case highlights the critical need for vigilant postoperative dietary management and early detection of nutritional deficiencies in bariatric surgery patients. Clinicians should prioritize comprehensive nutritional education and monitoring to prevent life-altering complications associated with thiamine deficiency.

Introduction

Wernicke's encephalopathy (WE) is a severe and life-threatening condition caused by vitamin B1 (thiamine) deficiency, with an estimated prevalence of 0.4% to 2.8% in the general population (1). Patients who undergo bariatric surgery are at increased risk for nutritional deficiencies and metabolic complications. Approximately 16% to 18% of cases develop neurological complications due to thiamine, folate, and cobalamin (vitamin B12) deficiencies, which typically appear within weeks to months after bariatric surgery (2,3). Since thiamine absorption primarily occurs in the proximal jejunum, Roux-en-Y gastric bypass presents the highest risk for WE, with an overall incidence of 4.29 cases per 100,000 surgeries, compared to 1.06 for sleeve gastrectomy (3). When WE is suspected, prompt Thiamine administration is crucial to prevent further neurological damage.

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Case Presentation

A 26-year-old woman diagnosed with severe obesity [body mass index (BMI) of 40.75 kg/m^2] presented without a history of hypertension, diabetes, or heart disease. She underwent laparoscopic sleeve gastrectomy on February 28, 2023. One month post-surgery, she resumed a regular diet, although her eating patterns were erratic. On May 12, 2023, she developed a fever and vomiting of gastric contents. Anti-infective treatment was only partially effective. Her condition gradually worsened, marked by fatigue and drowsiness, and on May 18, she experienced syncope and was hospitalized.

The patient was unconscious and uncooperative during the examination, but a withdrawal response was observed upon stimulation. The left pupil had a diameter of 2.5 mm with a sluggish light reflex, while the right pupil had a diameter of 3.0 mm with no light reflex. Muscle strength testing in all four limbs was inconclusive. Muscle tone was not increased, the neck was supple without resistance, physiological reflexes were present, and no pathological reflexes were elicited. Blood tests revealed elevated white blood cell count (13.69×10^9/L), neutrophil percentage (73.4%), and absolute neutrophil count (10.04×10^9/L), alongside a low blood phosphorus (0.59 mmol/L), potassium (2.5 mmol/L), and serum folate (2.4 ng/mL), though vitamin B12 was normal. Bacterial cultures, cerebrospinal fluid analysis, and autoimmune tests were negative; however, lumbar puncture showed elevated protein concentration and pressure (260 mmH_2O).

A cranial computed tomography scan was negative, but an electrocardiogram indicated sinus tachycardia and significant ST-segment depression. Sputum culture was positive for *Staphylococcus aureus*. Treatment included levofloxacin, electrolyte correction, and supportive care, but the patient's condition deteriorated further into a continuous coma with complications such as severe pneumonia, respiratory failure, sepsis, and multi-organ dysfunction. On May 30, brain magnetic resonance imaging (MRI) revealed symmetric T2-weighted imaging (T2WI) and fluid-attenuated inversion recovery (FLAIR) hyperintensities around the cerebral aqueduct and bilateral thalami (Figure 1). Considering the history of sleeve gastrectomy, persistent vomiting, and inadequate nutrition, the patient was diagnosed with WE. Intravenous thiamine (500 mg) was administered three times daily for five days, and the dosage was gradually reduced to 100 mg (Figure 2).

Following treatment, inflammatory markers and microbial cultures were negative, and respiratory and hemodynamic stability improved; however the patient remained in a coma.

Discussion

Obesity presents a global challenge, and for individuals with a BMI exceeding 40, traditional dietary and exercise interventions often prove ineffective, prompting the recommendation of bariatric surgery. Common procedures include sleeve gastrectomy, Roux-en-Y gastric bypass surgery, or duodenal switch (4,5). Thiamine deficiency can disrupt energy metabolism in the nervous system, provoke oxidative stress, and trigger inflammatory responses, ultimately leading to nerve damage, particularly in specific brain regions such as the thalamus, mammillary bodies, and the area surrounding the cerebral aqueduct, culminating in WE (6,7). In patients undergoing weight loss surgery, only a minority (0.0002% to 0.4%) develop vitamin B1 deficiency progressing to WE, typically manifesting within six months postoperatively (7).

WE is a neurological syndrome associated with a mortality of 20%. Due to the gradual onset and nonspecific neurological symptoms of WE, misdiagnosis is common. The classic clinical triad comprises ataxia, confusion, and ophthalmoplegia (1,7). WE is frequent in individuals with a history of alcohol abuse, and other risk factors include weight loss surgery, hemodialysis, severe vomiting during pregnancy, and malabsorption syndrome. Its diagnosis requires at least two of five features: dietary deficiency, ocular signs, cerebellar ataxia, memory impairment, or altered mental status (1,8). Moreover, some patients exhibit atypical manifestations, making diagnosis challenging. In cases where patients are at risk of nutritional malabsorption or imbalance, WE should be suspected, even if only part of the triad is observed.

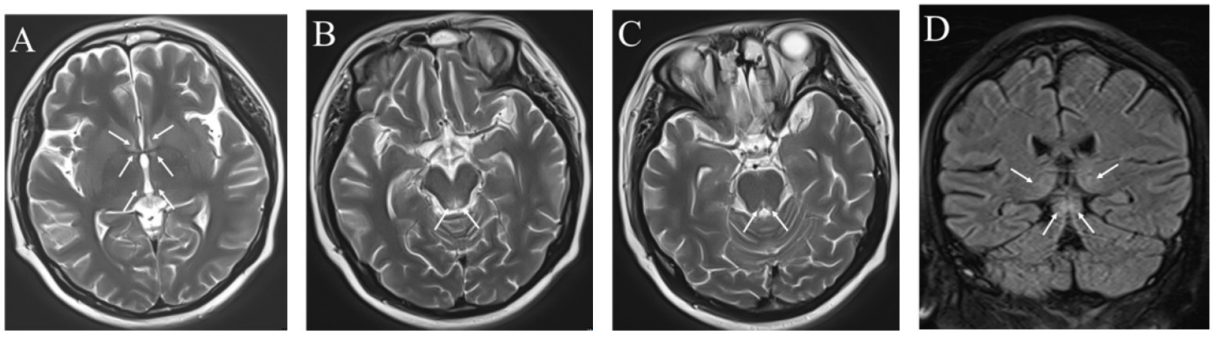


Figure 1. Brain MRI showed bilateral high-signal intensity lesions surrounding the cerebral aqueduct and thalamic regions, a typical finding of WE
MRI: Magnetic resonance imaging, WE: Wernicke's encephalopathy

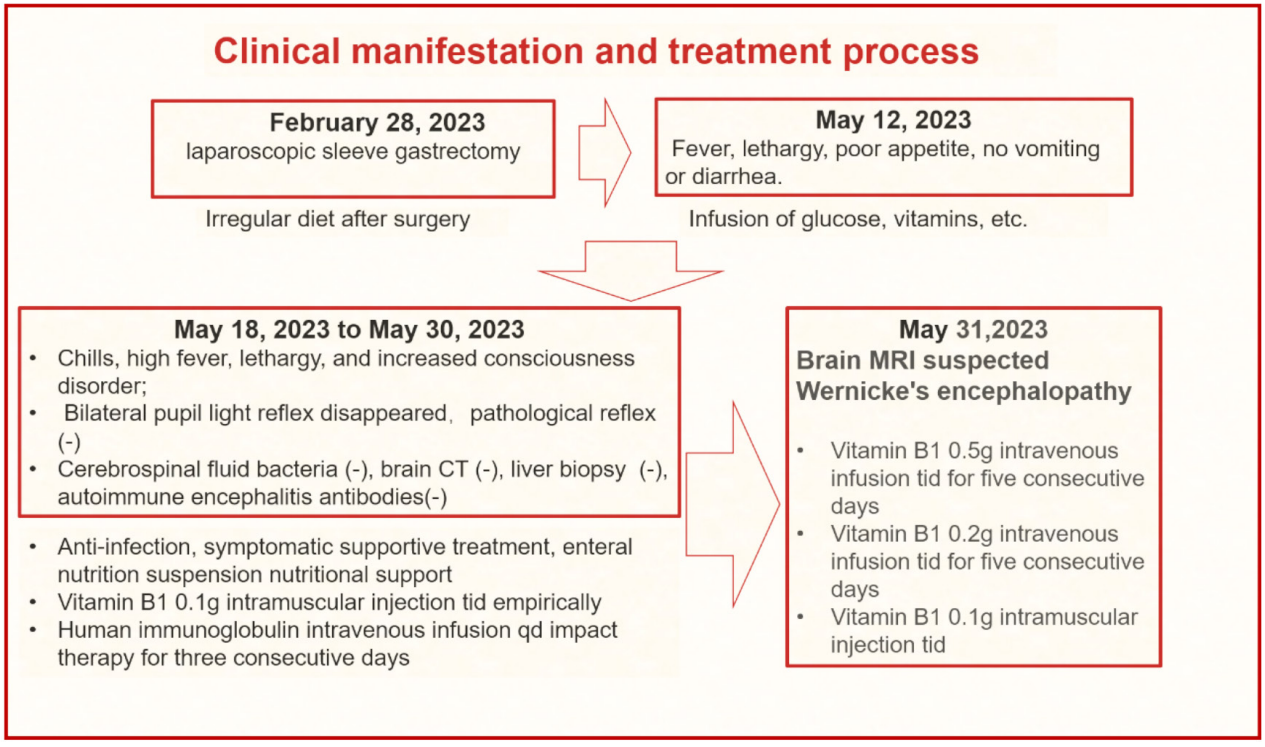


Figure 2. A flow chart of the patient's symptoms and treatment
CT: Computed tomography, MRI: Magnetic resonance imaging

In cases where WE is strongly suspected, immediate intravenous thiamine injection is crucial. The European Federation of the Neurological Societies guidelines (9) recommend thiamine 200 mg thrice daily for suspected or confirmed WE, preferably via intravenous line, because oral supplements are poorly absorbed in large doses. For bariatric surgery patients, the risk of developing WE persists in the long term, with follow-up on thiamine status recommended for at least six months: 94% of WE cases occur within this timeframe post-operatively. On the other hand, alcohol-dependent patients may require higher daily doses, with the suggested regimen of 500 mg three times daily. This intervention not only confirms the diagnosis but also prevents progression to severe Korsakoff sydrome, characterized by anterograde and retrograde amnesia, confabulation, apathy, and potentially coma or death. Moreover, serum thiamine levels and erythrocyte transketolase activity are commonly used as diagnostic measures. WE diagnosis can be confirmed through MRI, which typically reveals high signals on T2WI and FLAIR sequences in the mammillary bodies, around the cerebral aqueduct, thalamus, and hippocampus. In MRI studies, the sensitivity for diagnosing WE was found to be 53%, with a specificity of 93% (1).

Following weight loss surgery, the patient displayed erratic dietary patterns and insufficient nutritional intake, coupled with symptoms of fever and vomiting. Subsequently, the patient rapidly deteriorated, experiencing syncope and entering a coma, meeting at least two diagnostic criteria for WE. Moreover, MRI findings were consistent with the typical presentation. Due to the patient's unstable vital signs upon admission, the MRI examination and diagnosis were delayed until 18 days after symptom onset. Despite intravenous thiamine injections, the patient developed severe Korsakoff sydrome and remained comatose.

Conclusion

This case underscores the critical importance of comprehensive nutritional management and proactive monitoring of patients undergoing bariatric surgery. The progression of WE to irreversible Korsakoff syndrome, despite thiamine supplementation, illustrates the severe consequences of delayed diagnosis and inadequate dietary oversight. Early recognition of clinical symptoms and prompt intervention are paramount for preventing permanent neurological damage. This case serves as a reminder for clinicians to prioritize patient education on post-operative nutrition, reinforce adherence to dietary guidelines, and maintain vigilant follow-up to ensure early detection of nutritional deficiencies.

Ethics

Informed Consent: Informed consent was obtained from the patient's parents for the anonymous use and publication of clinical and imaging data.

Footnotes

Authorship Contributions

Concept: C.H., W.Y., Data Collection or Processing: W.Y., Literature Search: C.H., W.Y., Writing: C.H., W.Y.

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Massive cavernous sinus bleeding secondary to Valsalva maneuver in endoscopic pseudomeningocele surgery: a case report

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Keywords: Cavernous sinus, cerebrospinal fluid rhinorrhea, endoscopic endonasal approach, pseudomeningocele, skull base, Valsalva maneuver

ABSTRACT

Ventral skull base pseudomeningoceles (PMCs) are extremely rare. We report a life-threatening intraoperative complication of the endoscopic approach that has not been previously documented. A 64-year-old man presented with left-sided bloody rhinorrhea. Radiologic evaluation revealed a giant cystic lesion occupying nearly the entire ventral skull base, consistent with a PMC. Endonasal endoscopic surgery was planned. Since the site of cerebrospinal fluid leakage could not be identified intraoperatively, we requested the anesthesiologist to perform the Valsalva maneuver. This resulted in profuse bleeding from the left cavernous sinus (CS). Hemostasis was achieved, and the skull base defect was successfully repaired. Untreated skull base PMCs that erode the medial wall of the CS may progressively enlarge and pose a life-threatening risk. This case highlights the risk of CS hemorrhage during intracranial pressure-raising maneuvers such as the Valsalva maneuver in PMCs that erode the medial cavernous wall. Surgeons should remain alert to this potential complication in this type of high-risk case.

Introduction

A cranial pseudomeningocele (PMC) is defined as an abnormal extradural collection of cerebrospinal fluid (CSF). Although meningoceles (MC) and meningoencephaloceles (MECs) of the skull base are well-recognized conditions routinely encountered by skull base surgeons and rhinologists, PMCs involving the ventral skull base have been rarely reported. These lesions can result from iatrogenic, traumatic, or congenital defects (1-7). When symptomatic, PMCs typically present with CSF rhinorrhea and a pulsatile or compressible nasal mass (1,2,5,7). Untreated CSF rhinorrhea can lead to severe and well-recognized complications, including meningitis, pneumocephalus, and brain abscess (8,9).

Here, we report a case of massive cavernous sinus (CS) bleeding during endoscopic treatment of PMC, a life-threatening intraoperative complication that, to our knowledge, has not yet been reported. The patient has consented to the submission of the case report to the journal.

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Case Presentation

A 64-year-old man presented with a longstanding history of nasal obstruction that had recently worsened. Additionally, he described mild intermittent bloody rhinorrhea from the left nostril over the past two days. There was no history of recent trauma; however, the patient recalled undergoing paranasal sinus surgery 15 years earlier. On physical examination, a very mild bloody CSF leak was observed from the left nostril, particularly while standing. Neurological examination was unremarkable. The β-2 transferrin test result was positive. Nasal endoscopy revealed pulsatile mucosal bulging with a mild bloody CSF leak originating from a defect within the bulging area. The patient underwent imaging evaluation with computed tomography (CT), CT angiography, and magnetic resonance imaging (MRI), including diffusion sequences.

MRI revealed a massive cystic lesion (8×6×7 cm) occupying almost the entire ventral skull base and extending into the left middle cranial fossa and infratemporal fossa (Figure 1a,b,c,d). CT revealed extensive bone resorption involving the anterior cranial fossa, sella floor, clivus, and sphenoid sinuses, accompanied by focal bony defects (Figure 1e,f). Notably, the CSF rhinorrhea resolved spontaneously during the diagnostic work-up. Nevertheless, endoscopic endonasal surgery was planned to repair the identified dural and osseous defects.

Surgery

Following the induction of general anesthesia, 10 mg of dexamethasone and 45.5 mg of pheniramine hydrogen maleate were administered. A lumbar puncture was performed, revealing an opening pressure of 15 cm H_2O. Subsequently, a lumbar drain was inserted, and 10 mL of CSF was withdrawn, mixed with 0.2 mL of 10% fluorescein, and reinjected into the intrathecal space.

The mucosal bulging was incised and CSF was drained using rigid endoscopes. Clotted blood within the PMC cavity, which was suspected to be the source of the bloody rhinorrhea, was aspirated and the cavity was irrigated. No meningeal herniation was detected. As a result of bone resorption and remodeling of the skull base, the optic nerves, chiasma, the left parasellar carotid artery, and the intracavernous portions of cranial nerves III, VI, V1, and V2 were clearly visualized (Figure 2a).

Although a blue light filter was used, the site of CSF leakage could not be identified. Accordingly, we requested the anesthesiologist to perform the Valsalva maneuver. Immediately after the Valsalva maneuver was performed, profuse bleeding occurred from the left CS. The bleeding was controlled using gentle pressure, irrigation, and the application of topical hemostatic agents with cottonoids. Following hemostasis, the medial wall of the left CS was covered with a thin layer of fat graft. An oversized fascia lata graft was placed as an onlay, encompassing the entire exposed skull base. Finally, the vascularized septal mucosal flap was transposed over the fascia lata and tissue adhesive was applied to stabilize the reconstruction (Figure 2b). The nasal cavity was packed with a large piece of gelfoam and a Merocele® nasal tampon (Medtronic, Minneapolis, MN) to support the reconstruction. Postoperative CT performed in the early period was unremarkable (Figure 2c,d). External lumbar drainage was continued for three days. The Merocele® nasal tampon was removed on postoperative day 5. The patient was discharged on postoperative day 6 with no evidence of CSF leakage. At 1-year follow-up, the patient

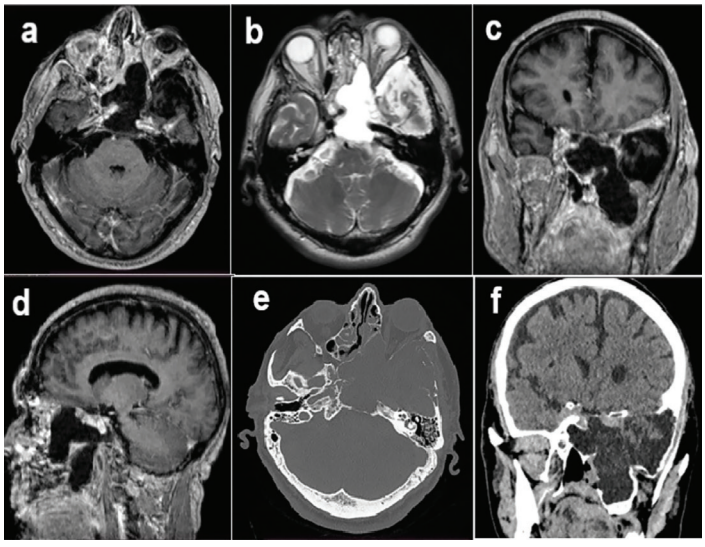


Figure 1. Preoperative axial T1-W (a), axial T2-W (b), coronal T1-W (c), and sagittal T1-W (d) MRI showing a giant cystic mass occupying almost the entire ventral skull base, involving the left cavernous sinus, and also extending into the left middle cranial fossa, and infratemporal fossa. Preoperative axial bone window (e), and coronal (f) CT scans demonstrating significant bone resorption in the ventral skull base including anterior fossa, sella floor, clivus, and sphenoid sinuses as well as bony defects in some areas

MRI: Magnetic resonance imaging, CT: Computed tomography

remained free of CSF leakage, and MRI showed no abnormalities related to the skull base reconstruction (Figure 2e).

Discussion

Skull base PMCs are rare lesions that are known to result from traumatic or iatrogenic causes and can also occur spontaneously (1-5,7,10,11). Regardless of etiology, a ventral skull base PMC of this size has not been previously reported.

A dural defect is a common pathological finding in MC, MEC, and PMC. In skull base PMC, CSF is not contained within a meningeal protrusion but accumulates behind the mucosa of the paranasal sinuses and may extend into the soft tissues of the infratemporal or pterygopalatine fossa (1-5,7,11-14). Although clear, watery rhinorrhea is the most common presenting symptom in all of these pathologies, our patient presented with bloody CSF rhinorrhea, an unusual finding. To our knowledge, MC, MEC, and PMC presenting with bloody CSF rhinorrhea in the absence of acute trauma or recent surgical intervention have not been reported in the literature. The finding of bloody CSF, as seen in our case, without recent surgery or trauma highlights the importance of comprehensive preoperative imaging.

According to some authors, increased hydrostatic pressure caused by fluid entrapment through a ball-valve or slit-valve mechanism can lead to bone resorption (1,3,4,15). In our case, we observed thinning and weakening of the medial meningeal wall of the CS, which lies adjacent to the lateral wall of the sphenoid sinus. We presume that increased pressure during the Valsalva maneuver led to rupture of the already weakened medial wall of the CS, resulting in bleeding. Therefore, in cases of PMC where the lateral wall of the sphenoid sinus appears to be thinning and weakening on preoperative imaging, the Valsalva maneuver should be avoided or applied with extreme caution both preoperatively and intraoperatively. This case also raises the concern that patients with giant PMC involving the CS may be at risk of similar bleeding complications during daily activities that increase intracranial pressure.

Conclusion

To our knowledge, this may represent the largest iatrogenic PMC of the ventral skull base reported to date. An untreated skull base PMC can enlarge over time and lead to life-threatening complications. This case highlights the risk of CS hemorrhage during intracranial pressure-raising maneuvers, such as the Valsalva maneuver, in patients with skull base PMCs eroding the medial cavernous wall. Surgeons should exercise particular caution in such high-risk cases and be prepared for potential complications.

Ethics

Informed Consent: The patient provided informed consent for publication of this case report.

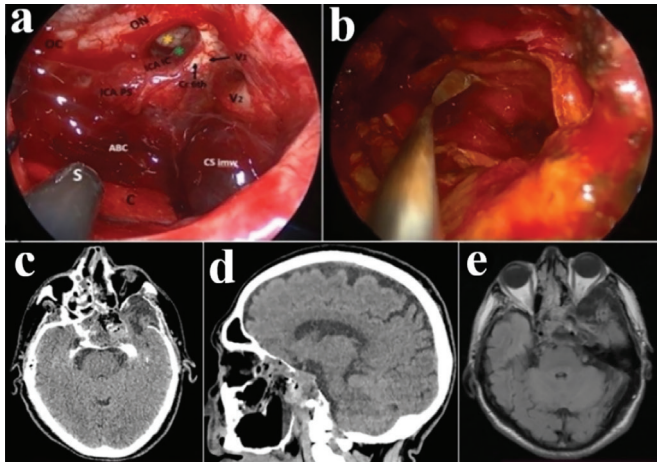


Figure 2. (a) Intraoperative endoscopic view. All neurovascular structures are visible because of bony dehiscence. OC=optic chiasm, ON=left optic nerve, ICA-PS=left parasellar carotid artery, ICA-IC=intracavernous horizontal segment of the left carotid artery, V1=left ophthalmic nerve, Cr 6th=left sixth cranial nerve, V2=left maxillary nerve, CS imw=inferior part of the medial wall of the left cavernous sinus, yellow asterisk=the base of the left anterior clinoid process, green asterisk=left third cranial nerve, C=cottonoid, S=suction. (b) Placement of the fascia lata in on-lay fashion. Axial (c), sagittal (d) CT scans obtained in the early postoperative period, and axial,T2-W MRI (e) obtained one year postoperatively showing acceptable outcome of skull base reconstruction

CT: Computed tomography, MRI: Magnetic resonance imaging

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.O.D., A.M.K., Concept: C.K., Design: C.K., Data Collection or Processing: A.D., Analysis or Interpretation: C.K., M.O.D., A.M.K., Y.İ., Literature Search: A.M.K., Y.İ., Writing: C.K., A.M.K.

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Cutaneous botryomycosis of the right elbow in an immunocompetent adult male: case report

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ABSTRACT

Botryomycosis is a rare, chronic bacterial infection that can affect the skin or internal organs. This report discusses a case of cutaneous botryomycosis in a 29-year-old male with nodular masses and discharging sinuses on his right elbow for two years. Differential diagnoses included actinomycosis, botryomycosis, and mycetoma. Aerobic culture identified methicillin-sensitive *Staphylococcus aureus*, the most common cause of botryomycosis. Accurate etiological diagnosis is crucial for effective treatment, since the patient responded well to antibiotics tailored to the sensitivity report. Early diagnosis and targeted therapy are key to managing this rare infection.

Introduction

Botryomycosis is a rare, chronic bacterial infection characterized by suppurative granulomatous inflammation, primarily in immunocompromised individuals (1,2). Risk factors include alcoholism, diabetes, immunosuppression, and malnutrition (3). Cutaneous lesions present as nodules, abscesses, and sinuses with purulent discharge containing granules. If untreated, these lesions may form fistulas, invade deeper tissues, create abscesses, mimic malignancies, and heal with atrophic scars (4). Diagnosis is challenging, often misidentified as actinomycetoma (5). Key diagnostic indicators include lesion progression, antibiotic response, and positive bacterial cultures (3). Despite its bacterial origin, the term "botryomycosis" misleadingly suggests a fungal etiology (6). *Staphylococcus aureus* is the most common pathogen, with others including *Pseudomonas aeruginosa*, coagulase-negative *Staphylococci*, *Streptococcus* spp., *Escherichia coli*, and *Proteus* spp. (7).

We report a case of cutaneous botryomycosis in a 29-year-old male with chronic discharging sinuses and indurated nodular masses over his right elbow. This study follows the CARE guidelines. Ethical approval was waived by the Institutional Ethics Committee of K. S. Hegde Medical Academy. The patient provided informed consent, and the study adhered to ethical

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principles of Nitte (Deemed to be University) and the Declaration of Helsinki.

Case Presentation

A 29-year-old male from Mangaluru, Karnataka, presented with a two-year history of multiple swellings over his right elbow following trauma sustained in a road traffic accident. Initial treatment at local healthcare facilities included analgesics, anti-inflammatory medications, and antiseptic lotions, but no antibiotics were administered. Despite these measures, the swelling worsened, prompting him to seek further evaluation at the present tertiary healthcare center.

The patient was well-nourished and well-built, with no comorbidities, signs of pallor, jaundice, cyanosis, or lymphadenopathy. Systemic examinations did not reveal any significant abnormalities. The cardiovascular, respiratory, gastrointestinal, and central nervous systems were within normal limits. The blood tests were within normal limits, including hemoglobin (14.4 g/dL), white blood cell count (6,500 cells/mm^3), platelet count (293,000 cells/mm^3), and C-reactive protein (4.8 mg/L). Cutaneous examination of the right elbow revealed hyperpigmented, indurated nodules and multiple discharging sinuses with seropurulent discharge (Figure 1).

The patient was evaluated for mycetoma, botryomycosis, and actinomycosis. Fungal culture, potassium hydroxide mount, and Ziehl-Neelsen staining were negative. Human immunodeficiency virus and tuberculosis tests also yielded negative results, ruling out immunosuppression. An X-ray of the right elbow (anteroposterior and lateral views) showed no abnormalities. However, ultrasonography of the soft tissue in the right elbow revealed findings suggestive of abscess formation.

Sample collection involved cleaning the area around the discharging sinus with an antiseptic to minimize contamination. A sterile needle or swab was then used to obtain material directly from the site of the discharging sinus infection. In cases where the lesion had penetrated deeper tissues, surgical debridement was performed for sampling. Gram staining of the soft tissue and discharge revealed numerous pus cells and moderate gram-positive cocci in clusters and pairs. The wound culture on 5% sheep blood agar (Himedia, Mumbai, India) yielded beta-hemolytic colonies (Figure 2). The isolate was identified as methicillin-sensitive *Staphylococcus aureus* (MSSA) using the VITEK 2 Compact System and the matrix-assisted laser desorption/ionization-time of flight bacterial identification system, both from bioMérieux (Marcy L'Etoile, France).



Figure 1. Cutaneous examination of the right elbow revealed hyperpigmented, indurated nodules and multiple discharging sinuses with seropurulent discharge

Antibiotic susceptibility testing, measuring minimum inhibitory concentrations in µg/mL, was conducted using the VITEK 2 system. Susceptibility cards were inoculated and interpreted according to the manufacturer's guidelines (8). The isolate of *S. aureus* was found to be resistant to erythromycin (≥8 µg/mL) and benzyl penicillin (≥0.5 µg/mL). It was sensitive to oxacillin (≤0.25 µg/mL), gentamicin (≤0.5 µg/mL), ciprofloxacin (1 µg/mL), levofloxacin (≤0.5 µg/mL), clindamycin (0.25 µg/mL), linezolid (2 µg/mL), vancomycin (≤0.5 µg/mL), tetracycline (≤1 µg/mL), and trimethoprim/sulfamethoxazole (≤10 µg/mL). The cefoxitin screen was negative.

Histopathological examination of the excised tissue, measuring 0.8 × 0.5 × 0.4 cm, revealed an ulcer on the skin surface (0.3 × 0.3 cm). The undersurface appeared normal, with pale white to brown areas on the cut surface. Microscopic analysis demonstrated dense chronic inflammation with lymphocytes, plasma cells, histiocytes, neutrophils, microabscesses, granulomas, multinucleated giant cells, and surrounding lymphocytic aggregates in the dermis and subcutaneous tissue.

Bacterial aggregates, identified as gram-positive cocci, were embedded in eosinophilic material, forming radiating,

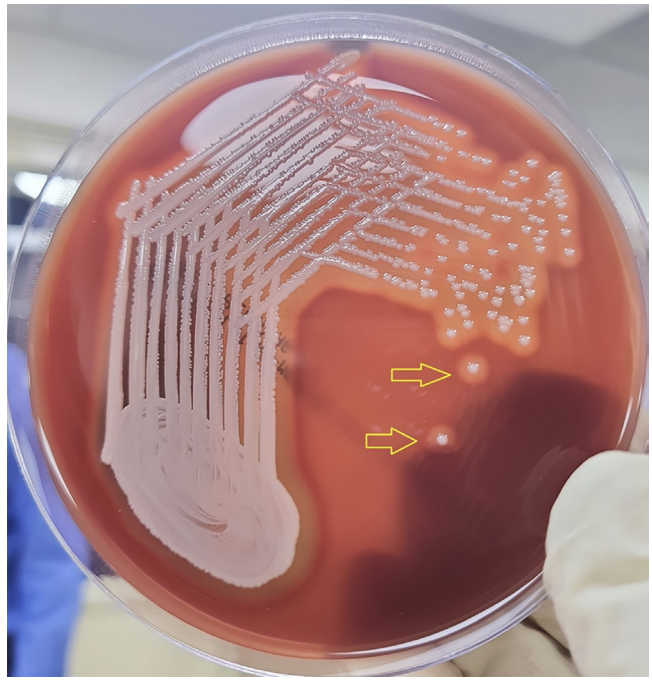


Figure 2. Wound culture on blood agar produced beta-hemolytic colonies

club-shaped structures consistent with the Splendore-Hoeppli phenomenon. Periodic Acid-Schiff was negative. The diagnosis of botryomycosis was confirmed, and no malignancy or fungal organisms were detected. The patient's lesions completely resolved with scarring following a 30-day course of oral clindamycin (300 mg four times daily).

Discussion

Due to the infrequent occurrence of botryomycosis, comprehensive epidemiological data on its prevalence remain poorly defined. However, case reports indicate that MSSA is a frequently associated pathogen. A case series by Sirka et al. (9) documented three cases of cutaneous botryomycosis in immunocompetent individuals; identifying MSSA in two instances, underscoring its etiological role. While MSSA is typically susceptible to methicillin and other beta-lactam antibiotics, emerging resistance necessitates careful antibiotic selection. In the aforementioned case series, MSSA isolates were sensitive to doxycycline, and affected patients responded well to doxycycline monotherapy (9).

Diagnosing cutaneous botryomycosis remains challenging due to its nonspecific clinical presentation, which can resemble actinomycosis, mycetoma, or chronic granulomatous infections. Histopathological examination, revealing characteristic granules, alongside microbiological culture for pathogen isolation, is essential for accurate diagnosis (10).

Therapeutic management often requires prolonged antibiotic therapy. Surgical debridement is considered for extensive lesions, bone invasion, or non-responsive cases to remove necrotic tissue. Given the risk of antimicrobial resistance, treatment should be guided by culture and sensitivity testing (9,10). Effective antibiotics include co-trimoxazole, rifampin, minocycline, erythromycin, and cephalosporins (5). Case reports highlight various treatment approaches, including vancomycin and surgical debridement in Taiwan (11), clindamycin in Sydney (3), and ceftriaxone sodium at the All-India Institute of Medical Sciences, Bhubaneswar (2). Singh et al. (12) reported successful treatment with clindamycin in a similar case.

In the present case, *S. aureus* was isolated from an immunocompetent adult without significant risk factors. Accurate diagnosis enabled appropriate management, leading to complete clinical resolution. At the four-week follow-up, the patient remained asymptomatic, with ultrasonography confirming complete resolution of the mass without residual disease.

Conclusion

This case highlights the significance of accurately diagnosing botryomycosis, distinguishing it from similar conditions like mycetoma and actinomycosis. Appropriate antibiotic therapy, guided by culture and sensitivity results, leads to successful outcomes, with surgical intervention as needed.

Ethics

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

Footnotes

Authorship Contributions

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

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