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The Official Journal of The Kuwait Medical Association

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Vol. 58 No. 3 SEPTEMBER 2026

KUWAIT MEDICAL JOURNAL

CONTENTS

Continued from cover

LETTER TO EDITOR

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PUBLISHER: The Kuwait Medical Journal (KU ISSN-0023-5776) is a quarterly publication of THE KUWAIT MEDICAL ASSOCIATION. Address: P.O. Box 1202, 13003 Safat, State of Kuwait; Telephone: 1881181 Fax: 25317972, 25333276. E-mail : kmj@kma.org.kw

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Kuwait Medical Journal

Published by the Kuwait Medical Association
Previously known as The Journal of the Kuwait Medical Association (Est. 1967)

EDITORIAL OFFICE

Editorial Manager : Vineetha Elizabeth Mammen

EDITORIAL ADDRESS

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Telephone: (00-965) 1881181(Ext. 114, 115) - Fax: (00-965) 25317972, 25333276
E-mail: kmj@kma.org.kw
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Review Article

Does lowering LDL levels reduce dementia?

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Kuwait Medical Journal 2026; 58 (3): 171 - 178

ABSTRACT

The brain, rich in lipids, is vulnerable to disruptions in lipid balance, which are associated with neurological and neurodegenerative disorders like Alzheimer's disease, while high levels of low-density lipoprotein (LDL) and triglyceride-rich lipoproteins foster arterial retention and inflammation, driving atherosclerosis. Multiple risk factors influence dementia development, with cerebral small vessel disease resulting from arteriolar wall infiltration by inflammatory cells and plasma constituents, being a significant contributor. Elevated plasma LDL cholesterol is now considered a modifiable risk factor for dementia, and statins—HMG-CoA reductase inhibitors—not only reduce LDL-C levels, but also provide pleiotropic benefits such as plaque stabilization, immunomodulation, anti-inflammatory effects, endothelial function enhancement, and antioxidant and antithrombotic actions. Evidence suggests that statins may provide neuroprotection through cholesterol reduction and additional mechanisms. Experimental studies associate cholesterol consumption with increased amyloid production, whereas observational research suggests that statin use correlates with a lower dementia risk. Reducing LDL-C may also curb systemic and central nervous system inflammation, yet the exact mechanisms remain uncertain, highlighting the need for prospective controlled trials to assess and compare the short- and long-term cognitive effects of different lipid-lowering treatments.

KEY WORDS: Alzheimer's disease, dementia, LDL, lipids

INTRODUCTION

Lipids are vital biomolecules that function as building blocks, fuel reserves and mediators of cellular communication[1]. They are essential nutrients for all living organisms, forming a diverse class of biomolecules that support both the architecture and function of cells and tissues across numerous biological processes[2]. Lipids are fundamental constituents of cellular membranes[3]. They are crucial for overall human health and brain function, with the brain being particularly rich in lipids, and disruptions in lipid balance have been linked to neurological and neurodegenerative conditions such as Alzheimer's disease[4]. Many cells have the capacity to transform carbohydrates into fatty acids, which are subsequently converted into neutral lipids and stored in lipid droplets, and research shows that lipogenesis is not only crucial for systemic energy balance in metabolic tissues but also for the proper function of the immune and nervous systems. Consequently, both excessive and inadequate lipogenesis disrupt lipid homeostasis and may contribute to conditions such as dyslipidemia, diabetes, hepatic steatosis, autoimmune diseases, neurodegenerative disorders and various cancers[1]. The low-density lipoprotein (LDL) / high-density lipoprotein (HDL) ratio, triglyceride levels and HDL cholesterol levels have been associated with certain cardiovascular conditions, including vascular mortality, stroke and myocardial infarction[5]. HDL promotes hepatic clearance of lipid peroxides and lysophospholipids through specific liver receptors and, together with its associated proteins—PON1, ApoAI, ApoM, PLA2, CETP and others—forms an integrated system that neutralizes lipid hydroperoxides, preventing their accumulation on LDL and protecting against atherogenic oxidative and glycation damage[6]. Synthesized in the liver and transported on HDL particles, PON1 exerts strong atheroprotective effects by degrading lipid hydroperoxides and alleviating oxidative stress,

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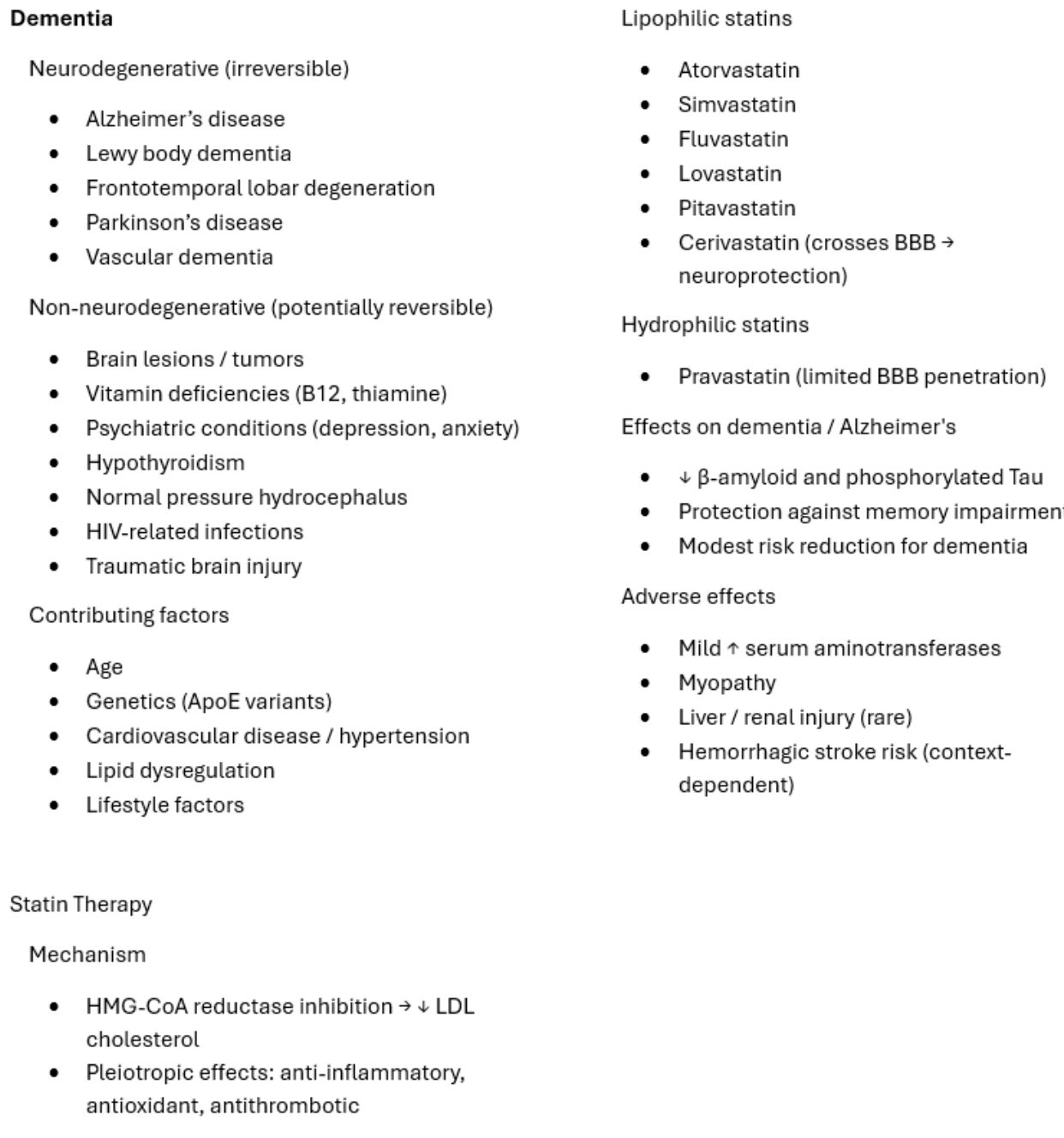

Figure 1: Dementia

whereas ApoAI maintains HDL's structural framework and provides the lipid environment essential for enzymes such as PON1 and lecithin, facilitating the redox neutralization of lipid hydroperoxides transferred to HDL; in parallel, CETP orchestrates the exchange of cholesteryl esters and phospholipid hydroperoxides, contributing to lipid balance and vascular protection[6].

LITERATURE REVIEW

Potential mechanisms underlying cognitive impairment

Extensive epidemiological evidence links higher circulating HDL levels with a reduced likelihood of developing Alzheimer's disease, while experimental studies in animal models demonstrate that HDL mitigates memory loss, neuroinflammation and

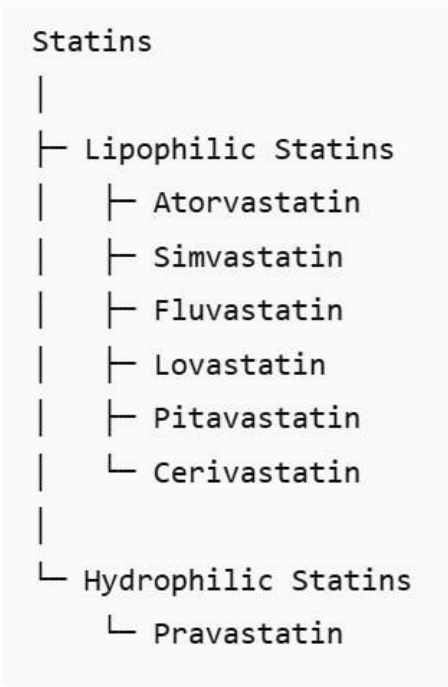

Figure 2: Statins

cerebral amyloid angiopathy, reinforcing its proposed role as a key protector of cerebrovascular integrity in Alzheimer's pathology[7].

Cholesterol and triglycerides, once absorbed from the intestine, are carried through the bloodstream by lipoproteins to supply energy, generate steroid hormones, and support bile acid formation, with cholesterol, LDL, triglycerides and HDL serving as the principal mediators of these vital metabolic pathways[8]. Disruptions in any of these elements, whether due to genetic or environmental factors, can result in dyslipidemia[8]. Dyslipidemia is characterized by abnormal lipid concentrations in the bloodstream, which can elevate the risk of cardiovascular disease[8,9]. The lipid profile comprises LDL, HDL, total cholesterol and triglyceride levels, while dyslipidemia is categorized into two groups: primary, which is genetically derived, and secondary, which arises from underlying diseases or external factors[8]. Primary dyslipidemia results from inherited genetic mutations that disrupt lipid metabolism, whereas secondary dyslipidemia develops later in life, typically due to lifestyle influences or comorbid conditions that disturb lipid balance[8]. High levels of LDL and triglyceride-rich lipoproteins promote their accumulation in the arterial wall, triggering vascular inflammation and driving the onset and progression of atherosclerosis, while dyslipidemia activates inflammatory cells like macrophages and T lymphocytes, along with cytokines and chemokines that infiltrate the endothelium and exacerbate vascular damage[8]. Dyslipidemia may deplete or disrupt the function of endothelial progenitor cells, compromising vascular repair and integrity, while LDL trapped within arterial walls becomes oxidized into oxLDL—a potent pro-inflammatory and pro-atherogenic agent that stimulates reactive oxygen species production, damaging cellular lipids, proteins and DNA; simultaneously, weakened antioxidant defenses under dyslipidemic conditions intensify oxidative stress and tissue injury[8].

Aging triggers dynamic changes in lipid metabolism, and early Alzheimer's disease is marked by disrupted fatty acid profiles and heightened lipid peroxidation within the brain, reflecting oxidative stress–driven alterations in neuronal membrane composition[4] (Figure 1).

Dementia refers to any condition that leads to impairments in domestic, occupational, or social functioning due to a significant decline from an individual's previous cognitive baseline[10]. It is generally regarded as a syndrome with multiple potential etiologies rather than a single disease entity[10]. Key risk factors for dementia include genetic predisposition, advancing age and systemic vascular disease[10]. Among demographic variables, age remains one of the most significant determinants of cognitive decline and Alzheimer's disease[11]. Alzheimer's disease is the most prevalent neurodegenerative disorder[12] and represents a clinically and pathologically defined syndrome of dementia that results in progressive cognitive impairment[13]. While its etiology is not fully elucidated, genetic variants play a substantial role[12]. The prevalence of Alzheimer's disease rises with age, affecting about 19% of individuals aged 75-84 and 30-35%, potentially reaching up to 50% in those over 85, with most pathological changes resembling normal aging but differing in severity, including age-related reductions in brain volume and weight, ventricular enlargement, and loss of synapses and dendrites in regions containing senile plaques and neurofibrillary tangles[11]. Dementia is typically classified into two groups: neurodegenerative, which is irreversible, and non-neurodegenerative, which is potentially reversible[10]. In the majority of dementia cases among older adults, neurodegenerative processes contribute to the condition to some extent[10]. In older adults, common neurodegenerative dementias include Alzheimer's disease, Lewy body dementia, Parkinson's disease, frontotemporal lobar degeneration and vascular dementia, whereas non-degenerative forms may stem from factors such as intracranial masses, subdural hematomas, metabolic or endocrine dysfunctions (like hypothyroidism or vitamin B12

Statins and Dementia: Stepwise Flow

Step 1: Statin Use

- HMG-CoA reductase inhibitors
- Lowers LDL cholesterol
- Classified as lipophilic (simvastatin, atorvastatin) or hydrophilic

Step 2: Mechanisms of Action

1. **Cholesterol-Lowering** → Reduces ischemic stroke risk
2. **Neuroprotective Effects**
   - ↓ Phosphorylated Tau (p-Tau) in CSF (Cerebrospinal Fluid)
   - ↓ β-amyloid accumulation (experimental evidence)
   - Anti-inflammatory effects on CNS (Central Nervous System) and systemic circulation
3. **Vascular & Hemostatic Effects**
   - Fibrinolytic and antithrombotic properties
   - No elevated hemorrhagic stroke risk in patients without prior stroke
   - Slightly higher risk in secondary prevention after ischemic stroke

Step 3: Clinical Outcomes

- **Dementia & Alzheimer's Disease Risk**
  - Large cohort studies: ↓ incidence
  - High-potency statins more effective than low-potency
  - Similar effects in men and women
- **Cognitive Progression**
  - Modest delay in dementia progression
  - Low probability of inducing cognitive decline

Step 4: Modifying Factors

- **Hypertension**: Midlife hypertension → higher later-life dementia risk
- **Diet & Nutrients**: Anti-inflammatory diets may reduce neuroinflammation
- **Statin Lipophilicity**: Lipophilic statins penetrate BBB (Blood-Brain Barrier) more efficiently → greater cognitive protection

Step 5: Research Gaps & Uncertainties

- Mechanisms linking hypertension to cognitive decline
- Optimal antihypertensive treatment and BP (Blood Pressure) targets
- Human evidence for diet → cognition limited
- Conflicting evidence: Some studies show no cognitive or anti-amyloid benefits; possible association with cognitive decline in certain populations

Figure 3: Statins and dementia, stepwise flow

deficiency), chronic alcohol exposure, psychiatric illnesses, infections such as HIV, the neurotoxic effects of chemotherapy, normal pressure hydrocephalus or head trauma[10]. Alzheimer's disease represents the leading cause of dementia, followed by vascular dementia—often linked to prior ischemic or hemorrhagic events and underlying cerebrovascular damage—while emerging research indicates that addressing cardiovascular risk factors through early lifestyle modifications may significantly lower the likelihood of developing dementia later in life[14].

Cerebrovascular changes are frequently seen as neuropathological features in elderly individuals with dementia, with remodeling and pathological alterations in both macro- and microvasculature undermining vascular integrity, potentially leading to neuronal damage, cerebrovascular disease with structural and functional brain deficits, and cerebral hypoperfusion[15]. Neuroimaging reveals white matter hyperintensities, cerebrovascular lesions and cerebral amyloid angiopathy, while aging-related changes—such as capillary wall deterioration, basal membrane

thickening, erythrocyte accumulation and increased blood–brain barrier permeability—contribute to vascular cognitive impairment[15].

Our findings suggest that immune-related mechanisms are crucial in the development of Alzheimer's disease, which accounts for nearly 70% of dementia cases, with neuropathological studies showing intraneuronal tangles formed by extracellular deposits of amyloid-beta peptides and hyperphosphorylated tau proteins[16]. Evidence from experimental, neuropathological, epidemiological and genetic studies indicates that both innate and adaptive immune activation contribute to Alzheimer's disease pathology, with substantial support for an inflammatory component, which is influenced by external factors such as systemic and local infections, brain injury, nutrition and gut microbiota, while cells including oligodendrocytes, peripheral myeloid cells, astrocytes and lymphocytes mediate neuroinflammation in the disease[16].

It is estimated that up to 45% of dementia cases may be preventable by managing cardiovascular risk factors such as hypertension, physical inactivity and diabetes, with elevated LDL-C also recognized as a contributing factor, while the role of other lipids and lipoproteins in dementia remains unclear, and since circulating cholesterol typically cannot cross an intact blood–brain barrier, the exact underlying mechanism is still unknown[17].

Age-related disturbances in lipid metabolism are increasingly recognized as central to the development of Alzheimer's disease, acting through interconnected mechanisms such as gut–brain axis dysregulation, altered neuronal signaling, mitochondrial impairment, oxidative and inflammatory stress, and blood–brain barrier breakdown, which together drive synaptic degeneration and the progressive decline of cognition and memory[4].

Apolipoprotein E, the brain's principal lipid and cholesterol transporter, represents the strongest genetic determinant of Alzheimer's disease risk, with its expression varying by context—astrocytes as the primary source under physiological conditions, microglia during neuroinflammation, and neurons following injury—collectively influencing neurodegenerative pathways and modulating disease susceptibility[18].

Statins

Statins are a class of medications employed in the management of hyperlipidemia and the prevention of cardiovascular disease[19–21] (Figure 2). Statins, essential in managing hypercholesterolemia, effectively prevent primary and secondary cardiovascular events, with most (atorvastatin, simvastatin, fluvastatin, lovastatin, pitavastatin, cerivastatin) being lipophilic and pravastatin hydrophilic[22]. These drugs inhibit β-hydroxy β-methylglutaryl–coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of the mevalonate pathway, thereby reducing endogenous cholesterol synthesis[19,20]. Inhibition of HMG-CoA reductase leads to a substantial decrease in total and LDL cholesterol levels, with minor effects on triglyceride and HDL concentrations[23]. Drugs in this group, including lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin and pitavastatin, have been associated with mild to moderate elevations in serum aminotransferases, which are typically transient, asymptomatic and resolve without dose modification[23]. Excessive or prolonged statin use may result in in vitro cytotoxicity, liver injury, hepatic necrosis, renal damage and myopathy[22].

Statins provide multiple benefits beyond cholesterol lowering, such as stabilizing atherosclerotic plaques, modulating immune responses, reducing inflammation, improving endothelial function and offering antioxidant and antithrombotic effects[19]. Statins may influence protein, DNA and lipid integrity, contributing to oxidative damage, which can activate specific oxidative stress signaling pathways. This may result in mitochondrial membrane potential disruption, imbalance in cellular antioxidant systems, increased oxidative stress and subsequent cellular injury[22].

Supporting evidence

Multiple studies have explored the link between statin use and dementia, with one reporting that statin therapy is associated with a lower incidence of both dementia and Alzheimer's disease, particularly providing greater protection in younger patients, while current evidence shows that higher doses and longer duration of statin treatment correlate with reduced dementia risk, alleviating concerns about potential harm. This analysis pooled data from thirty-five cohort studies involving 6,306,043 participants, confirming that statin use lowers the risk of developing dementia[24].

Another study found no significant evidence for cardiovascular outcomes but suggested that statins may confer a modest benefit in delaying dementia progression, based on three observational studies[25].

Olmastroni E *et al* found that statins are unlikely to induce dementia or cognitive decline, underscoring their safety and validating their established role in preventing cardiovascular events in adults and the elderly. In a gender-specific analysis, both men and women experienced similar reductions in dementia risk, with comparable benefits for dementia and

Alzheimer's disease from either lipophilic or hydrophilic statins, while high-potency statins achieved a 20% risk reduction compared with 16% for low-potency statins, emphasizing the superior effectiveness of high-potency formulations[26]. Statin use has been associated with a reduced risk of dementia[26,27].

Hypertension is a major contributor to age-related cognitive decline[28,29]. Although hypertension has traditionally been linked to vascular dementia, recent studies also associate it with Alzheimer's disease, the most common form of dementia in older adults, making midlife hypertension a risk factor for dementia later in life and a potential contributor to Alzheimer's neurodegenerative pathology, though the exact mechanisms remain unclear[28]. While it is well known that hypertension affects the structure and function of cerebral blood vessels, the mechanisms by which these cerebrovascular alterations contribute to cognitive decline and promote Alzheimer's disease pathology remain unclear, and key questions remain about whether antihypertensive therapy can prevent cognitive impairment, the ideal blood pressure targets, and the most effective classes of antihypertensive medications[28].

Emerging evidence indicates that nutrients and bioactive dietary molecules may modulate neuroinflammatory cascades implicated in neurodegeneration, possibly working in concert to enhance their neuroprotective efficacy, while diet itself appears to influence cognitive aging through a network of interconnected inflammatory pathways[30]. Anti-inflammatory diets may attenuate neuroinflammation by modulating brain immune responses and indirectly shaping gut microbiota–systemic interactions; however, human data remain scarce, and the exact inflammatory pathways through which dietary patterns influence cognitive performance are still largely unresolved[30].

In addition to their cholesterol-lowering effects, statins exhibit fibrinolytic and antithrombotic properties, which may theoretically increase the risk of hemorrhagic stroke[31,32]. The likelihood of hemorrhagic stroke associated with statin therapy appears to depend on factors such as individual patient profiles, comorbidities and stroke subtype; while evidence indicates no heightened risk among those without previous stroke, a meta-analysis of 26 randomized trials reported a slight, non-significant rise in hemorrhagic events alongside a 16% overall reduction in total stroke incidence per 1 mmol/L reduction in LDL-C—primarily due to fewer ischemic strokes—whereas patients with prior ischemic stroke receiving statins for secondary prevention showed an elevated susceptibility to hemorrhagic stroke[31].

Recent evidence indicates that statins may exert both cholesterol-lowering and neuroprotective effects through multiple mechanisms[33]. A 2017 randomized controlled trial found that patients treated with simvastatin showed greater decreases in cerebrospinal fluid phosphorylated Tau (p-Tau) levels than those on placebo—an important finding given p-Tau's role in Alzheimer's disease pathogenesis—highlighting the need for further research in humans; moreover, it has been suggested that individuals with certain genotypes or exposures may experience enhanced cognitive benefits from statin therapy[33]. Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors that effectively lower LDL cholesterol levels[33,34] making them a cornerstone in the treatment of hypercholesterolemia[33]. Current research is examining whether statin-related reductions in neuroinflammation and LDL cholesterol are associated with decreased systemic and cerebral inflammation and a reduced Alzheimer's disease pathological burden, potentially mitigating cognitive decline[33]. Statins can be classified as hydrophilic or lipophilic, which is relevant when considering cognitive effects, as lipophilic statins penetrate the blood-brain barrier more efficiently[27,33]. Statins, ranked by increasing lipophilicity, include pravastatin, rosuvastatin, fluvastatin, atorvastatin, lovastatin and simvastatin, with most cognitive research centered on simvastatin due to its high lipophilicity, while atorvastatin has been reported to lower the incidence of major cerebrovascular events, including stroke, by 13% compared with pravastatin, likely owing to its greater lipophilic nature[33].

Dementia is a progressive, multifactorial condition marked by deficits in memory, language and global cognition, arising from various risk factors and exposures, with cerebral small vessel disease—a form of cerebral atherosclerosis involving inflammatory cell infiltration and plasma component accumulation in vessel walls—being a major contributor[33]. As a result of this atherosclerosis, both white matter and gray matter may be damaged; inflammation can occur in the gray matter, hyperintensities can be observed in the white matter on imaging, and disruption of the blood-brain barrier may develop[33]. Intracerebral hemorrhage, vascular dementia, cognitive decline and ischemic stroke may be observed[33].

In experimental research, the link between cholesterol intake and amyloid synthesis is supported, whereas from an observational perspective, available data indicate that the incidence of dementia is reduced in patients receiving statins[35]. Some prospective studies report no cognitive or anti-amyloid benefits of statins and suggest a possible association between statin use and cognitive decline[35] (Figure 3).

CONCLUSION

High LDL cholesterol may trigger neuroinflammatory and oxidative stress cascades that, through mechanisms such as mitochondrial dysfunction, blood–brain barrier disruption, altered neuronal signaling and synaptic damage, collectively drive the development of Alzheimer's disease and associated memory decline.

Experimental studies support associations between cholesterol intake and amyloid synthesis, whereas observational data indicate that patients receiving statin therapy exhibit a reduced risk of dementia. Although the precise mechanisms underlying these effects remain unclear, potential pathophysiological links with other diseases cannot be excluded. Until definitive evidence demonstrates that hyperlipidemia directly influences cognitive function, clinicians should continue adhering to established management strategies for hyperlipidemia. Statin therapy is generally considered safe and well tolerated; however, various adverse effects, particularly those related to muscle injury, may occur and should be taken into account. Prospective, controlled studies are needed to compare the short- and long-term impacts of different lipid-lowering agents on cognitive function.

REFERENCES

1. Jeon YG, Kim YY, Lee G, Kim JB. Physiological and pathological roles of lipogenesis. Nat Metab 2023; 5(5):735-59.
2. Yin F. Lipid metabolism and Alzheimer's disease: clinical evidence, mechanistic link and therapeutic promise. FEBS J 2023; 290(6):1420-53.
3. Harayama T, Riezman H. Understanding the diversity of membrane lipid composition. Nat Rev Mol Cell Biol 2018; 19(5):281-96.
4. Kao YC, Ho PC, Tu YK, Jou IM, Tsai KJ. Lipids and Alzheimer's disease. Int J Mol Sci 2020; 21(4):1505.
5. Deplanque D, Amarenco P. Blood lipids and stroke: what more can we do besides reducing low-density lipoprotein cholesterol? Curr Atheroscler Rep 2011; 13(4):306-13.
6. Soran H, Schofield JD, Durrington PN. Antioxidant properties of HDL. Front Pharmacol 2015; 6:222.
7. Button EB, Robert J, Caffrey TM, Fan J, Zhao W, Wellington CL. HDL from an Alzheimer's disease perspective. Curr Opin Lipidol 2019; 30(3):224-34.
8. Pappan N, Awosika AO, Rehman A. Dyslipidemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 May 9]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK560891/
9. Dybiec J, Baran W, Dąbek B, Fularski P, Młynarska E, Radzioch E, *et al*. Advances in treatment of dyslipidemia. Int J Mol Sci 2023; 24(17):13288.
10. Gale SA, Acar D, Daffner KR. Dementia. Am J Med 2018; 131(10):1161-9.
11. Armstrong RA. Risk factors for Alzheimer's disease. Folia Neuropathol 2019; 57(2):87-105.
12. Schramm C, Wallon D, Nicolas G, Charbonnier C. What contribution can genetics make to predict the risk of Alzheimer's disease? Rev Neurol (Paris) 2022; 178(5):414-21.
13. Hunter S, Smailagic N, Brayne C. Dementia research: populations, progress, problems, and predictions. J Alzheimers Dis 2018; 64(s1):S119-43.
14. Nordestgaard LT, Christoffersen M, Frikke-Schmidt R. Shared risk factors between dementia and atherosclerotic cardiovascular disease. Int J Mol Sci 2022; 23(17):9777.
15. Raz L, Knoefel J, Bhaskar K. The neuropathology and cerebrovascular mechanisms of dementia. J Cereb Blood Flow Metab 2016; 36(1):172-86.
16. Heneka MT, van der Flier WM, Jessen F, Hoozemanns J, Thal DR, Boche D, *et al*. Neuroinflammation in Alzheimer disease. Nat Rev Immunol 2025; 25(5):321-52.
17. Rasmussen IJ, Luo J, Frikke-Schmidt R. Lipids, lipoproteins, and apolipoproteins: Associations with cognition and dementia. Atherosclerosis 2024; 398:118614.
18. Chen Y, Strickland MR, Soranno A, Holtzman DM. Apolipoprotein E: structural insights and links to Alzheimer disease pathogenesis. Neuron 2021; 109(2):205-21.
19. Mollazadeh H, Tavana E, Fanni G, Bo S, Banach M, Pirro M, *et al*. Effects of statins on mitochondrial pathways. J Cachexia Sarcopenia Muscle 2021; 12(2):237-51.
20. Chang Y, Robidoux J. Dyslipidemia management update. Curr Opin Pharmacol 2017; 33:47-55.
21. Cupido AJ, Reeskamp LF, Kastelein JJP. Novel lipid modifying drugs to lower LDL cholesterol. Curr Opin Lipidol 2017; 28(4):367-73.
22. Liu A, Wu Q, Guo J, Ares I, Rodríguez JL, Martínez-Larrañaga MR, *et al*. Statins: Adverse reactions, oxidative stress and metabolic interactions. Pharmacol Ther 2019; 195:54-84.
23. Statins. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012 [cited 2025 May 23]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK548067/
24. Du Y, Yu Z, Li C, Zhang Y, Xu B. The role of statins in dementia or Alzheimer's disease incidence: a systematic review and meta-analysis of cohort studies. Front Pharmacol 2025; 16:1473796.
25. Davis KAS, Bishara D, Perera G, Molokhia M, Rajendran L, Stewart RJ. Benefits and harms of statins in people with dementia: a systematic review and meta-analysis. J Am Geriatr Soc 2020; 68(3):650-8.
26. Olmastroni E, Molari G, De Beni N, Colpani O, Galimberti F, Gazzotti M, *et al*. Statin use and risk of dementia or Alzheimer's disease: a systematic review and meta-analysis of observational studies. Eur J Prev Cardiol 2022; 29(5):804-14.

27. Kuller LH. Statins, lipids and dementia? J Clin Lipidol 2021; 15(1):18-21.
28. Iadecola C, Gottesman RF. Neurovascular and cognitive dysfunction in hypertension. Circ Res 2019; 124(7):1025-44.
29. Vicario A, Cerezo GH. [The cognitive-behavioural impact of hypertension]. Hipertens Riesgo Vasc 2020; 37(3):125-32.
30. McGrattan AM, McGuinness B, McKinley MC, Kee F, Passmore P, Woodside JV, *et al*. Diet and inflammation in cognitive ageing and Alzheimer's disease. Curr Nutr Rep 2019; 8(2):53-65.
31. Goldstein LB, Toth PP, Dearborn-Tomazos JL, Giugliano RP, Hirsh BJ, Peña JM, *et al*. Aggressive LDL-C lowering and the brain: impact on risk for dementia and hemorrhagic stroke: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol 2023; 43(10):e404-42.
32. Pinal-Fernandez I, Casal-Dominguez M, Mammen AL. Statins: pros and cons. Med Clin (Barc) 2018; 150(10):398-402.
33. Chadha B, Frishman WH. Review of the protective effects of statins on cognition. Cardiol Rev 2021; 29(6):328-35.
34. Feingold KR. Cholesterol Lowering Drugs. In: Feingold KR, Ahmed SF, Anawalt B, Blackman MR, Boyce A, Chrousos G, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2025 May 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK395573/
35. Banach M, Rizzo M, Nikolic D, Howard G, Howard V, Mikhailidis D. Intensive LDL-cholesterol lowering therapy and neurocognitive function. Pharmacol Ther 2017; 170:181-91.

Original Article

Evaluation of hypercalcemia frequency with very high serum 25(OH) Vitamin D levels

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Kuwait Medical Journal 2026; 58 (3): 179 - 186

ABSTRACT

Objective: We aimed to investigate the frequency of hypercalcemia in patients with hypervitaminosis D and vitamin D intoxication.
Design: A retrospective study
Setting: Outpatient clinic of Internal Medicine, Sisli Etfal Training and Research Hospital, University of Health Sciences, Istanbul, Turkey
Subjects: A total of 770 patients with 25(OH) Vitamin D levels above 30 ng/ml were observed in our hospital between 2014 and 2020. The study groups were divided as follows: according to 25(OH) Vitamin D levels (Group 1: 30-50 ng/ml; Group 2: 50-80 ng/ml; Group 3: 80-100 ng/ml; Group 4: 100-150 ng/ml; Group 5: >150 ng/ml). The frequency of hypercalcemia and normocalcemia was identified in each group.
Interventions: Age, gender, calcium, phosphorus, magnesium, parathormone, thyroid stimulating hormone, alkaline phosphatase, 25(OH) vitamin D, urea, creatinine, uric asid, glomerular filtration rate, total protein and albumin were assessed.
Main outcome measures: The frequency of normocalcemia and hypercalcemia and complication of hypercalcemia in vitamin D excess were evaluated.
Results: Most patients with Vitamin D intoxication were asymptomatic and normocalcemic, but it was also found that 3 hypercalcemic patients died of hypercalcemia. The rate of hypercalcemia was statistically significantly different between Groups 3, 4, 5 and Groups 1, 2.
Conclusion: Most patients with high vitamin D levels were normocalcemic, but severe hypercalcemia was also observed. Vitamin D replacement therapy should be given according to clinical guideline recommendations.

KEY WORDS: hypercalcemia, intoxication, mortality, vitamin D

INTRODUCTION

Vitamin D, a fat soluble vitamin, is also a prohormone that plays a role in calcium homeostasis and bone mineralization. Vitamin D deficiency has been found to be associated with many chronic diseases such as cancer, cardiovascular diseases, infectious and autoimmune diseases[1-3].

With the increasing public awareness of the relationship between vitamin D deficiency and related health problems, vitamin D treatment has become popular and its use has increased markedly in recent years.

In recent years, due to the increased use of vitamin D, vitamin D intoxication has been reported more frequently. Vitamin D intoxication is usually iatrogenic and generally develops from high dose vitamin D prescription or unconscious use of patients[4]. Symptoms and signs associated with vitamin D intoxication are closely related to serum calcium levels. In addition, cases with vitamin D intoxication without clinical and biochemical signs of toxicity are reported in the literature. In our study, we aimed to investigate the frequency of normocalcemia and hypercalcemia in vitamin D excess.

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MATERIALS AND METHODS

770 patients with 25(OH)D level >30 ng/ml who applied to the internal medicine outpatient clinic in our hospital between 2013 and 2020 were included in the study. The study protocol was approved by the Local Ethics Commitee. Informed consent was obtained from all individual participants included in the study. In our study, 2530 patients with 25(OH) D level >30 ng/ml were analyzed. A total of 770 patients were included in our study after removing patients who lacked laboratory data and those meeting the exclusion criteria. Information regarding age, gender, calcium, phosphorus, magnesium, parathormone (PTH), alkaline phosphatase (ALP), 25(OH) vitamin D, urea, creatinine, uric acid, glomerular filtration rate (GFR), total protein and albumin were accessed from the database of our hospital. Serum magnesium, phosphate, urea, creatinine, uric acid, ALP, total protein and albumin levels were analyzed on the Cobas 8000 C 702 module (Roche Diagnostics, Manheim, Germany). Serum thyroid stimulating hormone (TSH), PTH and vitamin D levels were analyzed on the Cobas 8000 e 602 module (Roche Diagnostics, Manheim, Germany) automated analyzer using the electrochemiluminescence immunoassay (ECLIA) technique.

Patients under the age of 18, pregnant women, patients with hyperparathyroidism or hypoparathyroidism, patients with diseases such as sarcoidosis and tuberculosis causing high vitamin D level and hypercalcemia, patients with fungal diseases, berylliosis, granulomatosis disease, lymphoma and other malignant diseases were excluded from the study. Patients with 25(OH)D levels >30 ng/ml were grouped according to 25(OH)D concentration: 30-50 ng/ml, 158 patients (group 1), 50-80 ng/ml, 149 patients (group 2), 80-100 ng/ml, 171 patients (group 3), 100-150 ng/ml, 165 patients (group 4) and >150 ng/ml, 127 patients (group 5). Subgroup analysis of patients with 25(OH)D levels >30 ng/ml was performed according to calcium status, gender and vitamin D levels. Hypercalcemia was defined as serum total calcium level higher than the laboratory upper limit for males and females aged 18 and over (total calcium >10.2 mg/dl). If the serum calcium level was between 10.2-12 mg/dl, it was classified as mild, between 12-14 mg/dl as moderate, and above 14 mg/dl as severe hypercalcemia.

Statistical analysis

Descriptive statistical methods were used in the evaluations (mean ± standard deviation (SD), median, minimum and maximum values, numbers and percentage). The conformity of quantitative data distribution to normal distribution was assessed with the Shapiro-Wilk test and graphic methods. Mann-Whitney U test and Kruskal-Wallis test was used in the comparison of quantitative data not showing normal distribution. In the comparison of qualitative data, the Pearson Chi-square test was used. In case of difference between the groups, Bonferonni corrected pairwise comparison results were examined.

Data obtained in the study were analysed statistically using IBM SPSS Statistics 26.0 (IBM Corp. Released 2019), IBM SPSS Statistics for Windows, version 26.0, Armonk, NY: IBM Corp.) A *P*-value <0.005 was accepted as statistically significant.

RESULTS

In our study, 78.2% (n=602) of the 770 patients were female and 21.8% (n=168) were male. There were 483 people (62.7%) aged 18-64 years and there were 287 people (37.3%) who were 65 years of age or older. 716 (93%) of the 770 people who had vitamin D levels >30 ng/ml were detected as normocalcemic and 54 people (7%) as hypercalcemic (Table 1).

When comparing the 5 groups according to the vitamin D levels in terms of age and gender, no statistically significant difference was found (*P* >0.005); calcium groups were found to be related to vitamin D groups (*P* <0.05). It is found that phosphorus, magnesium, ALP, TSH, ST3, creatinine and total protein values had no significant difference between groups (*P* >0.05). However, calcium, PTH, urea, GFR, albumin and uric acid values had a significant

Table 1: Demographic information of the participants

Parameters (n=770)	Number	%
Gender		
Female	602	78.2
Male	168	21.8
Total	770	100
25(OH) Vitamin D		
Group 1 (30-50 ng/ml)	158	20.5
Group 2 (50-80 ng/ml)	149	19.4
Group 3 (80-100 ng/ml)	171	22.2
Group 4 (100-150 ng/ml)	165	21.4
Group 5 (> 150 ng/ml)	127	16.5
Total	770	100
Age		
18-64	483	62.7
65+	287	37.3
Total	770	100
Calcium		
Normocalcemic	716	93.0
Hypercalcemic	54	7.0
Total	770	100

Table 2: Descriptive statistics for vitamin D groups, comparison of relationship and differences

Parameters Mean ± S.D.	Group 1 (30-50 ng/ml) (n=158)	Group 2 (50.01-80 ng/ml) (n=149)	Group 3 (80.01-100 ng/ml) (n=171)	Group 4 (100.01-150 ng/ml) (n=165)	Group 5 (>150 ng/ml) (n=127)	*P*-value
Gender						
Female	117 (19.4)	119 (19.8)	141 (23.4)	135 (22.4)	90 (15.0)	0.063
Male	41 (24.3)	30 (17.9)	30 (17.9)	30 (17.9)	37 (22.0)	
Age						
18-64	111 (23.0)	89 (18.4)	110 (22.8)	97 (20.1)	76 (15.7)	0.189
65+	47 (16.4)	60 (20.9)	61 (21.3)	68 (23.7)	51 (17.8)	
Calcium						
Normocalcemic	153 (21.4)	141 (19.7)	160 (22.3)	150 (21.1)	111 (15.5)	**0.028**
Hypercalcemic	5 (9.3)	8 (14.8)	11 (20.4)	14 (25.9)	16 (29.6)	
	n = 154	**n = 141**	**n = 163**	**n = 145**	**n = 77**	
PTH (pg/ml)	39.27 ± 10.52	38.78 ± 12.09	34.37 ± 12.46	31.98 ± 12.54	30.17 ± 13.45	**< 0.001**
	n = 158	**n = 149**	**n = 171**	**n = 165**	**n = 127**	
Calcium (mg/dl)	9.54 ± 0.37	9.55 ± 0.48	9.64 ± 0.40	9.70 ± 0.57	9.80 ± 0.83	**0.001**
	n = 147	**n = 140**	**n = 146**	**n = 142**	**n = 86**	
Phosphorus (mg/dl)	3.50 ± 0.54	3.54 ± 0.58	3.56 ± 0.58	3.59 ± 0.51	3.68 ± 0.55	0.246
	n = 123	**n = 116**	**n = 111**	**n = 108**	**n = 76**	
Magnesium (mg/dl)	1.94 ± 0.19	1.93 ± 0.19	1.90 ± 0.30	1.91 ± 0.22	1.93 ± 0.21	0.069
	n = 130	**n = 127**	**n = 125**	**n = 131**	**n = 81**	
ALP (U/L)	67.48 ± 22.20	69.15 ± 23.48	69.44 ± 24.87	69.86 ± 25.13	79.65 ± 55.47	0.864
	n = 153	**n = 146**	**n = 135**	**n = 138**	**n = 101**	
TSH (mU/L)	2.09 ± 1.37	2.13 ± 1.69	2.30 ± 2.30	2.14 ± 1.84	2.23 ± 1.64	0.844
	n = 99	**n = 86**	**n = 77**	**n = 79**	**n = 38**	
ST3 (ng/L)	3.06 ± 0.47	3.01 ± 0.43	3.03 ± 0.61	3.05 ± 0.44	2.93 ± 0.68	0.969
	n = 155	**n = 149**	**n = 158**	**n = 160**	**n = 115**	
Urea (mg/dl)	31.19 ± 11.42	33.58 ± 11.45	34.27 ± 14.83	34.66 ± 14.11	38.40 ± 26.20	**0.044**
	n = 158	**n = 149**	**n = 169**	**n = 165**	**n = 125**	
Creatinine (mg/dl)	0.83 ± 0.30	0.83 ± 0.20	0.85 ± 0.27	0.88 ± 0.33	0.92 ± 0.62	0.321
GFR (ml/min/1.73 m^2)	84.57 ± 19.71	80.52 ± 19.99	82.37 ± 24.59	79.32 ± 29.62	85.73 ± 32.52	**0.021**
	n = 126	**n = 118**	**n = 127**	**n = 129**	**n = 76**	
Uric Acid (mg/dl)	4.69 ± 1.31	4.85 ± 1.31	5.07 ± 1.44	5.25 ± 1.63	5.54 ± 2.00	**0.008**
	n = 124	**n = 119**	**n = 123**	**n = 122**	**n = 79**	
Total Protein (g/L)	6.99 ± 0.51	6.94 ± 0.60	7.09 ± 0.50	7.02 ± 0.54	6.95 ± 0.65	0.268
	n = 136	**n = 130**	**n = 129**	**n = 127**	**n = 88**	
Albumin (g/L)	4.29 ± 0.39	4.40 ± 0.38	4.30 ± 0.46	4.30 ± 0.38	4.13 ± 0.59	**0.010**

PTH: parathormone; ALP: alkaline phosphatase; TSH: thyroid stimulating hormone; GFR: glomerular filtration rate

difference between groups (P <0.05). With the help of Bonferonni Correction (pairwise comparisons), it was examined which groups caused the differences related to variables that were found significant. As a result of the analysis, it was found that calcium and PTH values had a statistically significant difference between Group 3, Group 4, Group 5 and Group 1, Group 2 (P <0.05). It was found that there was a statistically significant difference in urea values between Group 2, Group 4, Group 5 and Group 1 (P <0.05). It was found that there was a statistically significant difference in GFR values between Group 4 and Group 5, between Group 1 and Group 4, between Group 1 and Group 2 (P <0.05). Uric acid values were found to have a statistically significant difference between Group 3, Group 4, Group 5 and Group 1 (P <0.05). Albumin values were found to have a statistical difference between Group 3, Group 4, Group 5 and Group 2. Albumin values also showed a statistical difference between Group 1 and Group 2 (Table 2).

There was no statistically significant relationship between the age groups of 18-64 years and ≥65 years in terms of gender (P >0.05), while it was found that there was a relationship between calcium groups and age groups (P <0.05). The incidence of hypercalcemia was determined to be statistically significantly higher in

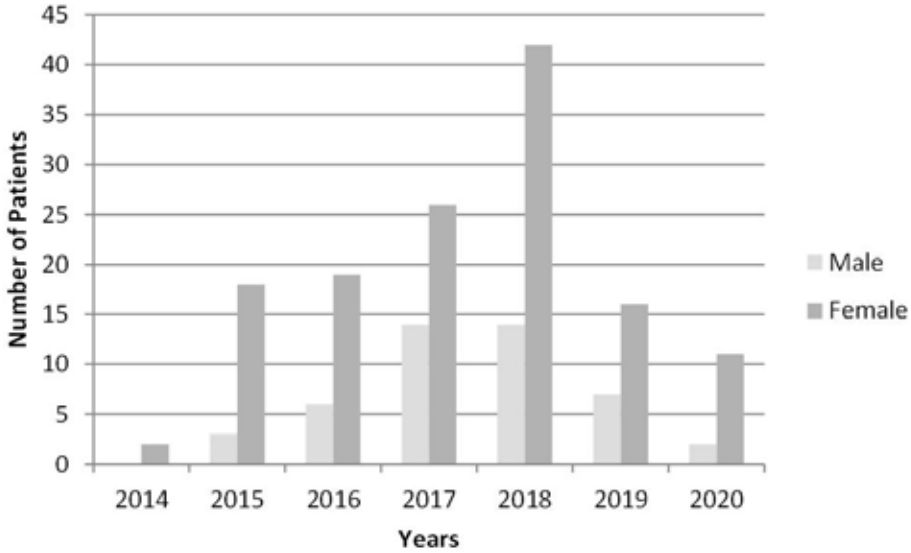

Figure 1: Distribution of patients with Vitamin D intoxication by years in our hospital (2014-2020)

the ≥65 age group (*P*=0.004). 25(OH) vitamin D, PTH, phosphorus, ALP and TSH values have no significant difference in age groups (*P* >0.05); however, magnesium, urea, creatinine, GFR, uric acid, total protein and albumin values were found to have a significant difference in age groups (*P* <0.05). Magnesium, GFR, total protein and albumin values showed no statistically significant difference in the 18-64 age group; on the other hand, urea, creatinine and uric acid values in the group aged 65 and over arose to be statistically significantly higher (Table 3).

No statistically significant relationship emerged between calcium groups and gender (*P* >0.05). 25(OH) vitamin D, calcium, ALP, TSH, GFR, total protein and albumin values had no statistically significant difference in terms of gender groups (*P* >0.05); PTH, phosphorus, magnesium, urea, creatinine and uric acid values were revealed to have a significant difference in gender groups (*P* <0.05). It was figured out that PTH and phosphorus values were significantly higher in women, while magnesium, urea, creatinine and uric acid values were significantly higher in men (Table 4).

Magnesium, ALP, TSH, total protein and albumin values of laboratory parameters in comparison of normocalsemic and hypercalcemic patients showed no statistically significant difference (*P* >0.05); 25(OH) vitamin D, PTH, phosphorus, urea, creatinine, GFR and uric acid values were found to have a statistically significant difference (*P* <0.05). It was concluded that compared to PTH and GFR values in normocalsemic patients, 25(OH) vitamin D, phosphorus, urea, creatinine and uric acid values in hypercalcemic patients were statistically significantly higher (Table 5). In our study, it was found that the likelihood of developing hypercalcemia in vitamin D excess was more common in elderly patients and patients with renal failure.

DISCUSSION

American Association of Poison Control Center reported that there were 25,397 people with vitamin D toxicity between 2000 and 2014. While the annual average number of cases was 196 between 2000 and 2005, it was reported that there were 4535 new cases per year between 2005 and 2011[5]. In our study, we found that the annual average number of patients with vitamin D intoxication who applied to our hospital by years tended to decrease in 2019 and 2020 (Figure 1). In the COVID-19 pandemic which affected the world, the intake of vitamin supplements became more popular. In addition to the increased awareness of chronic diseases associated with vitamin D deficiency, we welcome the decrease in the number of vitamin D intoxication in patients who have applied to our hospital in the last two years, which is the result of the increase in vitamin D screening and the increased awareness of negative conditions caused by vitamin D excess.

It is defined as vitamin D intoxication when the 25(OH) vitamin D level is 150 ng/ml[6]. The first laboratory findings of vitamin D toxicity are hypercalciuria and hypercalcemia. Other laboratory findings of vitamin D intoxication are high serum phosphorus levels, high ALP activity, low PTH and high serum 25(OH) vitamin D levels. These findings were seen in cases where the 25(OH) vitamin D level was above 88 ng/ml (220 nmol/l)[4]. Especially in recent years, the incidence of vitamin D intoxication has increased due to excessive and unnecessary use of vitamin D. The findings of vitamin D intoxication

Table 3: Descriptive statistics for age groups, comparison of relationships and differences

Parameters Mean ± S.D.	18-64 years (n=483)	65+ years (n=287)	*P*-value
Gender Female Male	 378 (62.8) 105 (62.5)	 224 (37.2) 63 (37.5)	 0.945
Calcium Normocalcemic Hypercalcemic	 459 (64.1) 24 (44.4)	 257 (35.9) 30 (55.6)	 **0.004**
	n = 483	**n = 287**	
25(OH) D Vitamin (ng/ml)	97.16 ± 72.24	99.81 ± 56.78	0.065
Calcium (mg/dl)	9.60 ± 0.41	9.71 ± 0.71	0.195
	n = 430	**n = 250**	
PTH (pg/ml)	34.95 ± 12.44	36.22 ± 12.70	0.176
	n = 409	**n = 252**	
Phosphorus (mg/dl)	3.56 ± 0.54	3.56 ± 0.52	0.798
	n = 334	**n = 200**	
Magnesium (mg/dl)	1.93 ± 0.17	1.90 ± 0.30	**0.009**
	n = 355	**n = 239**	
ALP (U/L)	68.86 ± 25.77	72.78 ± 36.03	0.178
	n = 432	**n = 241**	
TSH (mU/L)	2.18 ± 2.03	2.16 ± 1.62	0.967
	n = 459	**n = 278**	
Urea (mg/dl)	28.80 ± 9.04	43.15 ± 20.32	**< 0.001**
	n = 480	**n = 286**	
Creatinin (mg/dl)	0.80 ± 0.36	0.95 ± 0.33	**< 0.001**
GFR (ml/min/1.73 m^2)	90.41 ± 24.23	68.83 ± 21.87	**< 0.001**
	n = 336	**n = 240**	
Uric Acid (mg/dl)	4.65 ± 1.28	5.59 ± 1.70	**< 0.001**
	n = 336	**n = 231**	
Total Protein (g/L)	7.13 ± 0.48	6.82 ± 0.60	**< 0.001**
	n = 370	**n = 240**	
Albumin (g/L)	4.45 ± 0.32	4.06 ± 0.50	**< 0.001**

PTH: parathormone; ALP: alkaline phosphatase; TSH: thyroid stimulating hormone; GFR: glomerular filtration rate

develop as a result of hypercalcemia. Gastrointestinal findings as a result of hypercalcemia are anorexia, nausea, vomitting, constipation, abdominal pain and pancreatitis. Cardiac symptoms are arrhythmia and hypertension. Central nervous system findings such as lethargy, hypotonia, confusion, depression, psychosis, hallucinations and coma can be seen[7].

In the literature, it has been shown in studies that vitamin D intoxication findings can be seen in vitamin D levels that do not reach toxic levels, and that there is no relationship between increased vitamin D level and serum calcium levels[8]. In our study, we found that mild hypercalcemia could be even seen in the group with a recommended vitamin D level of 30-50 ng/ml.

In the study of Perez-Barrios *et al*, hypercalcemia was found in 51 (11.1%) people with 475 D hypervitaminosis, and only 15 (<4%) of hypercalcemic patients were found to be associated with high vitamin D level[9]. In our study, we found hypercalcemia in 14 (8.5%) out of 165 people with D hypervitaminosis and 16 (12.5%) out of 127 people with vitamin D intoxication.

For patients with normal calcium levels in vitamin D intoxication, the mechanism has not been fully elucidated. Possible mechanism is that serum calcium level may be found to be normal as a result of vitamin D not being stored in adipose tissue due to vitamin D receptor insensitivity and low body fat ratio[10].

Table 4: Descriptive statistics of gender groups, comparison of relationships and differences filtration rate

Parameters Mean ± S.D.	Female (n=602)	Male (n=168)	*P*-value
Calcium Normocalcemic Hypercalcemic	 564 (78.8) 38 (70.4)	 152 (21.2) 16 (29.6)	 0.149
	n = 602	**n = 168**	
25(OH) vitamin D (ng/ml)	97.67 ± 67.79	99.90 ± 63.65	0.649
Calcium (mg/dl)	9.62 ± 0.51	9.70 ± 0.66	0.100
	n = 541	**n = 139**	
PTH (pg/ml)	35.96 ± 12.53	33.27 ± 12.43	**0.033**
	n = 519	**n = 142**	
Phosphorus (mg/dl)	3.62 ± 0.52	3.35 ± 0.55	**< 0.001**
	n = 419	**n = 115**	
Magnesium (mg/dl)	1.91 ± 0.24	1.95 ± 0.19	**0.036**
	n = 477	**n = 117**	
ALP (U/L)	69.40 ± 26.76	74.67 ± 41.83	0.513
	n = 529	**n = 144**	
TSH (mU/L)	2.23 ± 2.04	1.96 ± 1.23	0.547
	n = 578	**n = 159**	
Urea (mg/dl)	33.24 ± 14.70	37.74 ± 19.53	**0.002**
	n = 601	**n = 165**	
Creatinine (mg/dl)	0.80 ± 0.27	1.07 ± 0.53	**< 0.001**
GFR (ml/min/1.73 m^2)	82.80 ± 25.86	80.73 ± 24.58	0.410
	n = 445	**n = 131**	
Uric acid (mg/dl)	4.85 ± 1.46	5.70 ± 1.63	**< 0.001**
	n = 439	**n = 128**	
Total Protein (g/L)	6.99 ± 0.54	7.03 ± 0.59	0.692
	n = 473	**n = 137**	
Albumin (g/L)	4.31 ± 0.41	4.26 ± 0.53	0.851

PTH: parathormone; ALP: alkaline phosphatase; TSH: thyroid stimulating hormone; GFR: glomerular

Table 5: Descriptive statistics of calcium groups, comparison of relationships and differences

Parameters Mean ± S.D.	Normocalcemic n = 716	Hypercalcemic n = 54	*P*-value
25(OH) vitamin D (ng/ml)	96.97 ± 67.86	113.81 ± 49.94	**0.002**
Calcium (mg/dl)	9.55 ± 0.35	10.82 ± 1.07	**<0.001**
	n = 635	**n = 45**	
PTH (pg/ml)	35.85 ± 12.22	29.26 ± 15.40	**0.005**
	n = 618	**n = 43**	
Phosphorus (mg/dl)	3.55 ± 0.53	3.80 ± 0.63	**0.004**
	n = 495	**n = 39**	
Magnesium (mg/dl)	1.92 ± 0.22	1.90 ± 0.27	0.404
	n = 559	**n = 35**	
ALP (U/L)	70.18 ± 30.52	74.49 ± 27.56	0.184
	n = 632	**n = 41**	
TSH (mU/L)	2.16 ± 1.91	2.32 ± 1.75	0.412
	n = 688	**n = 49**	
Urea (mg/dl)	33.13 ± 12.87	49.43 ± 35.82	**< 0.001**
	n = 714	**n = 52**	
Creatinine (mg/dl)	0.83 ± 0.26	1.18 ± 0.93	**< 0.001**
GFR (ml/min/1.73 m^2)	83.50 ± 24.76	66.63 ± 31.26	**< 0.001**
	n = 536	**n = 40**	
Uric acid (mg/dl)	4.95 ± 1.44	6.22 ± 2.23	**< 0.001**
	n = 528	**n = 39**	
Total Protein (g/L)	7.00 ± 0.53	6.98 ± 0.79	0.606
	n = 570	**n = 40**	
Albumin (g/L)	4.31 ± 0.41	4.11 ± 0.72	0.711

PTH: parathormone; ALP: alkaline phosphatase; TSH: thyroid stimulating hormone; GFR: glomerular filtration rate

In our study, a statistically significant difference was found in the comparison of hypercalcemic patients with normocalcemic patients as the former had high creatinine and low GFR (P <0.001). It is necessary to monitor vitamin D, calcium, phosphorus and parathormone values in people with kidney dysfunction and taking vitamin D replacement. In addition, we observed in our study that the age group at greatest risk for the development of hypercalcemia due to vitamin D excess is ≥65 years of age. Most of the patients with vitamin D intoxication used vitamin D ampoules at frequent intervals. Vitamin D ampoule in Turkey contains 300,000 IU (7.5 mg) vitamin D3 in each 1 ml ampoule. Health legislation needs to be changed to ensure limited use of preparations containing very high doses of vitamin D. The use of high dose vitamin D may be required of obese patients, patients with malabsorption, and patients using glucocorticoid, antiepileptic and AIDS drugs[11]. Patients receiving high dose vitamin D replacement should have patient education and close monitoring of 25(OH) vitamin D and calcium levels is necessary. In our study, it was confirmed in the medical record reviews of the patients that they had vitamin D supplements. It was observed that they used vitamin D drops in prescription, more often 1 ampoule of vitamin D per week for a few months. In the outpatient follow-up of the patients who were found to be mildly hypercalcemic, it was observed that the calcium levels returned to normal. In the excess of vitamin D, high 25(OH) vitamin D levels can be observed for up to 1 year due to vitamin D stored in fat, and persistent hypercalcemia can be caused by constantly high 25(OH) vitamin D levels[12]. Mortality due to hypercalcemia was observed in 3 of the patients with vitamin D excess. Necrotizing pancreatitis due to hypercalcemia (calcium value was 14.12 mg/dl) and mortality were observed in 1 patient in the group with 25(OH) vitamin D 100-150 ng/ml. Upon the detection of 25(OH) vitamin D (6.9 ng/ml; calcium value 3 months earlier: 9.4 mg/dl) in the examinations of our patient who developed necrotizing pancreatitis 3 months earlier, it was observed that he consumed 300,000 IU of cholecalciferol-containing vitamin D weekly and took a daily calcium pill containing 1000 mg. In the literature, there are case reports of hypercalcemia and pancreatitis due to vitamin D intoxication[13,14]. Both in 1 patient in the group with 25(OH) vitamin D of 100-150 ng/ml (calcium level 14.12 mg/dl) and in 2 patients in the group with 25(OH) vitamin D >150 ng/ml (calcium levels 13.44 mg/dl and 16.15 mg/dl), mortality due to hypercalcemia was observed. The potential for chronic adverse events in vitamin D excess is, therefore, of concern. For the extra-bone effects of vitamin D, a 25(OH) vitamin D level of 30-50 ng/ml is recommended[15]. Hypervitaminosis D is defined as 25(OH) vitamin D level >100 ng/ml[16]. Vitamin D intoxication is defined as 25(OH) vitamin D level >150 ng/ml[17]. There is a wide range between the recommended values of 30-50 ng/ml for 25(OH) vitamin D level and 100 ng/ml described for vitamin D excess. Although the detrimental effects of acute vitamin D intoxication have been described, it has not been clarified whether chronic moderate-dose vitamin D has potential harmful effects on health. Until studies prove the reliability of keeping 25(OH) vitamin D above 50 ng/ml, 25(OH) vitamin D and calcium levels should be closely monitored in people prescribed vitamin D.

No single standard value has been established for optimal 25(OH) vitamin D levels in bone health. The American Institute of Medicine (IOM) stated that the 25(OH) vitamin D level should be above 20 ng/ml (50 nmol/L)[18]. American Endocrine Society and American Geriatrics Society recommended 25(OH) vitamin D level to be above 30 ng/ml (75 nmol/L)[17,19]. Optimal 25(OH) vitamin D level for extra-skeleton effects of

vitamin D could not be determined. For the extra-skeleton effects of vitamin D, a 25(OH) vitamin D level of 30-50 ng/ml is recommended[15].

IOM recommends a minimum daily intake of 600 IU for bone health between ages 17-71 and 800 IU for ages 71 and older[20]. The highest dose of vitamin D that will pose no risk of side effects is unknown. Complications and mortality occurred in three patients who developed hypercalcemia due to high-dose vitamin D use in our study. In order to prevent prescription errors that lead to negative results, care should be taken about the use of high-dose formulations and the daily requirement recommended in the guidelines. In the study of Bischoff-Ferrari *et al*, it was shown that the risk of falling is higher in men and women over the age of 70 who are given monthly high-dose vitamin D compared to the group given lower-dose vitamin D, and this treatment approach has been abandoned[21].

Our study has limitations as it was planned retrospectively. The hypercalciuria value of the patients is not available in our database. The amount of hypercalciuria could not be evaluated in the evaluation of acute toxicity in normocalcemic patients with 25(OH) vitamin D excess. The acute toxicity of the patients was evaluated, and the long-term side effects could not be evaluated.

As a result, both inadequate treatment of vitamin D deficiency and excessive, high-dose treatment can have significant health consequences.

Learning Points

Vitamin D toxicity is mostly iatrogenic and preventable. Awareness should be raised among physicians about the careful use of over-the-counter and uncontrolled vitamin D supplements in the community, where high-dose prescribed vitamin D may cause toxicity. Patients taking vitamin D supplements should be followed up clinically, as well as their laboratory values.

CONCLUSION

In our study, most patients with D hypervitaminosis and vitamin D intoxication were normocalcemic but severe hypercalcemia was also observed. Vitamin D supplementation should be given according to the clinical guideline recommendations.

ACKNOWLEDGMENT

All the authors designed the study and contributed to literature search. Dr. Calim acquired data and drafted the article.

The authors declare that they have no conflict of interest.

REFERENCES

1. Holick MF. Vitamin D: a D- lightful health perspective. Nutr Rev 2008; 66:S182-94.
2. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, *et al*. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-A review of recent evidence. Autoimmun Rev 2013; 12:976-89.
3. Souberbielle JC, Body JJ, Lappe JM, Plebani M, Shoenfeld Y, Wang TJ, *et al*. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. Autoimmun Rev 2010; 9:709-15.
4. Dudenkov DV, Yawn BP, Oberhelman SS, Fischer PR, Singh RJ, Cha SS, *et al*. Changing incidence of serum 25-hydroxyvitamin D values above 50 ng/ml: A 10-year population-based study. Mayo Clin Proc 2015; 90:577-86.
5. Spiller HA, Good TF, Spiller NE, Aleguas A. Vitamin D exposures reported US poison centers 2000-2014: Temporal trends and outcomes. Hum Exp Toxicol 2016; 35(5):457-61.
6. Hossein-Nezhad A, Holick MF. Vitamin D for health: a global perspective. Mayo Clin Proc 2013; 88(7):720-55.
7. Awumey EM, Mitra DA, Hollis BW, Kumar R, Bell NH. Vitamin D metabolism is altered in Asian Indians in the southern United States: a clinical research center study. J Clin Endocrinol Metab 1998; 83:169-73.
8. Lee JP, Tansey M, Jetton JG, Krasowski MD. Vitamin D toxicity: A 16- year retrospective study at an Academic Medical Center. Lab Med 2018; 49(2):123-9.
9. Pérez-Barrios C, Hernández-Álvarez E, Blanco-Navarro I, Pérez-Sacristán B, Granado-Lorencio F. Prevalence of hypercalcemia related to hypervitaminosis D in clinical practice. Clin Nutr 2016; 35(6):1354-8.
10. Curran JS, Barness LA. Hypervitaminosis D. Nelson Textbook of Pediatrics' de. Ed. Behrman RE, Kliegman RM, Jenson HB. Nelson Textbook Pediatrics. Philaldelphia, W. B. Saunders, 2000; p 87-8.
11. Wacker M, Holick MF. Vitamin D effects on skeletal and extraskeletal health and the need for supplementation. Nutrients 2013; 5:111-48.
12. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations and safety. Am J Clin Nutr 1999; 69:842-56.
13. Waele BD, Smitz J, Willems G. Recurrent pancreatitis secondary to hypercalcemia following vitamin D poisoning. Pancreas 1989; 4:378-80.
14. de Paula ALT, Gonzaga WPF, Oliveria LM, Feibelmann TCM, Markus J. Exogenous intoxication by non-prescribed use of vitamin D, a case report. BMC Geriatr 2020; 20(1):221.
15. Pludowski P, Holick MF, Grant WB, Konstantynowicz J, Mascarenhas MR, Haq A, *et al*. Vitamin D supplemantation guidelines. J Steroid Biochem Mol Biol 2018; 175:125-35.
16. Ozkan B, Hatun S, Bereket A. Vitamin D intoxication. Turk J Pediatr 2012; 54(2):93-8.

17. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, *et al*. Endocrine Society: Evaluation, treatment and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96:1911-30.
18. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, *et al*. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011; 96(1):53-8.
19. Judge J, Birge S, Gloth FM, Heaney RP, Hollis BW, Kenny A, *et al*. Recommendations abstracted from the American Geriatrics Society Consensus Statement on vitamin D for Prevention of Falls and their Consequences. J Am Geriatr Soc 2014; 62:147-52.
20. Institute of Medicine Committee to Review Dietary Reference Intakes for Calcium and Vitamin D. In: Ross AC, Taylor CL, Yaktine AL, Valle HBD; editors. Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC), National Academies Press, 2011; 5. p 345-390.
21. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, *et al*. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. JAMA Intern Med 2016; 176:175-83.

Original Article

Expression levels and clinical significance of CEA, fibrinogen and D-dimer in lung adenocarcinoma patients

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Kuwait Medical Journal 2026; 58 (3): 187 - 192

ABSTRACT

Objective: To explore the levels of carcinoembryonic antigen (CEA), fibrinogen and D-dimer in lung adenocarcinoma (LUAD) patients with different clinical stages and metastatic states.
Design: Prospective study
Setting: Department of Respiratory Medicine, The Affiliated Suqian Hospital of Xuzhou Medical University, China
Subjects: A total of 207 LUAD patients and 196 normal volunteers were enrolled in this study.
Interventions: CEA, fibrinogen and D-dimer levels in peripheral blood of LUAD patients and normal subjects were compared, and their expression levels were explored in patients with different clinical stages and metastasis status.
Main outcome measure: In this study, we detected the CEA, fibrinogen and D-dimer levels in LUAD patients with different clinical stages and metastatic states.
Results: CEA, fibrinogen and D-dimer levels were increased in LUAD patients compared with those in normal subjects [17.96±15.62 ng/mL, 5.38±3.12 g/L, 1.31±1.41 mg/L *vs*. 4.21±2.31 ng/mL, 3.57±2.17 g/L, 0.48±0.31 mg/L; P <0.001]. Patients with stages III-IV LUAD presented higher levels of CEA, fibrinogen and D-dimer than those with stages I-II [32.16±9.20 ng/mL, 5.88±0.98 g/L, 1.81±0.67 mg/L *vs*. 7.01±5.22 ng/mL, 4.02±1.01 g/L, 0.64±0.44 mg/L; P <0.05]. Higher levels of CEA, fibrinogen and D-dimer were observed in patients with pleural metastases compared to those without pleural metastases [32.75±12.10 ng/mL, 6.47±1.05 g/L, 1.88±0.50 mg/L *vs*. 7.63±4.03 ng/mL, 4.11±1.09 g/L, 0.52±0.90 mg/L; P <0.001]. Moreover, CEA levels in patients with lymph node (29.20±10.73 ng/mL) and bone metastases (33.46±24.54 ng/mL) were higher than those without metastases [8.45±5.71 ng/mL, 6.27±6.02 ng/mL] (P <0.05).
Conclusion: CEA, fibrinogen and D-dimer levels are associated with clinical stages and pleural metastases in LUAD patients. The elevated CEA levels indicate a high risk of lymph node or bone metastases.

KEY WORDS: carcinoembryonic antigen, D-dimer, fibrinogen, lung adenocarcinoma

INTRODUCTION

Lung cancer is one of the most prevalent malignant diseases worldwide with increasing morbidity and mortality. Among different types of lung cancer, lung adenocarcinoma (LUAD) is a common subtype that has a poor prognosis, although a combination of therapies were typically used[1]. Insufficient early screening and distant metastases are significantly associated with poor survival. At present, positron emission tomography/computed tomography (PET/CT) plays an important role in detecting the presence of distant metastases[2]. However, some patients are reluctant to undergo this examination due to financial burdens or subjective factors, thus limiting their individualized treatment.

Substantial studies pose insights into the changes of some biomarkers in lung cancer, such as carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC-Ag), gastrin-releasing peptide (pro-GRP) and cytokeratin 19 fragment (CYFRA21-1)[3-5]. CEA, a type of glycoprotein with human embryo antigen specificity, is one of the earliest applied tumor biomarkers, especially in the diagnosis of LUAD. Now, the abnormal coagulation and fibrinolysis-related indicators are commonly observed in various cancers[6]. Fibrinogen and

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D-dimer are the key components of the coagulation and fibrinolytic system[7]. There is now solid evidence that elevated fibrinogen and D-dimer levels are associated with poor prognosis in non-small cell lung cancer patients[8]. However, their clinical value in predicting lung cancer metastases and clinical stages remains obscure.

The aim of our study was to assess the levels of CEA, fibrinogen and D-dimer in LUAD patients with different clinical stages and metastatic states.

SUBJECTS AND METHODS

Study population

A total of 207 LUAD patients hospitalized in Suqian Hospital Affiliated to Xuzhou Medical University from November 2018 to June 2023 were selected, including 109 males and 98 females. All patients were diagnosed with LUAD by histological or cytological examinations of specimens taken from bronchoscopy or computerized tomography-guided fine needle biopsies. Exclusion criteria were as follows: (1) patients receiving antitumor or anticoagulation therapy; (2) patients with coagulation disorders; (3) patients with extrapulmonary cancer; (4) severe acute or chronic inflammatory disease. At the same time, 196 healthy volunteers were enrolled as normal control group. There were no significant differences in age, gender, BMI, comorbidities, smoking status and alcohol consumption habits between LUAD patients and normal subjects (P >0.05). Ethical approval was granted by the Ethics Committee of Suqian Hospital Affiliated to Xuzhou Medical University, and written informed consents were obtained from all subjects.

Data for demographic and clinical assessments were obtained at the time of recruitment. We assessed the clinical TNM stages of tumors according to the American Joint Committee on Cancer (AJCC) TNM staging criteria[9]. As for the diagnosis of distant metastasis, brain or bone metastases were identified by routine brain contrast-enhanced magnetic resonance imaging or PET/CT; lymphatic metastases were determined by endobronchial ultrasound-guided transbronchial needle aspiration or PET/CT; pleural metastases were confirmed by cytological testing of pleural effusion.

Blood sampling and laboratory analysis

Peripheral blood CEA, fibrinogen and D-dimer levels were detected from all subjects on admission. Serum CEA levels were measured using an electrochemiluminescence immunoassay (Roche Diagnostics, Rotkreuz, Switzerland); plasma fibrinogen levels were measured using a clotting assay (Siemens Healthcare Diagnostics Products GmbH, Germany); plasma D-dimer levels were measured using a nephelometry immunoassay (Axis-Shield PoC AS, Norway). Both assays were performed according to the manufacturer's instructions. The normal upper limits of CEA, fibrinogen and D-dimer were 5.00 ng/mL, 4.00 g/L and 0.55 mg/L, respectively.

Table 1: Demographic and clinical characteristics in LUAD patients

Variables	n (%)
Sex	
Male	109 (52.66)
Female	98 (47.34)
Age	
≤ 60	95 (45.89)
> 60	112 (54.11)
Smoking status	
Ever/current	131 (63.29)
Never	76 (36.71)
Alcohol	
Yes	77 (37.20)
No	130 (62.80)
Tumor location	
Peripheral	111(53.62)
Central	96(46.38)
Differentiation	
Well	20 (9.67)
Moderate	93 (44.93)
Poor	83 (40.10)
TNM stages	
I	22 (10.63)
II	43 (20.77)
III	86 (41.55)
IV	56 (27.05)
Metastases	
Pleura	41 (19.81)
Lymph node	82 (39.61)
Brain	18 (8.70)
Bone	21 (10.14)
Comorbidities	
Cardiovascular diseases	52 (25.12)
Diabetes	29 (14.01)
Cerebrovascular disease	49 (23.67)

TNM: tumor node metastasis

Statistical analysis

All statistical analyses were performed using SPSS, version 18.0. Continuous variables were expressed as mean ± standard deviation (SD), and the between-group differences were compared using a student's t-test. Enumeration data were expressed as numbers (percentages), and the between-group differences were compared using the Chi-square test. P <0.05 was considered statistically significant.

RESULTS

Baseline clinical characteristics of patients

The baseline characteristics of 207 LUAD patients are summarized in Table 1. Among them, 98 patients

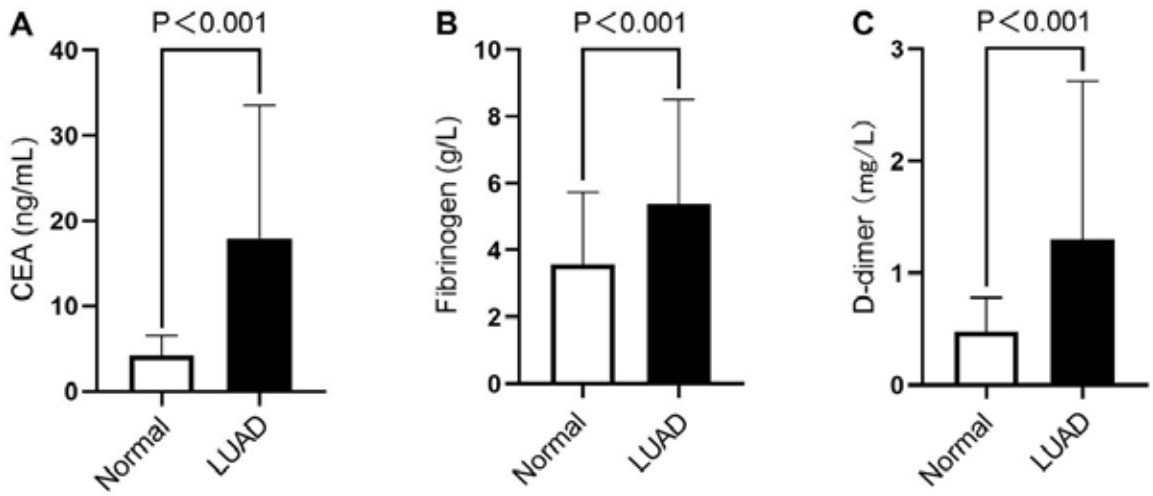

Figure 1: Levels of CEA, fibrinogen and D-dimer in normal and LUAD subjects

were female, 131 had a smoking history and 142 were diagnosed with stage III-IV. Those with pleural, lymph node, brain and bone metastases account for 19.81%, 39.61%, 8.70% and 10.14% of all LUAD patients. Fifty-two patients had cardiovascular diseases, 29 patients had diabetes, and 49 patients had cerebrovascular diseases.

CEA, fibrinogen and D-dimer levels were upregulated in LUAD patients

As shown in Figure 1, we compared the levels of CEA, fibrinogen and D-dimer in 207 LUAD patients and 196 normal subjects. CEA, fibrinogen and D-dimer levels in LUAD patients were significantly higher than those in normal control subjects (17.96±15.62 vs. 4.21±2.31 ng/ml; 5.38±3.12 vs. 3.57±2.17 g/L; 1.31±1.41 vs. 0.48±0.31 mg/L, respectively) (P <0.001).

Levels of the three markers in patients with different clinical stages and metastatic status

The levels of CEA, fibrinogen and D-dimer in LUAD patients at different clinical stages and metastatic status are shown in Table 2. Blood concentrations of the three markers were significantly higher in patients at stage III-IV than those at stage I-II (P <0.05). Fibrinogen and D-dimer levels were elevated in patients with pleural metastases compared with those without pleural metastases (P <0.05). In addition, patients with pleural, bone or lymph node metastases had higher serum CEA levels than those without (P <0.05). The sex, age, smoking status, alcohol consumption habits, tumor location and differentiation degree showed no statistical differences in LUAD patients with different metastatic status and clinical stages (Table 3).

Table 2: Plasma levels of CEA, fibrinogen and D-dimer in LUAD patients with different metastatic status and TNM stages

Variables	CEA (ng/mL)	*P*-value	Fibrinogen (g/L)	*P*-value	D-dimer (mg/L)	*P*-value
Pleural metastases		0.020		0.017		0.003
Yes (n=35)	32.75±12.10		6.47±1.05		1.88±0.50	
No (n=6)	7.63±4.03		4.11±1.09		0.52±0.90	
Lymphatic metastases		0.038		0.612		0.856
Yes (n=69)	29.20±10.73		5.59±1.11		1.51±1.02	
No (n=13)	8.45±5.71		4.87±1.04		0.89±0.81	
Brain metastases		0.066		0.078		0.412
Yes (n=15)	29.73±20.22		6.15±4.09		1.89±1.10	
No (n=3)	8.67±7.35		4.40±1.25		0.65±0.56	
Bone metastases		0.037		0.091		0.301
Yes (n=19)	33.46±24.54		5.53±3.98		1.51±1.58	
No (n=2)	6.27±6.02		4.81±1.30		1.03±0.67	
TNM stages		0.018		0.045		0.027
I-II (n=65)	7.01±5.22		4.02±1.01		0.64±0.44	
III-IV (n=142)	32.16±9.20		5.88±0.98		1.81±0.67	

TNM: tumor node metastasis

Table 3: The clinical parameters of LUAD patients with different metastatic status and clinical stages

Variables	Pleural metastases Yes/No (n)	*P*-value	Lymphatic metastases Yes/No (n)	*P*-value	Brain metastases Yes/No (n)	*P*-value	Bone metastases Yes/No (n)	*P*-value	TNM stages I-II/III-IV (n)	*P*-value
Sex		0.622		0.959		0.813		0.979		0.946
Male	23/86		43/66		9/100		11/98		34/75	
Female	18/80		39/59		9/89		10/88		31/67	
Age		0.679		0.917		0.897		0.768		0.959
≤ 60	20/75		38/57		8/87		9/86		30/65	
> 60	21/91		44/68		10/102		12/100		35/77	
Smoking status		0.481		0.577		0.841		0.890		0.111
Ever/Current	24/107		50/81		11/120		13/118		36/95	
Never	17/59		32/44		7/69		8/68		29/47	
Alcohol		0.321		0.056		0.723		0.297		0.236
Yes	18/59		24/53		6/71		10/67		28/49	
No	23/107		58/72		12/118		11/119		37/93	
Tumor location		0.730		0.574		0.863		0.733		0.577
Peripheral	21/90		42/69		10/101		12/99		33/78	
Central	20/76		40/56		8/88		9/87		32/64	
Differentiation		0.703		0.857		0.774		0.906		0.853
Well/Moderate	22/91		45/68		7/106		9/104		34/79	
Poor	18/65		32/51		6/77		7/76		26/57	

TNM: tumor node metastasis

DISCUSSION

LUAD is a subtype of lung malignancy originating from the bronchial mucosa and its gland epithelium[2]. The detection of tumor biomarkers is a simple and non-invasive method for diagnosis, disease monitoring and efficacy assessment for LUAD[10]. Our study revealed that the levels of CEA, fibrinogen and D-dimer were significantly correlated with clinical stages of LUAD patients, and were closely associated with pleural metastases. Furthermore, CEA concentrations were associated with lymph node and bone metastases. These findings could deepen our understanding of those biomarkers and may guide the comprehensive treatment for LUAD patients.

CEA, a broad-spectrum tumor biomarker, has been identified at high expression levels in many solid tumors. It is widely used for differential diagnosis, disease monitoring and efficacy determination of malignancies[2,11]. Specifically, it is a robust biomarker for diagnosing LUAD. Many studies suggested that elevated CEA levels were related to higher TNM stages in patients with LUAD[3,4]. In our study, we found elevated CEA levels were associated not only with higher TNM stages but also with pleural, bone and lymph node metastases in LUAD patients. Wang *et al*[12] reported that increased CEA levels were correlated with the development of brain metastases in LUAD patients. Similarly, we also found the CEA levels tend to be higher in patients with brain metastases, but this difference was not statistically significant. This may be attributed to the small sample size of patients with brain metastases (8.70%). Therefore, the role of CEA in predicting brain metastases requires further discussion in the context of LUAD.

Abnormalities of the coagulation and fibrinolytic system have been observed in various malignancies, such as gastric cancer, pancreatic cancer and colon cancer. Clinical studies have shown that tumor-induced coagulation and fibrin formation are necessary for tumor metastasis and invasion[8]. Levi M *et al*[6] revealed disseminated intravascular coagulation or venous thromboembolism occurred in 50% of malignant tumor patients. Blom JW *et al*[13] reported that the risk of venous thrombosis in lung cancer patients was 20-fold higher than that in the general population. More than that, they found patients with adenocarcinoma have the highest risk of developing venous thrombosis. Nowadays, many studies emphasize the involvement of coagulation and fibrinolytic indicators in tumor angiogenesis, metastases and invasion[6,13].

Fibrinogen, an essential constituent of the coagulation system, is mainly synthesized by hepatic cells[14]. It mediates many biological processes in malignant tumors, such as adhesion, invasion and angiogenesis[15]. High plasma fibrinogen levels were reported in various carcinomas. Palumbo *et al*[16] found that fibrinogen contributes to the adhesion and survival of tumor cells, which results in distant metastases. Furthermore, they revealed that the deficiency of fibrinogen markedly reduced the spontaneous metastasis through both hematogenous and lymphatic routes in mice tumor model. In lung cancer, high plasma fibrinogen levels were associated with poor progression-free survival and overall survival[15]. Our

study showed that the patients with advanced LUAD presented higher fibrinogen levels than those at an early tumor stage (P <0.05). Furthermore, increased fibrinogen levels are associated with pleural metastases. We also found an increasing trend of plasma fibrinogen in patients with bone or lymph node metastases compared with those without these metastases, however, without statistical significance. In a word, fibrinogen is a potential biomarker for predicting tumor progression and metastasis in LUAD patients.

D-dimer is an end product of fibrin degradation. The increase of D-dimer often indicates active thrombosis and fibrinolysis in the body. It plays an important role in the diagnosis of venous thromboembolism, cardiovascular disease, disseminated intravascular coagulation and infectious diseases[17]. High levels of plasma D-dimer have been found in many human malignancies, which is of great significance for the clinical exclusion of tumor-associated thrombosis[18]. According to previous investigation, elevated D-dimer levels were associated with lymph node metastases in LUAD patients[19]. Guo *et al*[20] also found that plasma D-dimer levels were significantly increased in lung cancer patients with distant metastases. Consistent with these studies, we found elevated plasma D-dimer levels were correlated with tumor stage and pleural metastases in LUAD patients. Therefore, monitoring the D-dimer levels in LUAD patients can help to judge and predict the disease condition.

There were a few limitations to our study. First, all metastatic lesions were not confirmed by histopathologic biopsy. Second, the selection bias must be considered because all subjects were recruited from a single center. Moreover, it should be pointed out that our study was exclusively carried out on LUAD patients. Thus, more extensive multicenter studies containing other types of lung cancer are necessary to further confirm these results.

CONCLUSION

Our study confirms that CEA, fibrinogen and D-dimer can serve as viable biomarkers for clinicians to assess the condition of LUAD patients. In addition, these biomarkers can be detected using conventional instruments, which are economical and practical. Further studies are necessary to elucidate their exact roles and specific mechanisms in LUAD.

ACKNOWLEDGMENT

Funding: This research was supported by Suqian Sci & Tech Program, Suqian, China (K202007).

Conflicts of interest: There are no conflicts of interest.

Authors' Contributions: Bin Shi, Xing Liu and Wei Shen: proposal writing, data collection, analysis of data, interpretation of data; Xing Liu and Xiaoyu Wang: manuscript preparation and review of the manuscript. Bin Shi, Rui Wang and Xing Liu: data collection, analysis and draft preparation.

REFERENCES

1. Bade BC, Dela Cruz CS. Lung Cancer 2020: epidemiology, etiology, and prevention. Clin Chest Med 2020; 41(1):1-24.
2. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, *et al*. Non-Small Cell Lung Cancer, Version 3.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2022; 20(5):497-530.
3. Hashinokuchi A, Haratake N, Takenaka T, Matsudo K, Nagano T, Watanabe K, *et al*. Clinical significance of the combination of preoperative SUVmax and CEA in patients with clinical stage IA lung adenocarcinoma. Thorac Cancer 2022; 13(18):2624-32.
4. Wang Z, Huang J, Wang M, Bi W, Fan T. Analysis on the effects of CT- and ultrasound-guided percutaneous transthoracic needle biopsy combined with serum CA125 and CEA on the diagnosis of lung cancer. J Healthc Eng 2022; 2022:2289432.
5. Khanmohammadi A, Aghaie A, Vahedi E, Qazvini A, Ghanei M, Afkhami A, *et al*. Electrochemical biosensors for the detection of lung cancer biomarkers: A review. Talanta 2020; 206:120251.
6. Levi M. Disseminated intravascular coagulation in cancer: an update. Semin Thromb Hemost 2019; 45(4):342-7.
7. Marcianò T, Franchini S. Could a D-dimer/fibrinogen ratio have a role in ruling-out venous thromboembolism? Emerg Med J 2022; 39(12):941-4.
8. Shiina Y, Nakajima T, Yamamoto T, Tanaka K, Sakairi Y, Wada H, *et al*. The D-dimer level predicts the postoperative prognosis in patients with non-small cell lung cancer. PLoS One 2019; 14:e0222050.
9. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017; 67(2):138-55.
10. Dal Bello MG, Filiberti RA, Alama A, Orengo AM, Mussap M, Coco S, *et al*. The role of CEA, CYFRA21-1 and NSE in monitoring tumor response to Nivolumab in advanced non-small cell lung cancer (NSCLC) patients. J Transl Med 2019; 17(1):74.
11. Zhou W, Yang Y, Wang Z. Impact of HSP90α, CEA, NSE, SCC, and CYFRA21-1 on lung cancer patients. J Healthc Eng 2021; 2021:6929971.
12. Wang W, Bian C, Xia D, He JX, Hai P, Zhao R, *et al*. Combining carcinoembryonic antigen and platelet to lymphocyte ratio to predict brain metastasis of resected lung adenocarcinoma patients. Biomed Res Int 2017; 2017:8076384.
13. Blom JW, Osanto S, Rosendaal FR. The risk of a venous thrombotic event in lung cancer patients: higher risk for adenocarcinoma than squamous cell carcinoma. J Thromb Haemost 2004; 2(10):1760-5.

14. Bialkower M, Garnier G. Fibrinogen diagnostics in major hemorrhage. Crit Rev Anal Chem 2022; 52(1):194-209.
15. Iwasaki M, Ishihara S, Okada S, Shimegi R, Shimomura M, Inoue M. Prognostic impact of using combined plasma fibrinogen level and neutrophil-to-lymphocyte ratio in resectable non-small cell lung cancer. Ann Surg Oncol 2022; 29(9):5699-707.
16. Palumbo JS, Kombrinck KW, Drew AF, Grimes TS, Kiser JH, Degen JL, *et al*. Fibrinogen is an important determinant of the metastatic potential of circulating tumor cells. Blood 2000; 96(10):3302-9.
17. Patel P, Patel P, Bhatt M, Braun C, Begum H, Nieuwlaat R, *et al*. Systematic review and meta-analysis of outcomes in patients with suspected deep vein thrombosis. Blood Adv 2020; 4:2779-88.
18. Di Nisio M, Candeloro M, Potere N, Federici C, Rutjes AWS, Guglielmi MD, *et al*. Age- versus clinical pretest probability-adjusted D-dimer to rule out lower-extremity deep vein thrombosis in ambulatory patients with active cancer. Thromb Res 2023; 225:22-27.
19. Fan S, Zhao G, An G. High pretreatment plasma D-dimer levels are associated with shorter overall survival in patients with small cell lung cancer. J Int Med Res 2019; 47:215-24.
20. Guo J, Gao Y, Gong Z, Dong P, Mao Y, Li F, *et al*. Plasma D-dimer level correlates with age, metastasis, recurrence, tumor-node-metastasis classification (TNM), and treatment of non-small-cell lung cancer (NSCLC) patients. Biomed Res Int 2021; 2021:9623571.

Original Article

Is there any difference between pediatric and adult gastroenterologists in terms of celiac disease management and diagnosis in Turkey?

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Kuwait Medical Journal 2026; 58 (3): 193 - 197

ABSTRACT

Objective: We aimed to assess whether there is any difference among pediatric gastroenterologists (PGs) and adult gastroenterologists (AGs) in terms of CD management and diagnosis in Turkey.
Design: A prospective multi-centre study
Setting: Multicentre in Turkey
Subjects: 119 PGs (71.4% female) and 46 AGs (39.1% female) were included in the study.
Interventions: PGs and AGs from different cities participated in the study. Communication with PGs and AGs was established by face to face or phone, and then a link was sent via Whatsapp to those who voluntarily participated in the study. PGs and AGs were asked to answer and complete web-based questions about CD (https://tr.surveymonkey.com/r/Q4_CD_in_Focus_TUR).
Main outcome measure: 119 PGs (71.4% female; group 1) and 46 AGs (39.1% female; group 2) were analysed in the study.
Results: There was no difference between the two groups in starting tests to investigate celiac disease in the case of malabsorption and in patients with other suggestive gastrointestinal symptoms (100% in PGs vs 100% in AGs). There was a significant difference between the number of biopsies obtained from the duodenum ($P<0.05$). 71.4% of PGs had at least 4 or more duodenal biopsies compared to 52.2% in adults. Regular screening of patients in risk groups (HLA analysis and celiac serologic tests) was higher in PGs than AGs (84.0% vs 65.2%) ($P<0.05$).
Conclusion: PGs obtained at least 4 or more duodenal biopsies compared to AGs. Regular screening of patients in risk groups (HLA analysis and celiac serologic tests) was higher in PGs than AGs (84% vs 65.2%).

KEY WORDS: adult gastroenterologist, celiac disease, intestinal biopsy, pediatric gastroenterologist

INTRODUCTION

Celiac disease (CD) is a life-long systemic disease that causes an immune-mediated enteropathy triggered by gluten intake in genetically susceptible individuals[1,2]. Around the world, 1% of people are considered to be affected by CD. The prevalence of it varies depending on patient age, sex and regional variances. The prevalence of CD has significantly increased over the past three decades due to greater medical knowledge and awareness, as well as the

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widespread use of exceptionally sensitive and specific diagnostic tests for CD[2-4]. It causes a wide range of typical or non-specific symptoms including both intestinal and extra-intestinal manifestation[2,5]. Infants typically have distinct symptoms than older kids do. Younger children are typically affected by gastrointestinal symptoms such as diarrhea, anorexia, abdominal distension and abdominal pain[2]. However, adults frequently have unusual or pauci-symptomatic symptoms and a number of concurrent autoimmune disorders, which can make them more difficult to treat[6].

Despite the fact that the diagnosis of CD in children often initiates with blood testing and is typically followed by an intestinal biopsy, European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines from 2020 recommend that the diagnosis of CD can be done with tissue transglutaminase antibody (tTG) levels greater than 10 times the upper limit of normal and anti-endomysial antibody (EMA) positivity without human leukocyte antigen (HLA) analysis in the absence of clinical findings[7]. As for adults with CD, diagnosis is based on the presence of duodenal villous atrophy and findings from serological testing including tTG and/or EMA levels[8].

In practical applications, we see that there are differences between pediatric gastroenterologists (PGs) and adult gastroenterologists (AGs) in the diagnosis, follow-up and treatment of CD. Considering the fact that CD initiates in childhood and continues into adulthood, there should be consistency between PGs and AGs responsible for the management of the disease. Since there is no study investigating the differences in CD management between PGs and AGs, we aimed to assess whether there is any difference among PGs and AGs in terms of CD management. To our knowledge, this is the first report to explore differences in CD management between PGs and AGs in Turkey.

SUBJECTS AND METHODS

A prospective multi-centre study was conducted on PGs and AGs in the scope of CD SKILLS project which aim to overcome these shortcomings to ensure sustainable public healthcare sector in Turkey. The current study was carried out between June 2021 and December 2022 prospectively, as a part of the Focus on CD SKILLS project. The study was executed following the Declaration of Helsinki. Local Ethics Committee approved the study (Sanko University, Gaziantep, Turkey, 02 June 2021/06). Since Turkey, where the study was conducted, has different geographical regions, the selection of PGs and AGs was based on their working in tertiary hospitals in different geographical regions. Communication with PGs and AGs was established by face to face or phone, and then a link was sent via Whatsapp to those who voluntarily participated in the study. Also, PGs and AGs who did not answer all the questions were excluded from the study. PGs and AGs were asked to answer and complete web-based questions about CD (https://tr.surveymonkey.com/r/Q4_CD_in_Focus_TUR). The questionnaires including ''clinical presentation, diagnostic methodology and treatment with follow-up''; 82 questions in total.

Statistical analysis

The Statistical Package for Social Sciences application, version 22.0 (IBM Corporation, Chicago, IL, United States), was used to conduct the statistical analysis. Descriptive statistics were used for the frequencies, percentages and mean standard deviations (SDs). To ascertain whether the data distribution followed a normal pattern, the Kolmogorov-Smirnov test was used. For nominal data, the independent samples t-test was used. The chi-square test was used to compare categorical variables, whereas the Mann-Whitney U test was used to analyze ranges of numerical variables. If *P*-value is 0.05 or lower, it is considered statistically significant.

RESULTS

One hundred and nineteen PGs (71.4% female; group 1) and 46 AGs (39.1% female; group 2) were included in the study (Table 1). No difference was found between the two groups in initiating tests to investigate CD in terms of malabsorption, other suggestive gastrointestinal symptoms, iron deficiency anaemia of unknown cause and unexplained weight loss. However, there was a statistically significant difference between them when investigating patients in the risk group for CD ($P<0.05$). Also, regular screening of patients in risk groups (HLA analysis and celiac serologic tests) was higher in group 1 than group 2 (84% vs 65.2%; $P<0.05$; Table 2).

We found that the rate of diagnosing CD by histology and serology was 96.6% in children and 89.1% in adults. The rates of diagnosis without biopsy were low in both groups (3.4% in PGs vs 10.9% in AGs).

No difference was found between the two groups in diagnosing with histology and serology (89.9% vs 91.3%; $P>0.05$), and the cases diagnosed based on serology according to the ESPGHAN guideline (3.4% vs 2.2%; $P>0.05$; Table 2).

Even though there was no difference in the number of biopsies taken from the bulb for diagnosis ($P>0.05$), there was a statistically significant difference between the number of biopsies obtained from the duodenum ($P<0.05$). 71.4% of PGs had obtained at least 4 or more

Table 1: Demographic features of pediatric and adult gastroenterologists

Variable	PGs (n=119)	AGs (n=46)
Sex (F/M)	85/34	18/28
ESPGHAN membership	22	-
Membership of Turkish Society of Pediatric Gastroenterology, Hepatology and Nutrition	80	-
Membership of Turkish Society of Gastroenterology	-	13
Academic institution	82	38
Non-academic institution	32	6
Both in academic institution and private practice	2	2
Private practice	3	-

ESPGHAN: European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; PGs: pediatric gastroenterologists; AGs: adult gastroenterologists

duodenal biopsies compared to 52.2% of AGs. Histopathology laboratory used Marsh classification 85% in both groups. AGs used intestinal biopsy more in follow-up of celiac patients especially in selected cases or with ongoing symptoms or in differential diagnosis (P<0.05; Table 2).

There was no statistically significant difference between the groups in the referral of celiac patients to a dietitian and psychologist, and in routine vitamin or trace element supplementation to them at the time of diagnosis (P>0.05). PGs used anthropometric measurements more than AGs during diagnosis and follow-up (98.3% vs 58.7%; P<0.05; Table 2). There was no difference in regularly assessing the quality of life and nutritional compliance of celiac patients (P>0.05).

DISCUSSION

In the current study, the rates of diagnosis without biopsy were low in both groups. 22 (18.5%) of the PGs participating in the study were members of ESPGHAN. Furthermore, we determined that diagnosis without biopsy was mostly applied during the pandemic period and in cases where patients refused to diagnose with biopsy. When CD is diagnosed without biopsy, Turkish families do not strictly follow a gluten-free diet due to socio-cultural reasons.

There are few studies on diagnosing celiac disease without biopsy. Most studies have been conducted in adults and no consensus has been reached. The biopsy-free approach in adults is premature, according to the British Society of Gastroenterology, because the kits are incompatible[9]. In the current study, the cut-off point of tTG level is 20 U/L. Similar to the recommendations of the British Gastroenterological Association, the European Society for the Study of Coeliac Disease (ESsCD) published a guideline in 2019 stating that the issue is under investigation and more data is required prior to a recommendation[10]. On the

Table 2: The differences and similarities between pediatric and adult gastroenterologists

Variable	PGs (n=119)	AGs (n=46)	*P*
The number of biopsies obtained from the duodenum	71.4%	52.2%	<0.05
Investigating patients in the risk group for CD	94.9%	76.0%	<0.05
Regular screening of patients in risk groups (HLA analysis and celiac serologic tests)	84.0%	65.2%	<0.05
Using anthropometric measurements	98.3%	58.7%	<0.05
Initiating tests to investigate CD in terms of malabsorption, other suggestive gastrointestinal symptoms, iron deficiency anaemia of unknown cause and unexplained weight loss.	98.3%	91.3%	>0.05
Diagnosing with histology and serology	96.6%	89.1%	>0.05
The rates of diagnosis without biopsy were low in both groups	3.4%	10.9%	>0.05
The cases diagnosed based on serology according to the ESPGHAN guideline	3.4%	2.2%	>0.05
The number of biopsies taken from the bulb for diagnosis	75.6% (≥2 biopsies)	67.3% (≥2 biopsies)	>0.05
Histopathology laboratory used Marsh classification	85%	85%	>0.05
The referral of celiac patients to a dietitian	50.4%	60.9%	>0.05
The referral of celiac patients to a psychologist	45.4%	43.4%	>0.05

ESPGHAN: European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; PGs: pediatric gastroenterologists; AGs: adult gastroenterologists; CD: Celiac disease; HLA: human leukocyte antigen

other hand, in a study conducted in Turkey in 2022, when no-biopsy approach for diagnosis of CD were applied to adult patients according to the 2020 ESPGHAN guideline, sensitivity for the diagnosis of CD was 71.64%, specifity was 100%. With a cut-off point of 29.4 U/L, its sensitivity was 100% and specificity 99.5%[7,11]. According to the ESPGHAN criteria, this study supports a biopsy-free approach in individuals over the age of 18. This strategy could have an impact on lowering the expense, risk and case load related to diagnostic endoscopy in adult CD. However, this strategy won't be able to significantly affect adult patients until local validation of the test-specific thresholds has taken place[11].

The major drawback of a biopsy-based diagnostic technique is how challenging it is to make a diagnosis because of patchy disease involvement and vague histopathologic alterations. False positives are less frequent than false negatives. Misinterpretations due to various reasons vary between 10% and 20%[12]. Despite the fact that geographical variations in tTGA levels appear to be a significant problem and there are studies suggesting that tTGA tests have low accuracy, at this stage, non-biopsy diagnosis of CD is possible in children with tTGA levels >10 times the upper limit of normal and positive EMA[13,14].

It has long been known that people with diarrhea, abdominal pain, bloating, unintentional weight loss, unexplained iron deficiency anemia or vitamin B12 or folate deficiency anemia, diabetes mellitus and autoimmune thyroid disease are at risk for CD. Typically, initial screening for CD includes serologic tests followed by a small bowel biopsy[15]. In the present study, patients in the risk group with abdominal symptoms were screened for CD in both groups (98.3% in PGs vs 91.3% in AGs). Interestingly, screening for risk groups was more common in the PGs group, regardless of whether there were symptoms suggestive of CD (94.9% vs 76%; $P<0.05$). Nevertheles, we found no difference between the two groups in initial tests to investigate CD in the case of malabsorption, in patients with other suggestive gastrointestinal symptoms, in patients with iron deficiency anemia of unknown cause and in patients with unexplained weight loss. In addition to that, regular screening of patients in risk groups (HLA analysis and celiac serologic tests) was higher in PGs than AGs (84% vs 65.2%; $P<0.05$). ''If a patient from the risk group is found to have negative celiac disease-specific antibodies at the first visit, would you repeat the tests?'' When this question was asked, the rate of repeating the tests was very high in both groups, there was no difference between them (99.6% in PGs vs 91.3% in AGs; $P>0.05$).

Re-intestinal biopsy is recommended, especially in selected cases or with ongoing symptoms or in differential diagnosis[7,16]. Adult gastroenterologists used intestinal biopsy more in follow-up of celiac patients especially in selected cases or with ongoing symptoms or in differential diagnosis. However, there was no statistical difference between them. Especially in school-age children and adolescents, the rate of re-intestinal biopsy was less because it was more difficult to question and follow up dietary compliance. When these patients were followed closely, it was observed that most of them did not comply with the diet. In other words, performing re-intestinal biopsy in the early period both increased the workload and caused financial loss.

After being diagnosed with CD, anthropometric measurements during follow-up are recommended by ESPGHAN guideline[17]. In the current study, PGs used anthropometric measurements more than adult gastroenterologists during diagnosis and follow-up (98.3% vs 58.7%). The reason for this was that anthropometric measurements are not recommended during follow-up and diagnosis in the adult guideline.

The guidelines recommend referral to a specialist dietitian for evaluation of nutritional status and dietary compliance after diagnosis[7,16]. However, both PGs and AGs were less likely to refer patients to a specialist dietitian (50.4% in PGs vs 60.9% in AGs), mainly due to the fact that the doctors evaluated the patients themselves. The patients were evaluated by dietary interview, questioning the compliance with the diet and carefully questioning the symptoms. Other reasons may be the absence of a nutritionist in every center and the insufficient follow up of the guidelines.

Adult and pediatric guidelines recommend referral to a psychologist for both assessment of patients' quality of life and patients who do not adhere to diet[7,16]. In the present study, it was found that patients who did not comply with the diet were referred to a psychologist. The rate of referral to a psychologist at the time of diagnosis was similar in both groups (45.4% in PGs vs 43.4% in AGs). Also, unfortunately both AGs and PGs did not adequately evaluate the quality of life at the time of diagnosis and during follow-up. No statistical difference was observed in regularly assessing the quality of life in celiac patients ($P>0.05$).

The current study has a number of limitations. First, because the study was conducted online, we had to omit the responses of 7 PGs and 4 AGs who did not complete the entire questionnaire. Second, because the majority of PGs and AGs failed to identify their home location, we were unable to compare PGs and AGs on a regional level. Third, there was a small number of AGs who participated in the study. This will definitely affect the results because adult physicians differ in their practice from pediatricians in all specialties.

CONCLUSION

We found no statistical difference between PGs and AGs in diagnosing all cases with biopsies. While the rate of PGs taking at least 4 or more duodenal biopsies to diagnose celiac disease was 71.4%, this rate was 52.2% in AGs. Between two groups, there was a notable difference when investigating patients in the risk group for CD. In addition to that, regular screening of patients in risk groups (HLA analysis and celiac serologic tests) was higher in PGs than AGs (84% vs 65.2%). Pediatric gastroenterologists used anthropometric measurements more than AGs during diagnosis and follow-up (98.3% vs 58.7%). We found that no-biopsy approach for diagnosing CD was very low in our country.

ACKNOWLEDGMENTS

We would like to thank the pediatric gastroenterologists and adult gastroenterologists for participating in the study. Additionally, we are appreciative of all the Focus IN CD project collaborators.

Funding: None

Conflict of Interest: None

Author contributions: Sahin Y designed the study, collected the data, analyzed the data, interpreted the data, conception, and statistical analysis, and wrote the manuscript; Sevinc E collected the data, analyzed the data and wrote the manuscript; Bayrak NA, Varol FI, Akbulut UA and Bukulmez A collected the data, and analyzed the data. All authors had read and approved the final manuscript.

REFERENCES

1. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, *et al*. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012; 54:136-60.
2. Sahin Y. Celiac disease in children: A review of the literature. World J Clin Pediatr 2021; 10:53-71.
3. Lindfors K, Ciacci C, Kurppa K, Lundin KEA, Makharia GK, Mearin ML, *et al*. Coeliac disease. Nat Rev Dis Primers 2019; 5:3.
4. Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, *et al*. Global prevalence of celiac disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018; 16:823-836.e2.
5. Catassi C, Verdu EF, Bai JC, Lionetti E. Coeliac disease. Lancet (London, England) 2022; 399:2413-26.
6. McAllister BP, Williams E, Clarke K. A comprehensive review of celiac disease/gluten-sensitive enteropathies. Clin Rev Allergy Immunol 2019; 57:226-43.
7. Husby S, Koletzko S, Korponay-Szabó I, Kurppa K, Mearin ML, Ribes-Koninckx C, *et al*. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. J Pediatr Gastroenterol Nutr 2020; 70:141-156.
8. Lebwohl B, Rubio-Tapia A. Epidemiology, presentation, and diagnosis of celiac disease. Gastroenterology 2021; 160:63-75.
9. Ludvigsson JF, Bai JC, Biagi F, Card TR, Ciacci C, Ciclitira PJ, *et al*. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. Gut 2014; 63:1210-28.
10. Al-Toma A, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, *et al*. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterol J 2019; 7:583-613.
11. Baykan A, Cerrah S, Ciftel S, Vural MK, Kasap E. A no-biopsy approach for the diagnosis of celiac disease in adults: can ıt be real?. Cureus 2022; 14:e26521.
12. Penny HA, Raju SA, Lau MS, Marks LJ, Baggus EM, Bai JC, *et al*. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. Gut 2021; 70:876-83.
13. Popp A, Kivelä L, Fuchs V, Kurppa K. Diagnosing celiac disease: towards wide-scale screening and serologybased criteria?. Gastroenterol Res Pract 2019; 2019: 2916024.
14. Ylönen V, Lindfors K, Repo M, Huhtala H, Fuchs V, Saavalainen P, *et al*. Non-biopsy serology-based diagnosis of celiac disease in adults ıs accurate with different commercial kits and pre-test probabilities. Nutrients 2020; 12:2736.
15. Al-Toma A, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, *et al*. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterology Journal 2019; 7(5):583-613.
16. Bai JC, Fried M, Corazza GR, Schuppan D, Farthing M, Catassi C, *et al*. World Gastroenterology Organisation global guidelines on celiac disease. J Clin Gastroenterol. 2013; 47:121-6.
17. Mearin ML, Agardh D, Antunes H, Al-Toma A, Auricchio R, Castillejo G, *et al*. ESPGHAN position paper on management and follow- up of children and adolescents with celiac disease. J Pediatr Gastroenterol Nutr 2022; 75(3):369-86.

Original Article

Long-term outcome of bileaflet mechanical valve replacement

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Kuwait Medical Journal 2026; 58 (3): 198 - 204

ABSTRACT

Objectives: The aim of this study was to determine long-term outcomes after bileaflet mechanical valve replacement.
Design: Cohort study
Setting: Department of Surgery, Division of Cardio-thoracic Surgery, Jordan University Hospital, Faculty of Medicine, Amman, Jordan between January 2001 to December 2008. Follow-up was 97.4% over a period of 14-23 years up to January 2024.
Subjects: One hundred and eleven patients with valvular disorders
Intervention: One hundred and eleven patients who had undergone bileaflet mechanical valve replacement
Main outcome measures: Survival rate, valve-related complications and valve related mortality
Results: Overall actuarial survival was 73%. Actuarial freedom from prosthetic valve dysfunction was 95.5%. Mortality was 27% (30 patients out of 111). Complications included thromboembolic events (6.3%), bleeding (7.2%), prosthetic valve endocarditis (3.6%), Warfarin toxicity (9.3%), myocardial infarction (0.9%) and valvular thromboses (0.9%). No structural valvular dysfunction was reported.
Conclusion: Using mechanical bileaflet valve replacement, a low late mortality rate and a low incidence of valve-related events are achievable for at least 14 years. Bileaflet mechanical heart valve prosthesis remains a great choice for patients who require mechanical prosthetic valve replacement. Thromboembolic events and bleeding are major causes for long-term morbidity.

KEY WORDS: bileaflet mechanical heart valve, long-term results, valve related complication

INTRODUCTION

Valve surgery remains the best treatment option for most significant valve lesions and has proved superiority over conservative medical management for most patients with advanced valve disease. Mechanical prostheses have been used worldwide for valvular disease. Lifelong anticoagulation is mandatory for these patients due to the risk of thromboembolism and thrombosis; however, this carries the risk of bleeding related complications. Despite the improvement in surgical techniques and the continuous research to decrease the thrombogenicity of replacement heart valves, the long-term complications of thrombosis, thromboembolism and bleeding are still a major cause of morbidity and mortality and one of the major long-term outcomes of valve replacement surgery[1].

Mechanical valves are very useful as a form of surgical treatment for valvular heart disease. However, owing to improvements in bio-prostheses durability in addition to patient preference to avoid lifetime anticoagulation therapy, the use of bio-prostheses has seen an increase among patients[2,3]. Transcatheter valve implantation has recently been used increasingly as an alternative primary treatment, especially for older patients, due to the lowered risks[4].

In our previous study, we investigated the operative mortality and mid-term (up to eight years) results of mechanical valve replacement. In addition, our data showed that valve replacement with mechanical valves might be performed with low morbidity and mortality[5].

Survival has improved drastically in recent years, with a reported 10-year survival rate following implantation of at least 60%[6-9]. However, many patients experience different unfavorable complications after valve surgery.

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The primary aims of this study were to document patient survival and valve-related events, and the long-term morbidity and mortality, whether cardiac related mortality or not, over the course of 14-23 years post valve replacement.

Our study follows the guidelines for reporting morbidity and mortality after valvular surgery, as published in the European Journal of Cardiothoracic Surgery[10].

MATERIALS AND METHODS

Ethics statement

The Institutional Review Board of Jordan University Hospital approved this study, and all procedures followed and adhered to national and institutional research committee ethical guidelines as well as the World Medical Association Declaration of Helsinki's tenets. Since this study was retrospective, met minimal-risk research requirements, and had no impact on patient safety or clinical care, informed permission was not required. Personal identities were eliminated from spreadsheets used for data analyses and all reports to preserve patient anonymity.

Table 1: Baseline patient characteristics

Patient characteristics	Percentage	
Age (years; mean±SD)	45.5±14.4	
Female sex, n(%)	50 (45.1%)	
Male sex, n(%)	61 (54.9%)	
NYHA class, n(%)		
I-II	29 (25%)	
III-IV	89 (75%)	
Chest pain, n(%)	69 (58%)	
Dyspnea, n(%)	110 (93%)	
Syncope, n(%)	10 (8.5%)	
Palpitation, n (%)	45 (38%)	
AF, n(%)	31 (26%)	
CAD, n(%)	31 (26%)	
CHF, n(%)	35 (30%)	
Renal failure, n (%)	5 (4%)	
COPD, n(%)	11 (9%)	
Previous cardiac surgery	8 (7%)	
EF% (mean±SD)	48±10	
DM, n(%)	22 (19%)	
HTN, n(%)	59 (50%)	
CVA, n(%)	7 (6%)	
Prosthetic valve endocarditis, n(%)	4 (3.4%)	
Causes of valve disease, n (%)	Aortic valve	Mitral valve
Rheumatic	39 (61%)	58 (80.5%)
Degenerative	14 (22%)	9 (12.5%)
Native valve endocarditis	6 (9.3%)	
Ischemic		5 (7%)
Brucellosis endocarditis	2 (3.1%)	
Aneurysm ascending aorta	3 (4.6%)	

NYHA: New York Heart Association; CHF: congestive heart failure; HTN: hypertension; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; CAD: coronary artery disease; DM: diabetes mellitus; EF: ejection fraction; CVA: cerebrovascular accidents

Clinical material and methods

Patient population: From January 2001 to December 2008, 118 patients underwent prosthetic valve replacement at the Jordan University Hospital cardiac surgery unit, using a bileaflet mechanical prosthesis. Forty-six patients received a prosthetic aortic valve; 54 patients had a prosthetic mitral valve inserted and 18 patients had a double valve replacement. The entire population was made up of 63 men (53%) and 55 women (47%); mean age at time of surgery was 45±14 years. One hundred and eleven out of 118 patients from those who underwent prosthetic valve replacement were included in this study (7 patients were excluded; 3 patients due to operative mortality and 4 patients were lost in follow up).

Concomitant surgery was performed in a total of 18 patients (16.2%). The most common procedures were coronary artery bypass grafting in 15 patients (13.5%) and replacement of the ascending aorta in 5 patients (4.5%) for aneurysm of the ascending aorta.

We reviewed the clinical inpatient and outpatient records and the surgical reports of all our patients who received mechanical heart valve replacement and were included in our previous article "Evaluation of Mechanical Valve Replacement at Jordan University Hospital"[5], which included the early and mid-term results of patients who underwent mechanical valve replacement at Jordan University Hospital.

We considered baseline characteristics at the time of the operation which included age, gender, cardiac symptoms, New York Heart Association functional class, congestive heart failure, diabetes, atrial fibrillation, chronic obstructive pulmonary disease, renal failure, cerebrovascular accidents, coexistent coronary artery disease, previous cardiac surgery, mitral valve disease, endocarditis and left ventricular ejection fraction (Table 1).

The results of quantitative variables were expressed in means with standard deviation (SD). This study involved human subjects and was reviewed and approved by the Institutional Review Board of the University of Jordan. The main aim of our study was to document patient survival and valve-related events over the course of 14-23 years.

Records of patient deaths were retrieved from hospital records to determine the cause. All unknown or sudden causes of death were considered valve-related, in accordance with standards described by Akins *et al*[10]. Outcomes were recorded according to the Society of Thoracic Surgery Guidelines for Reporting Mortality and Morbidity after Cardiac Valve Interventions[10].

Our study's primary outcome was death from any cause and was divided into early mortality (30 days

Table 2: Operative data

Surgical Procedure	n (%)
AVR	34 (29%)
AVR + CABG	9 (8%)
AVR + MVR	17 (14%)
AVR+MVR+CABG	1 (0.8%)
AVR + Aortic aneurysm repair	3 (2.5%)
MVR	49 (42%)
MVR + CABG	5 (4%)
Elective surgery, n (%)	114 (97%)
Urgent surgery, n (%)	4 (3%)
CPB time (mean ±SD) (min)	101±30.1
Cross clamp time (mean ±SD) (min)	69.9±20.1
Type of aortic valve, n (%)	
Carbomedics	32 (50%)
St. Jude	19 (30%)
Medtronic	13 (20%)
Type of mitral valve, n (%)	
Carbomedics	17 (23.5%)
St. Jude	51 (71%)
Medtronic	4 (5.5%)
Size of aortic valve, n (%)	
19	5 (8%)
21	29 (45%)
23	23 (36%)
25	7 (11%)
Size of mitral valve, n (%)	
27	30 (42%)
29	32 (44%)
31	9 (12.5%)
33	1 (1.4%)

AVR: aortic valve replacement; CABG: coronary artery bypass grafting; MVR: mitral valve replacement; CPB: cardiopulmonary bypass

following surgery) and late mortality. The secondary outcomes reported were structural and non-structural prosthesis dysfunction, endocarditis, valve thrombosis, thromboembolic events (stroke, transient ischemic attack and non-cerebral embolic events), and significant hemorrhage defined as any hemorrhagic event that required hospitalization or transfusion. Causes of death were reported as non-cardiac or cardiac.

Surgical approach

All valve replacements were carried out under cardiopulmonary bypass using a midline vertical sternotomy. Cardioplegia using cold blood was used to protect the heart. The prosthesis was sutured in place using interrupted sutures composed of woven, non-resorbable polyester material. The patients were administered a therapeutic dose of unfractionated heparin by continuous intravenous infusion as anticoagulation throughout the initial postoperative phase. On the second postoperative day following surgery, oral anticoagulation with a vitamin K antagonist was started. The target international normalized ratio (INR) for aortic valve replacement (AVR) was between 2 and 3 (2-2.5 if the patient was in sinus rhythm, and 2.5-3 if in atrial fibrillation), in line with European guidelines[10]. The target INR for mitral valve replacement and double valve replacement (mitral and aortic valves) was between 2.5 and 3.5 (2.5-3 if in sinus rhythm, and 3-3.5 if in atrial fibrillation).

RESULTS

One hundred and eighteen patients who were included in our previous study underwent mechanical valve replacement (isolated or concomitant with other surgical procedures) between January 2001 and December 2008. The mean age of our population was 45.5±14 years (63 men, 55 women). Eighteen patients (15%) underwent double valvular procedures, while 15 patients (13%) underwent concomitant CABG. Eighty-nine of our patients (75%) were in NYHA class III or IV.

The most common presenting symptoms were dyspnea in 110 patients (93%) and chest pain in 69 patients (58%). The mean ejection fraction was 48±10%. The patients' baseline information and the operative data are shown in Tables 1 and 2, respectively.

In our study, operative mortality was 2.5% (3 patients). The first patient died due to bleeding and low cardiac output intraoperatively. The second patient death occurred two weeks after surgery due to cardiac tamponade, the third patient death occurred due to non-cardiac causes; the patient was on hemodialysis and died two weeks after aortic valve replacement due to sepsis and respiratory insufficiency.

Four patients were lost in follow up, could not be reached, and were therefore not included in this paper.

Long-term survival

One hundred and eleven patients included in this study (61 males (54.9%), 50 females (45.1%)) underwent mechanical valve replacement (isolated or concomitant with other surgical procedures) at our institution between January 2001 to December 2008. The late complications and mortality were followed retrospectively over 14-23 years up to January 2024.

Late mortality occurred in 30 patients (27%) during the follow-up period. The cause of death was cardiac related in 6 patients (20%) and noncardiac related in 24 patients (80%)). The most common cause of cardiac related death was sudden death, followed by heart failure and myocardial infarction. Breast cancer, cancer

Table 3: Causes of late cardiac death

Causes of death	Percentages
Noncardiac-related death	24 (80%)
Cardiac-related death	6 (20%)
Sudden unexplained death	2 (1.8%)
Myocardial infarction	1 (0.9%)
Heart failure	3 (2.7%)

Table 4: Late complications

Complication	Percentages
Thromboembolism	7 (6.3%)
Massive hemorrhage	3 (2.7%)
Minor hemorrhage	5 (4.5%)
Warfarin toxicity without bleeding	10 (9.3%)
Endocarditis	4 (3.6%)
Mediastinal infection	1 (0.9%)
Patient-prosthesis mismatch	2 (1.8%)
Prosthesis thrombosis	1 (0.9%)
Valve reintervention	4 (3.6%)

colon and renal tubular acidosis were the most common non-cardiac causes of death. Details on causes of late cardiac deaths are presented in Table 3.

Prosthesis related issues were reported in five patients: two paravalvular leaks (1.8%), two patient-prosthesis mismatches as determined by echo gradients (1.8%), and one patient developed valve thrombosis (0.9%) which was treated by thrombolytic therapy. There was no correlation between valve dysfunction and any specific valve type.

Four of our patients developed prosthetic valve endocarditis (PVE; 3.6%). All four patients had undergone double valve replacement surgery with bileaflet mechanical prostheses. Three were successfully treated with antibiotics, and the fourth died prior to scheduled reoperation due to congestive heart failure.

Reintervention was necessary in 4 patients. The indications for reoperation were paravalvular leak (2 patients) and patient-prosthesis mismatch (2 patients). The mean interval between the first operation and the repeat operations was 4.6±4.4 years (median 5.5 years).

Thromboembolic and major bleeding events

Thromboembolic events occurred in seven patients. Of those, four were strokes (3.6%); three were transient ischemic events (2.7%). No patients experienced any non-cerebral embolic event that was identified.

Eight patients developed bleeding (7.2%). Three were reported to have major hemorrhagic events (two cerebral hemorrhage necessitating craniotomy) in patients with an INR greater than 5, and one patient developed rectus sheath hematoma and was treated conservatively.

The remaining 5 patients had minor bleeding: 3 nasal, 1 urinary tract bleeding and 1 vaginal bleeding. In our study, 10 patients (9%) developed warfarin toxicity (INR more than 5) without obvious bleeding and 1 patient (0.9%) developed myocardial infarction post operatively. Details on late complications are present in Table 4.

DISCUSSION

Mechanical prostheses show obvious durability but require lifelong anticoagulation. The trend toward the use of bioprosthetic has increased to avoid risks and complications associated with long-term anticoagulation[11-13].

Most of our patient population was less than 60 years of age at the time of operation and the proper choice of operation at the time was mechanical valve replacement. Therefore, owing to our young patient population, we were able to follow up the long-term outcomes for our patients.

The major cause of valve-related events in patients with mechanical prostheses is the need to administer lifetime anticoagulation therapy. A target prothrombin time/INR of approximately 2.5-3.0 for both patients with mechanical aortic prostheses and those with mechanical mitral prostheses is recommended according to the 2014 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines[14].

The ACC/AHA recommends the addition of aspirin (80 to 100 mg/day) to warfarin should be strongly considered for all patients with mechanical valves[14].

2021 ESC/EACTS Guidelines for the management of valvular heart disease recommend that the target INR should be based on thrombogenicity of the used prosthesis and patient specific risk factors. Studies have shown that targeting a median value for the INR rather than a range can help avoid extreme values in the target range and avoid over or under medication[15].

Our patients were started on a low-intensity anti-coagulation treatment with a target INR in isolated AVR between 2-2.5, and in mitral and double valve replacement 2.5-3.0.

The rate of occurrence of thromboembolic events in patients with prosthetic valves is estimated to be 0.6% to 2.3% per patient year[16]. The rate is similar for patients with mechanical valves on anticoagulation therapy to that of patients with bioprosthetic valves. There is a variation in the rate of thromboembolic events with other risk factors such as left ventricular dysfunction, atrial fibrillation, previous thromboembolism or hypercoagulable state[17]. Both obstructing and non-obstructing thrombosis may lead to systemic emboli. However, patients with non-obstructing thrombosis present more commonly with systemic symptoms. Most patients who experience a thromboembolic event are found to be inadequately anticoagulated.

Causes of prosthetic valve obstruction include thrombosis, pannus formation or a combination of both. Thrombosis of these valves may be obstructive or non-obstructive. Thrombosis may be a slow chronic progressive worsening of function or may be a more

acute process. Inadequate anticoagulation is associated with left-sided heart valve thrombosis in a majority of patients[18].

Thrombosis of a prosthetic valve is an uncommon complication associated with a high morbidity and mortality rate. In a literature review conducted by Huang *et al*[19] aimed at surveying the clinical outcomes of patients with obstructive thrombosed prosthetic heart valves, it was concluded that thrombolytic therapy was an easier option than surgery, and had a recurrence rate of 13%, while 30% of cases with failure of thrombolytic therapy needed surgery, and it was associated with a mortality rate of at least 12%.

Valve thrombosis treatment is controversial; many recommend the use of thrombolytic therapy as first-line agents[20] with a success rate ranging between 71-88%, and rates of significant bleeding or embolism ranging from 15-25%. While the mortality rate from thrombolytic therapy is estimated to range between 3-12%, this rate remains significantly lower than the mortality rate for valve thrombosis surgery, which ranges from 12-46%[20].

Most studies of fibrinolytic therapy for prosthetic valve thrombosis (PVT) have focused mainly on left-sided PVT. Studies using an echocardiogram-guided slow or ultraslow infusion, low-dose fibrinolytic protocol have demonstrated high rates of efficacy (85-90% or higher[21-23]) with relatively low rates of complications (10.5% including no deaths with a six-hour infusion[22]; 6.7% [including a 0.8% mortality rate] with a 25-hour infusion[21]).

Complications following fibrinolytic therapy include major bleeding, systemic embolism, recurrent PVT and death[19,24]. Risk factors for complications in patients receiving slow (or ultraslow) infusion fibrinolytic therapy include NYHA class III or IV and large thrombus size (e.g., area on TEE ≥1.0 cm^2[21,25]).

In patients with mechanical heart valves, the incidence of major bleeding was shown to range from 0.34 to 2.91 per 100 patient-years[26]. Risk factors traditionally include supratherapeutic INR, hypertension, and age >75 years, previous stroke, concomitant antiplatelet use and a previous history of hemorrhage[27]. Major bleeding sites include the urinary tract, gastrointestinal tract, intracranial hemorrhage, subdural hematoma and retroperitoneal hemorrhage.

The 2020 ACC/AHA guidelines state that patients with mechanical heart valves and supratherapeutic INR (>5.0) with no active bleeding are unlikely to benefit from routine vitamin K administration in addition to temporary vitamin K antagonist cessation. The recommendation was based on a systematic review that showed a non-significant increased risk of mortality and thromboembolism with vitamin K administration, with moderate certainty of the evidence[28]. In patients who develop life-threatening bleeding and are receiving the 4-factor prothrombin complex concentrate (4F-PCC), it is recommended to administer a 10-mg intravenous dose of vitamin K only when restarting anticoagulation is not planned within the next week[14]. For any non-intracranial bleeding, the recommended dose of 4F-PCC is 1000 units and 1500 units for intracranial hemorrhage[29].

Bleeding developed in 8 patients (7.2%), and the majority were considered minor bleeding (epistaxis, gingival oozing) with only 3 cases of major bleeding (intracerebral hemorrhage, rectus sheath hematoma); and the three patients were not compliant with regular follow-ups and had warfarin toxicity at the time of the bleeding event. An additional 10 patients (9.3%) developed warfarin toxicity (INR more than 5). It is worth mentioning that non-compliant patients for regular follow-ups and regular INR check-ups contribute to this avoidable, yet risky complication related to lifelong anticoagulation necessity.

PVE refers to infection of one or more prosthetic heart valves. PVE can be early (≤12 months postoperatively) or late (>12 months postoperatively). PVE comprises 20% of all cases of endocarditis; it occurs in 1- 6% of patients with valve prostheses, with an incidence of 0.3 to 1.2% per patient-year[30]. The risk is greatest during the initial year after implantation. In general, PVE occurs with equal frequency at aortic and mitral sites[31]. Despite improvements in the diagnosis, prophylaxis and treatment of PVE, it remains a serious complication of heart valve surgery. The AHA recommends at least six weeks of antibiotic treatment[32].

Early surgery is a reasonable option in PVE in the following scenarios: recurrent emboli development despite the appropriate antibiotic treatment, large mobile vegetations >10 mm, or relapse of PVE[33]. In patients with PVE who develop heart failure, surgical intervention has been shown to decrease mortality[34].

In our study, 4 patients (3.4%) developed post-operative early endocarditis. All four patients had undergone double valve replacement surgery with bileaflet mechanical prostheses. Three were successfully treated with antibiotics, and the fourth died prior to scheduled reoperation due to congestive heart failure.

Hemolysis without a paravalvular leak has been reported rarely[35,36]. Borman *et al*[35] showed that simultaneous aortic and mitral valve replacement increased the rate of hemolysis when compared to single valve replacements. Hemolysis severe enough to produce anemia is rare (<1 percent) with newer generation prosthetic valves[37]. In patients with these valves, hemolysis is associated with paravalvular

regurgitation[38] or, less commonly, bioprosthetic structural degeneration.

Our study found that a low late mortality rate and a low incidence of valve-related events are achievable for more than 14-23 years with mechanical bileaflet valve replacement.

These results represent a substantial update to our previous investigation: "Evaluation of Mechanical Valve Replacement at Jordan University Hospital"[5]. Our results also show survival rates similar to other studies conducted on different types of bileaflet mechanical valves, such as CarboMedics valves and ATS valves[39,40]. The durability of the bileaflet mechanical prosthesis is further shown by the observation of non-structural valve deterioration in this study.

CONCLUSION

The main limitations of the present study were its retrospective nature. We found that a low late mortality rate and a low incidence of valve-related events are achievable for at least 14 years using mechanical bileaflet valve replacement. For patients who require mechanical prosthetic valve replacement, bileaflet mechanical heart valve prosthesis remains an excellent choice of treatment. Hemorrhagic and thromboembolic events related to anticoagulation should be taken into account during life-long follow-up.

ACKNOWLEDGMENT

Conflict of interests: We the authors declare no conflicts of interests.

Moaath M. Alsmady, Basil Al Bakri, Huthaifa W Almaaiath and Amjad Bani Hani wrote the main manuscript. Zeenah Moaath, Sereen Aloran and Akram Alsaleh were involved in data collection and tables. All the authors review the final manuscript together.

REFERENCES

1. Koertke H, Zittermann A, Minami K, Tenderich G, Wagner O, El-Arousy M, *et al*. Low-dose international normalized ratio self-management: A promising tool to achieve low complication rates after mechanical heart valve replacement. Ann Thorac Surg 2005; 79:1909-14.
2. Minakata K, Tanaka S, Okawa Y, Shimamoto M, Kaneko T, Takahara Y, *et al*. Long-term outcome of the Carpentier-Edwards pericardial valve in the aortic position in Japanese patients. Circ J 2014; 78:882-9.
3. Chiang YP, Chikwee J, Moskowitz AJ, Itagaki S, Adams DH, Egorova N. Survival and long-term outcome following bioprosthetic vs mechanical aortic valve replacement on patients aged 50-69 years. JAMA 2014; 312:1323-9.
4. Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, *et al*. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med 2012; 366:1705-15.
5. Alsmady MM, Abu Abeeleh MM, Ennab RM, Hassuneh SS, Massad IM, Bustami BB. Evaluation of mechanical valve replacement at Jordan University Hospital. Kuwait Med J 2010; 42(1):55-60.
6. Misawa Y, Saito T, Konishi H, Ohki S, Kaminishi Y, Sakano Y, *et al*. Clinical experience with the Bicarbon heart valve prosthesis. J Cardiothorac Surg 2007; 25(2):8.
7. Misawa Y, Fuse K, Saito T, Konishi H, Oki S. Fourteen-year experience of the Omnicarbon prosthetic heart valve. ASAIO J 2001; 47:677-83.
8. Aoyagi S, Oryoji A, Nishi Y, Tanaka K, Kosuga K, Oishi K. Long-term results of valve replacement with the St. Jude Medical valve. J Thorac Cardiovasc Surg 1994; 108:1021-9.
9. Shanmugam G, MacArthur K, Pollock J. Mechanical aortic valve replacement: long-term outcomes in children. J Heart Valve Dis 2005; 14:166-71.
10. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, *et al*. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Eur J Cardiothorac Surg 2008; 33:523-8.
11. Yanagawa B, Whitlock RP, Verma S, Gersh BJ. Anticoagulation for prosthetic heart valves: Unresolved questions requiring answers. Curr Opin Cardiol 2016; 31(2):176-82.
12. Thourani VH, Suri RM, Gunter RL, Sheng S, O'Brien SM, Ailawadi G, *et al*. Contemporary real-world outcomes of surgical aortic valve replacement in 141,905 low-risk, intermediate-risk, and high-risk patients. Ann Thorac Surg 2015; 99(1):55-61.
13. Brennan JM, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS, *et al*. Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: Results from the society of thoracic surgeon's adult cardiac surgery national database. Circulation 2013; 127(16):1647-55.
14. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin 3rd JP, Gentile F, *et al*. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. Circulation 2021; 143:e72-e227.
15. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, *et al*. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2022; 43:561-632.
16. Sun JC, Davidson MJ, Lamy A, Eikelboom JW. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. Lancet 2009; 374:565-76.
17. Poli D, Antonucci E, Pengo V, Migliaccio L, Testa S, Lodigiani C, *et al*. Mechanical prosthetic heart valves: quality of anticoagulation and thromboembolic risk. The observational multicenter PLECTRUM study. Int J Cardiol 2018; 267:68-73.

18. Butany J, Ahluwalia MS, Munroe C, Fayet C, Ahn C, Blit P, *et al*. Mechanical heart valve prostheses: identification and evaluation. Cardiovasc Pathol 2003; 12:322-44.
19. Huang G, Schaff HV, Sundt TM, Rashimtoola SH. Treatment of obstructive thrombosed prosthetic heart valve. J Am Coll Cardiol 2013; 62:1731-6.
20. Lengyel M, Horstkotte D, Voller H, Mistiaen WP; Working Group Infection, Thrombosis, Embolism and Bleeding of the Society for Heart Valve Disease. Recommendations for the management of prosthetic valve thrombosis. J Heart Valve Dis 2005; 14:567-75.
21. Özkan M, Gündüz S, Gürsoy OM, Karakoyun S, Astarcioglu MA, Kalcik M, *et al*. Ultraslow thrombolytic therapy: A novel strategy in the management of PROstheticMEchanical valve Thrombosis and the prEdictors of outcomE: The Ultra-slow PROMETEE trial. Am Heart J 2015; 170:409-18.
22. Özkan M, Gündüz S, Biteker M, Astarcioglu MA, Cevik C, Kaynak E, *et al*. Comparison of different TEE-guided thrombolytic regimens for prosthetic valve thrombosis: the TROIA trial. JACC Cardiovasc Imaging 2013; 6:206-16.
23. Özkan M, Çakal B, Karakoyun S, Gursoy OM, Cevik C, Kalcik M, *et al*. Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. Circulation 2013; 128:532-40.
24. Karthikeyan G, Senguttuvan NB, Joseph J, Devasenapathy N, Bahl VK, Airan B. Urgent surgery compared with fibrinolytic therapy for the treatment of left-sided prosthetic heart valve thrombosis: a systematic review and meta-analysis of observational studies. Eur Heart J 2013; 34:1557-66.
25. Gündüz S, Özkan M, Yesin M, Kalcik M, Gursoy MO, Karkoyun S, *et al*. Prolonged infusions of low-dose thrombolytics in elderly patients with prosthetic heart valve thrombosis. Clin Appl Thromb Hemost 2017; 23:241-7.
26. John S, Bashi VV, Jairaj PS, Muralidharan S, Ravikumar E, Sathyamoorthy I, *et al*. Mitral valve replacement in the young patient with rheumatic heart disease. Early and late results in 118 subjects. J Thorac Cardiovasc Surg 1983; 86:209-16.
27. Labaf A, Svensson PJ, Renlund H, Jeppsson A, Själander A. Incidence and risk factors for thromboembolism and major bleeding in patients with mechanical valve prosthesis: a nationwide population-based study. Am Heart J 2016; 181:1-9.
28. Khatib R, Ludwikowska M, Witt DM, Ansell J, Clark NP, Holbrook A, *et al*. Vitamin K for reversal of excessive vitamin K antagonist anticoagulation: a systematic review and meta-analysis. Blood Adv 2019; 3:789-96.
29. Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, *et al*. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2020; 76:594-622.
30. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Prosthetic valve endocarditis after surgical aortic valve replacement. Circulation 2017; 136(3):329-31.
31. Mutuberría-Urdaniz M, Rodríguez-Palomares JF, Ferreira I, Baneras J, Teixido G, Gutierrez L, *et al*. Non-obstructive prosthetic heart valve thrombosis (NOPVT): Really a benign entity? Int J Cardiol 2015; 197:16-22.
32. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, *et al*; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015; 36(44):3075-128.
33. Baddour LM, Wilson WR, Bayer AS, Fowler VG, Tleyjeh IM, Rybak MJ, *et al*; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals from the American Heart Association. Circulation 2015; 132(15):1435-86.
34. López J, Sevilla T, Vilacosta I, García H, Sarriá C, Pozo E, *et al*. Clinical significance of congestive heart failure in prosthetic valve endocarditis. A multicenter study with 257 patients. Rev Esp Cardiol (Engl Ed) 2013; 66(5):384-90.
35. Borman JB, De Riberolles C. Sorin Bicarbon bileaflet valve: a 10-year experience. Eur J Cardiothorac Surg 2003; 23:86-92.
36. Azarnoush K, Laborde F, de Riberolles C. The Sorin Bicarbon over 15 years' clinical outcomes: multicenter experience in 1704 patients. Eur J Cardiovasc Surg 2010; 38:759-66.
37. Shapira Y, Vaturi M, Sagie A. Hemolysis associated with prosthetic heart valves: a review. Cardiol Rev 2009; 17:121-4.
38. Buellesfeld L, Meier B. Treatment of paravalvular leaks through interventional techniques. Multimed Man Cardiothorac Surg 2011; 2011:1-8.
39. Nishida T, Sonoda H, Oishi Y, Tanoue Y, Nakashima A, Shiokawa Y, *et al*. Single-institution, 22-year follow-up of 786 CarboMedics mechanical valves used for both primary surgery and reoperation. J Thorac Cardiovasc Surg 2014; 147:1493-8.
40. Aoyagi S, Hori H, Yoshikawa K, Arinaga K, Fukunaga S. Mid-term results of valve replacement with the ATS valve: a seven-year follow up. J Heart Valve Dis 2007; 16:267-74.

Case Report

Posterior dislocation of the sacrococcygeal joint: A rarely seen case treated with percutaneous leverage reduction

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Kuwait Medical Journal 2026; 58 (3): 205 - 208

ABSTRACT

Dislocation of the sacrococcygeal joint is an infrequent injury. Anterior dislocation of the joint is a relatively common injury, while posterior dislocation, published only twice in the relevant literature up to date, is quite rare. Since those two cases were treated with conservative methods, no surgical procedure was either reported or recommended previously. Here, an adult case with traumatic posterior dislocation of the sacrococcygeal joint, which was managed with percutaneous leverage reduction after failed closed reduction attempts, is described. Excellent alignment accomplished in the procedure was maintained during the follow-up. The patient returned to work by the end of fifth postoperative month and was almost pain-free at twelfth postoperative month. Due to the rarity of posterior sacrococcygeal dislocation, the approach to management of this injury remains unestablished. Percutaneous leverage reduction appears to be a viable option in the management of posterior sacrococcygeal dislocation that cannot be reduced with closed methods.

KEY WORDS: caudal vertebra, coccyx, sacrococcygeal region, joint dislocations, minimally invasive surgery

INTRODUCTION

The sacrococcygeal joint, an amphiarthrodial joint, connects the apex of the sacrum to the base of the coccyx[1]. Dislocation of the sacrococcygeal joint is an infrequent injury. It is classified considering the direction of the dislocation: namely, anterior and posterior[2-4]. The anterior dislocation is a relatively common injury, while the posterior dislocation, published twice in the relevant literature up to date, is quite rare[2,3]. Those two cases of posterior sacrococcygeal dislocation were reported to be treated with conservative methods that had remained the joints dislocated[2,3]. The management of sacrococcygeal dislocation involves analgesic use, steroid injection, closed reduction and surgical interventions that include open reduction with fixation and coccygectomy[2,4]. An adult case, diagnosed with traumatic posterior dislocation of the sacrococcygeal joint and managed with percutaneous leverage reduction, is reported here.

CASE REPORT

A 49-year-old male worker, who had had uneventful medical history by then, was referred to the clinic due to a fall from the first floor. The patient readily recalled impact to the posterior aspect of the sacrum, caused by the contact of wheelbarrow tire in the event of falling. On admission, the vital signs were within the normal ranges (pulse: 90/min; temperature: 36.7 °C; systolic and diastolic arterial pressures: 140 mmHg and 80 mmHg, respectively). The skin overlying the sacrum and the coccyx was lesion-free (*i.e.*, no dermabrasion, bruise or laceration). Tenderness and irregular contour over the sacrococcygeal junction were evident upon palpation of the injured area. No crepitation was evident. Sacral reflexes, the bulbocavernosus reflex and the anal reflex, were normal. Roentgenograms and CT scan demonstrated posterior dislocation of the sacrococcygeal joint and S2-S3 fracture-dislocation with mild displacement (Figure 1). No associated injuries related to other body regions (*i.e.*, thorax,

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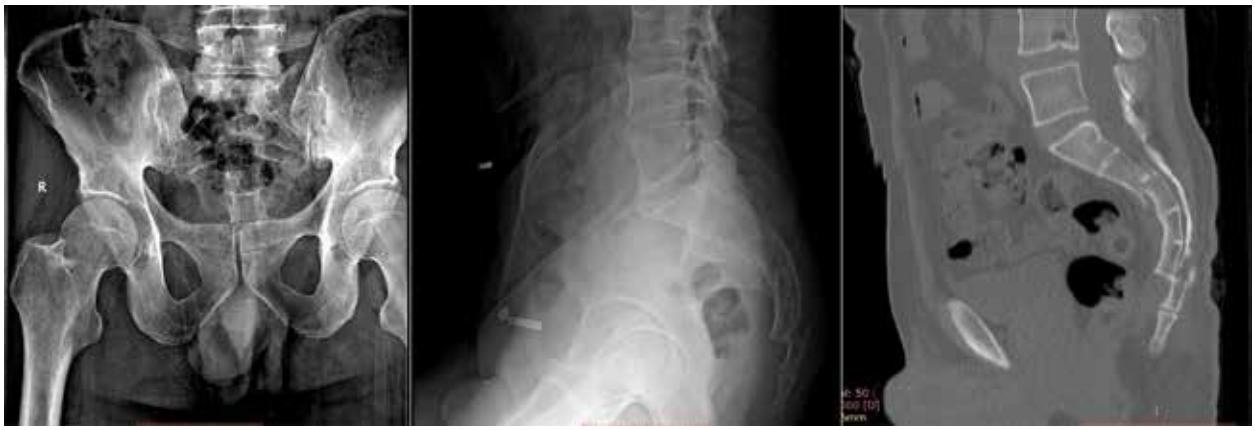

Figure 1: Radiologic images obtained at admission. The left frame includes the AP view of the pelvis. The middle frame includes the lateral view of the pelvis and coccyx, clearly demonstrating posterior dislocation of the sacrococcygeal joint. The right frame includes a sagittal view of the CT scan, indicating the posterior sacrococcygeal dislocation and mild displacement of the S2-S3 fracture-dislocation.

abdomen, cranium and extremities) were evident in the physical examination and radiological evaluation.

Closed, percutaneous or open reduction was opted for the posterior sacrococcygeal dislocation since the patient had frequently been involved in occupation-related intense physical activity. The patient underwent an operation on the day of admission. Following spinal anesthesia and prone positioning, closed reduction maneuver to the dislocated sacrococcygeal joint was applied. Despite several imaging-guided attempts, any degree of joint reduction could not be accomplished. A stab incision over the dislocated sacrococcygeal joint was made to insert curved hemostatic forceps to the joint, and the coccyx was successfully relocated using the percutaneous leverage technique (Figure 2). Although fixation with Kirschner wire(s) was preoperatively considered in this case, the anatomical reduction was sufficiently stable to abandon the fixation. The S2-S3 fracture-dislocation was also noticed to be sufficiently stable, based on the non-existence of radiological signs of further displacement. The stab incision was closed with suture at the skin level. Although the tip of the forceps was not advanced beyond the anterior border of the sacrum during the procedure, digital rectal examination was made at the end of the operation, and the examination was normal.

The antibiotic prophylaxis included the intravenous administration of 1 gr of Cefazolin 30 minutes before the operation and for every eight hours during the first day. The patient was admitted to the outpatient clinic on the tenth and thirtieth days and then, monthly for the follow-up. The roentgenograms were obtained in every follow-up visit to evaluate the relocated sacrococcygeal joint and mildly displaced S2-S3 fracture-dislocation. No wound problem, reduction loss in the sacrococcygeal joint or further displacement of S2-S3 fracture-dislocation was evident in the follow-up visits. Therefore, restricted and unrestricted weight-bearing was allowed by the end of the sixth and tenth postoperative weeks, respectively. Sitting upright using donut cushion was allowed at the sixth postoperative week. Upon uneventful and complete healing of the sacrococcygeal joint and S2-S3 fracture-dislocation considering radiologic evaluation (including roentgenograms and MRI) as well as significant relief of the symptoms, the patient returned to work by the end of the fifth postoperative month (Figure 3). Regular use of the donut cushion during sitting was discontinued at the eighth postoperative month. The patient was almost pain-free at the twelfth postoperative month and reported mild pain (pain score 2 on 0-10 visual analog scale) due to sitting on hard surfaces for more than 30 minutes.

DISCUSSION

Traumatic posterior dislocation of the sacrococcygeal joint is quite rare[2]. One report of posterior sacrococcygeal joint dislocation in a 19-year-old female, who had sustained a fall from the first floor[2], and another report of posterior intercoccygeal joint dislocation in 19-year-old male, who had sustained a traffic accident with a motorcycle, could be retrieved from the English literature[3]. The former case, more comparable to the present case than the latter, was reported to have concomitant sacral ala fracture and bilateral pubic rami fractures[2]. The authors notified favorable outcome that had been accomplished with surgical treatment of the sacral fracture (*i.e.*, closed reduction and percutaneous fixation with two cannulated screws) and conservative treatment (*i.e.*, observation) of the dislocated sacrococcygeal joint. According to the report, the case with posterior intercoccygeal joint dislocation (more specifically, the dislocation between the first and second coccygeal

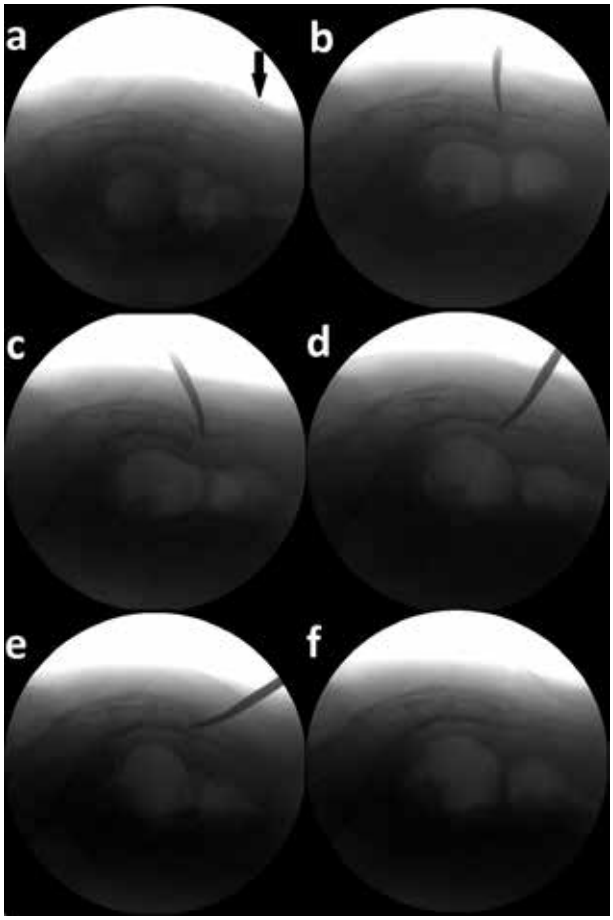

Figure 2: a. Closed reduction attempt of the posterior sacrococcygeal dislocation with gentle digital pressure to avoid further displacement of S2-S3 fracture-dislocation. The solid arrow indicates the phalanx of the surgeon applying reduction maneuver to the dislocated joint. **b.** Following the stab incision, 5-inch hemostatic forceps with curved tip was inserted into the dislocated sacrococcygeal joint. Please take note that the concave side of the forceps faced caudal direction in this step, an approach to facilitate its insertion. **c.** The hemostatic forceps was rotated 180 degrees around its axis. Thus, the convex side of the clamp abutted against the superior end-plate of the first coccygeal vertebra. **d.** As the tip of the forceps was engaged to the lower border of S5, the handle of the forceps was gradually pushed in the caudal direction. **e.** The completion of the reduction maneuver. **f.** The steadiness of joint relocation after the removal of the forceps.

vertebrae) had also been treated with conservative methods[3]. The authors reported favorable clinical outcome in that case as well.

Percutaneous leverage reduction has been utilized to treat several types of injuries including displaced pediatric radial neck fracture[5], calcaneal fracture[6], pediatric supracondylar humeral fracture[7] and Bennett's fracture[8]. This technique has not been described for the injuries of sacrococcygeal region to date. The present case was managed with percutaneous leverage reduction for the posterior sacrococcygeal dislocation and conservative methods (analgesic use as required and bed rest) for mildly displaced S2-S3 fracture-dislocation. Since the posterior dislocation at the sacrococcygeal joint produced a sort of retroverted coccyx, reported formerly as a cause of coccydynia[9], the risk of persistent coccydynia could be avoided with the reduction of the joint. Due to the potential risk of further displacement of S2-S3 fracture-dislocation and failed attempts at closed reduction, the percutaneous reduction under C-arm imaging was performed. Being reasonably stable after the percutaneous leverage reduction, the fixation procedure was canceled to avoid the potential hardware complications and the possibility of hardware removal. In addition to anatomical alignment of the sacrococcygeal joint, favorable clinical outcome with an uneventful follow-up period was eventually accomplished in this case.

The mechanism of the injury in this case was a blunt trauma to the posterior aspect of the sacrococcygeal region due to a fall, similar to the cases of traumatic anterior dislocation of the sacrococcygeal joint[3]. The most logical explanation for the occurrence of rarely encountered posterior dislocation is that axial loading to the tip of the coccyx in association with physiologic kyphosis of the sacrum and coccyx caused a force in postero-superior direction, intense enough to destruct the stabilizer periarticular structures.

CONCLUSION

The approach to the management of posterior coccygeal dislocation remains unestablished since few cases have previously been reported in the literature. Based on the favorable clinical and radiological outcomes accomplished in this case, percutaneous leverage reduction technique appears to be a viable treatment option in irreducible posterior dislocation of the sacrococcygeal joint. Although the fixation of the joint dislocation was abandoned in the present case due to the stability obtained following anatomical reduction, a fixation procedure should always be considered in the event of instability of the reduced sacrococcygeal joint.

ACKNOWLEDGMENTS

The authors received no financial support for the authorship and/or publication of this article.

Conflict of Interest: The authors declare no conflicts of interest.

Author contributions: Bulent Guneri: conception and study design, analysis of data, drafting of the manuscript, final approval of the version to be published; Tolga Kececi: conception, data acquisition, final approval of the version to be published; Ozkan Kose: analysis of data, critical revision, final approval of the version to be published.

Funding: Nil

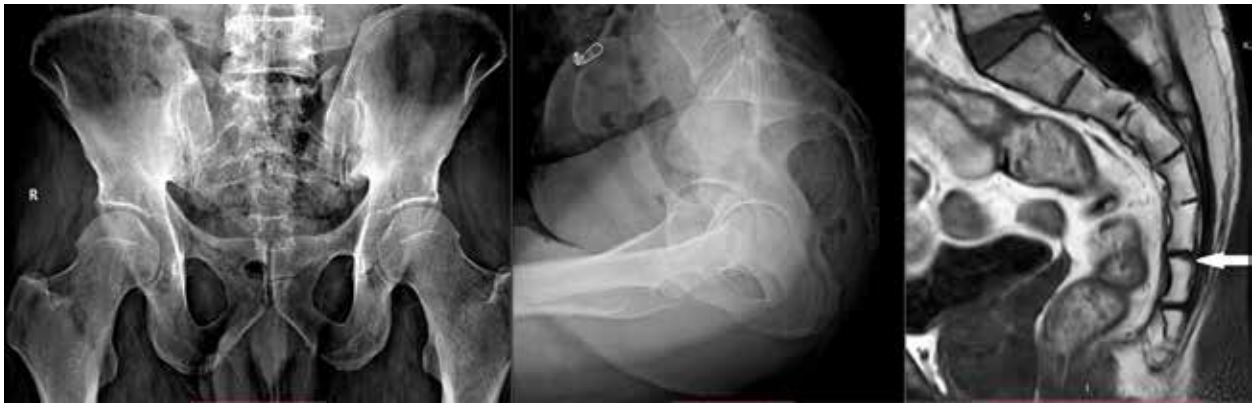

Figure 3: Radiologic images obtained at the follow-up of fifth postoperative month before the patient's return to work. The left frame includes the AP view of the pelvis. The middle frame includes the lateral view of the pelvis and coccyx, displaying anatomical alignment of the sacrococcygeal junction and the uneventful union of S2-S3 fracture-dislocation. The right frame includes the sagittal T1-weighted MR image, demonstrating the satisfactory healing of the sacrococcygeal junction and S2-S3 fracture-dislocation. The solid white arrow indicates an insignificant indentation at the superior end-plate of the first coccygeal vertebra, caused by the percutaneous leverage reduction maneuver.

Ethical statement: Informed consent has been obtained from the patient. This report has been approved by the Institutional Review Board (Date: 2023.12.7, document number: 2989).

REFERENCES

1. Kapetanakis S, Gkasdaris G, Pavlidis P, Givissis P. Concurrent lumbosacral and sacrococcygeal fusion: a rare aetiology of low back pain and coccygodynia? Folia Morphol (Warsz) 2018; 77(2):397-9.
2. Panigrahi VP, Adsul N, Chahal RS, Kalra KL, Acharya S. Traumatic posterior dislocation of sacrococcygeal joint: A case report and review of the literature. Surg Neurol Int 2020; 11:197.
3. Hamoud K, Abbas J. Fracture dislocations of the coccyx: A case series and literature review. J Clin Case Rep 2017, 7:8.
4. Kanabur P, Gowd A, Bulkeley JA, Behrend CJ, Carmouche JJ. Symptomatic sacrococcygeal joint dislocation treated using closed manual reduction: A case report with 36-month follow-up and review of literature. Trauma Case Rep 2017; 12:11-5.
5. Song KS, Kim BS, Lee SW. Percutaneous leverage reduction for severely displaced radial neck fractures in children. J Pediatr Orthop 2015; 35(4):e26-30.
6. Rammelt S, Amlang M, Barthel S, Zwipp H. Minimally-invasive treatment of calcaneal fractures. Injury 2004; 35 Suppl 2:SB55-63.
7. Pei X, Mo Y, Huang P. Leverage application on Gartland type IV supracondylar humeral fracture in children. Int Orthop 2016; 40(11):2417-22.
8. Sawaizumi T, Nanno M, Nanbu A, Ito H. Percutaneous leverage pinning in the treatment of Bennett's fracture. J Orthop Sci 2005; 10(1):27-31.
9. Garg B, Ahuja K. Coccydynia A comprehensive review on etiology, radiological features and management options. J Clin Orthop Trauma 2021; 12(1):123-9.

Case Report

Lipschütz ulcer: a rare case of vulvar ulceration in a young female patient

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Kuwait Medical Journal 2026; 58 (3): 209 - 210

ABSTRACT

Acute genital ulceration or Lipschütz ulcer is a rare, self-limiting condition characterized by painful vulvar ulcers and most commonly affects young females. This disease may be accompanied by systemic symptoms, such as fever, malaise, tonsillitis and lymphadenitis, making diagnosis challenging. Herein, we report a case of Lipschütz ulcer in a sexually inactive 11-year-old girl who was successfully treated with anti-inflammatory drugs and analgesics. Recognition of Lipschütz ulcer is essential to avoid misdiagnosis and overtreatment. Moreover, appropriate and timely treatment is also important to avoid complications.

KEY WORDS: female, genital ulcer, Lipschütz ulcer

INTRODUCTION

Acute genital ulceration or Lipschütz ulcer is a rare, self-limiting condition characterized by painful vulvar ulcers and most commonly affects young females. This disease may be accompanied by systemic symptoms, such as fever, malaise, tonsillitis and lymphadenitis, making diagnosis challenging. The etiology has been linked to viral or bacterial infections, including Epstein–Barr virus (EBV), cytomegalovirus (CMV), mumps virus, *Salmonella* and *Mycoplasma*. However, Lipschütz ulcer is not caused by or associated with sexually transmitted infections[1,2].

CASE REPORT

An 11-year-old girl was admitted to our hospital through the emergency department complaining of 4 days of severe vulvar pain and ulceration. Six days before admission, she had been diagnosed with influenza A infection, which was accompanied by fever and malaise. Then, the patient developed secondary urinary retention due to severe pain. She had no known comorbidities and no history of recurrent oral or genital aphthous lesions. She also denied any history of sexual activity.

The patient had a blood pressure of 106/67 mmHg, pulse rate of 92 beats/min, body temperature of 37.8°C, and respiratory rate of 20 breaths/min. Physical examination revealed two partially symmetrical ulcerations, known as kissing lesions, on the inner aspects of the bilateral labia minora (Figure 1A). Complete blood cell count and liver function test were within normal limits, but the C-reactive protein level was elevated at 3.96 mg/dL (reference 0.0 - 0.5 mg/dL). Viral and bacterial tests for CMV, EBV, herpes simplex virus (HSV), mumps virus, hepatitis B, hepatitis C, human immunodeficiency virus (HIV) and syphilis were all negative. Blood and urine cultures were also negative. Rheumatologic evaluations, such as antinuclear antibody, rheumatoid factor, HLA B51, serum immunoglobulins and serum complement levels were either normal or negative. Based on these clinical and laboratory findings, the patient was diagnosed with reactive acute genital ulceration (Lipschütz ulcer) triggered by influenza A infection.

Pain and inflammation management was administered with topical lidocaine 2% solution, naproxen 250 mg twice a day and systemic prednisolone 10 mg twice a day. Catheter bladder drainage was also required to relieve severe pain and manage secondary

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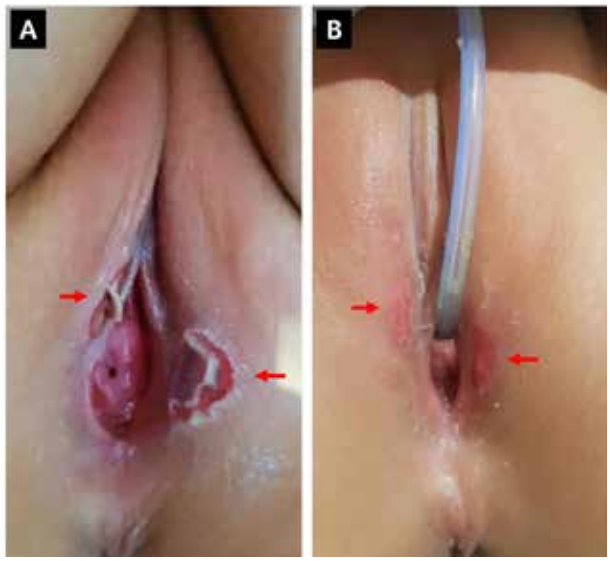

Figure 1: (A) Two deep, partially symmetrical ulcerations in the inner labia minora (kissing lesions) observed at admission. (B) On day 13 after admission, ulcerations were mostly healed without any sequelae.

urinary retention. Vulvar pain improved and genital ulceration healed without scarring within 3 weeks (Figure 1B).

DISCUSSION

Lipschütz ulcer commonly affects young female patients. The ulcers are typically large, deep and well-demarcated, frequently affecting the labia minora but may also extend to the labia majora, perineum, vestibule and lower vagina. Ulcerations typically present with a partially symmetrical appearance (kissing lesions). Severe pain and dysuria can cause secondary urinary retention, and patients may require hospitalization for parenteral analgesia and indwelling Foley catheter. Given its manifestations and rarity, Lipschütz ulcer is often misdiagnosed as a sexually transmitted disease, which can lead to unnecessary investigations, pharmacologic management and significant psychological anxiety, especially in children who may not be sexually active[3].

The diagnosis of Lipschütz ulcer is challenging. Clinical diagnosis is based on a detailed history and complete physical examination. Laboratory tests may be needed to exclude sexually transmitted infections (e.g., HSV, HIV and syphilis) and autoimmune diseases (e.g., Behcet's syndrome and inflammatory bowel diseases). Differential diagnosis should also be made for dermatologic inflammatory conditions, such as fixed drug eruption, erosive lichen planus and lichen sclerosus[4]. Prodromal systemic symptoms, such as fever, malaise, tonsillitis, lymphadenopathy and elevated liver enzymes, may be presented to rheumatologists, dermatologists, gynecologists, pediatricians or infectious disease doctor for assessment.

Lipschütz ulcers are self-limiting and generally heal spontaneously. Thus, the primary goals of treatment are reassuring patients and parents, relieving pain and ulcer treatment. Topical anesthetics can be used for temporary pain relief. When pain cannot be controlled with a topical agent, oral analgesics such as acetaminophen or nonsteroidal anti-inflammatory drugs may be administered. Topical or systemic steroids may also help reduce inflammation and pain[5].

CONCLUSION

Lipschütz vulvar ulcer is a rare clinical entity that may be confused with other diseases characterized by genital ulcerations, including sexually transmitted diseases and autoimmune diseases. Recognition of Lipschütz ulcer is essential to avoid misdiagnosis and overtreatment. Moreover, appropriate and timely treatment is also important to avoid complications.

ACKNOWLEDGMENT

Conflicts of interest: The authors have no conflicts of interest to disclose.

Funding: None

Author contributions: Doo-Ho Lim: case study design, data acquisition, revision of the manuscript, final approval of the version to be published and agreement to be accountable for all aspects of the work; Sungwon Ko: drafting of manuscript, revision of the manuscript, final approval of the version to be published and agreement to be accountable for all aspects of the work.

REFERENCES

1. Moise A, Nervo P, Doyen J, Kridelka F, Maquet J, Vandenbossche G. Ulcer of Lipschutz, a rare and unknown cause of genital ulceration. Facts Views Vis Obgyn 2018; 10:55-7.
2. Horie C, Kano Y, Mitomo T, Shiohara T. Possible involvement of mycoplasma fermentans in the development of nonsexually acquired genital ulceration (Lipschütz Ulcers) in 3 young female patients. JAMA Dermatol 2015; 151:1388-9.
3. Krapf JM, Casey RK, Goldstein AT. Reactive non-sexually related acute genital ulcers associated with COVID-19. BMJ Case Rep 2021;14.
4. Hsu T, Sink JR, Alaniz VI, Zheng L, Mancini AJ. Acute genital ulceration after Severe Acute Respiratory Syndrome Coronavirus 2 vaccination and infection. J Pediatr 2022; 246:271-3.
5. Rosman IS, Berk DR, Bayliss SJ, White AJ, Merritt DF. Acute genital ulcers in nonsexually active young girls: case series, review of the literature, and evaluation and management recommendations. Pediatr Dermatol 2012; 29:147-53.

Case Report

A case of neuroendocrine carcinoma first suspected on an echocardiogram

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Kuwait Medical Journal 2026; 58 (3): 211 - 215

ABSTRACT

Neuroendocrine carcinomas are infrequent malignant neoplasms with diverse manifestations, including the development of carcinoid heart disease (CHD), which impacts approximately 6-7% of afflicted individuals. This report highlights the instance of a 56-year-old male exhibiting echocardiographic evidence indicative of CHD, affecting all four heart valves, coupled with elevated 5-hydroxy indole acetic acid (5-HIAA) levels, prompting further investigative measures. Subsequent imaging analyses, along with chromogranin A and synaptophysin staining on liver biopsy, disclosed metastatic neuroendocrine carcinoma involving the liver, lung and bone. Significantly, the combination of echocardiography and elevated 5-HIAA levels played a pivotal role in instigating initial suspicion and subsequently confirming the presence of neuroendocrine carcinoma. This case underscores the importance of considering CHD in patients with pathognomonic valve findings on echocardiogram to enable early diagnosis and management.

KEY WORDS: carcinoid heart disease, echocardiography, heart valve disease, neuroendocrine carcinoma

INTRODUCTION

Neuroendocrine carcinomas are uncommon neoplasms with an incidence rate of 1.2 - 2.1 cases per 100,000 individuals in the general population annually and originate from enterochromaffin cells[1]. Vasoactive chemicals such as prostaglandins, tachykinins and serotonin are released by carcinoid tumors and their activity is mainly neutralized in the liver and lungs. The prevalence of carcinoid heart disease (CHD) is 6-7% of patients with neuroendocrine carcinomas[2].

CASE REPORT

A 56-year-old male patient presented to our cardiology outpatient clinic with a complaint of chest pain. He had a history of coronary artery stent implantation 5 years ago. He also reported a loss of appetite, indigestion and a history of weight loss of up to 30 kilos in 2 years. A transthoracic echocardiogram (TTE) and then a transesophageal echocardiogram (TEE) were performed. The TTE showed normal left ventricular (LV) systolic function. The right heart cavities were enlarged. The tricuspid valve leaflets were thickened, non-mobile and coaptation was impaired consistent with carcinoid changes with severe tricuspid regurgitation (Fig. 1A-C). The aortic valve leaflet also appeared thickened and there was moderate aortic regurgitation (Fig. 1D). The posterior mitral valve leaflet also appeared thickened and reduced in mobility, and there was moderate to severe eccentric mitral regurgitation (Fig. 1E). The pulmonary valve was not well visualized on TTE, but moderate pulmonary regurgitation was present (Fig. 1F). Upon TEE examination, further details of the valve anatomy were delineated. The TEE provided clearer images of the mitral, aortic and tricuspid valves, confirming the TTE findings of thickening and restricted movement (Fig. 2A-B). However, despite the detailed imaging capabilities of the TEE, the pulmonary valve morphology remained difficult to visualize clearly due to technical limitations. The TEE did not add significant additional information regarding the pulmonary valve compared to the TTE findings. A small pericardial effusion was present. There was no evidence of an intracardiac shunt by

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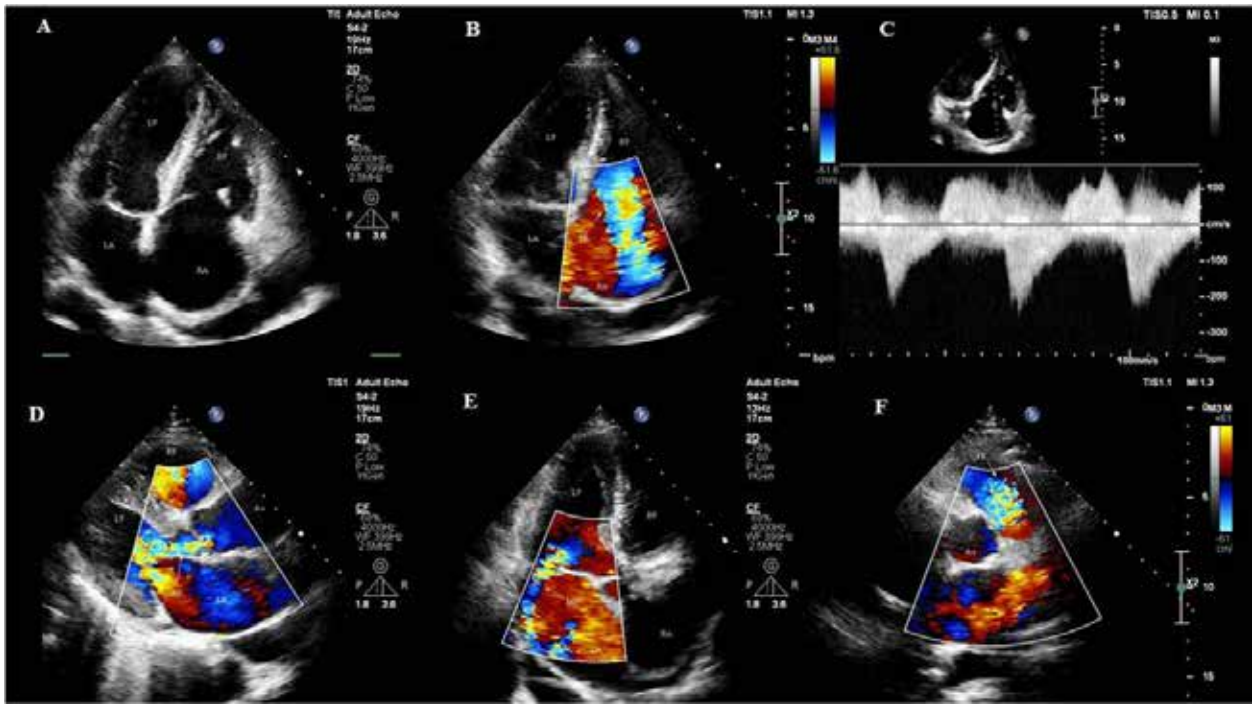

Figure 1: Apical 4-chamber view in systole displaying an opened and retracted tricuspid valve, while mitral valve is closed. **(A)** There is a large vena contracta confirming severe tricuspid regurgitation (TR); **(B)** Continuous-wave Doppler shows the characteristic dagger-shaped profile of the TR, with an early peak velocity and a rapid decline, indicating rapid pressure equalisation between the right-sided cardiac chambers; **(C)** Color Doppler imaging reveals the presence of moderate aortic regurgitation in the parasternal long-axis view in diastole; **(D)** In the apical 4-chamber view in systole, Color Doppler imaging discloses the existence of eccentric moderate mitral regurgitation; **(E)** In the parasternal short-axis view in diastole, the presence of moderate tricuspid regurgitation is revealed by Color Doppler imaging; **(F)** Ao: aorta; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.

color Doppler. Considering that the patient may have carcinoid heart disease based on echocardiography findings, 5-hydroxy indole acetic acid (5-HIAA) level was measured in a 24-hour urine sample, which was modestly elevated at 46 mg/24 hr (normal <14.0 mg/24hr). In abdominal ultrasonography, isoechoic lesions with cystic areas in the right lobe of the liver were observed. Magnetic resonance imaging showed a lobulated contoured mass at the lower lobe of the left lung, multiple masses in the liver, and masses in the L2 corpus and the T10 corpus. F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) was performed. Elevated F-18 FDG uptake was noted in the inferior lobe of the left lung, vertebral body and hepatic region (Fig. 3A-C). Morphological and immunohistochemical findings on liver biopsy were reported primarily consistent with large cell neuroendocrine carcinoma (Fig. 4A-D).

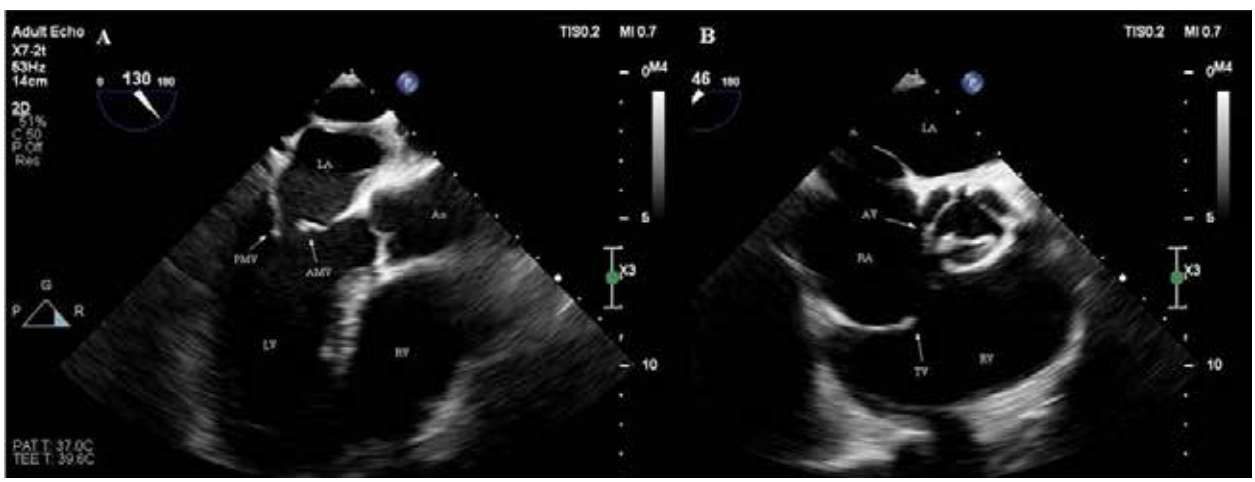

Figure 2: Mid-esophageal long-axis view in diastole displaying a thickened posterior mitral valve leaflet with reduced mobility. **(A)** Mid-esophageal short-axis view displaying thickened aortic valve leaflets; **(B)** AMV: anterior mitral valve; Ao: aorta; AV: aortic valve; LA: left atrium; LV: left ventricle; PMV: posterior mitral valve; RV: right ventricle; TV: tricuspid valve.

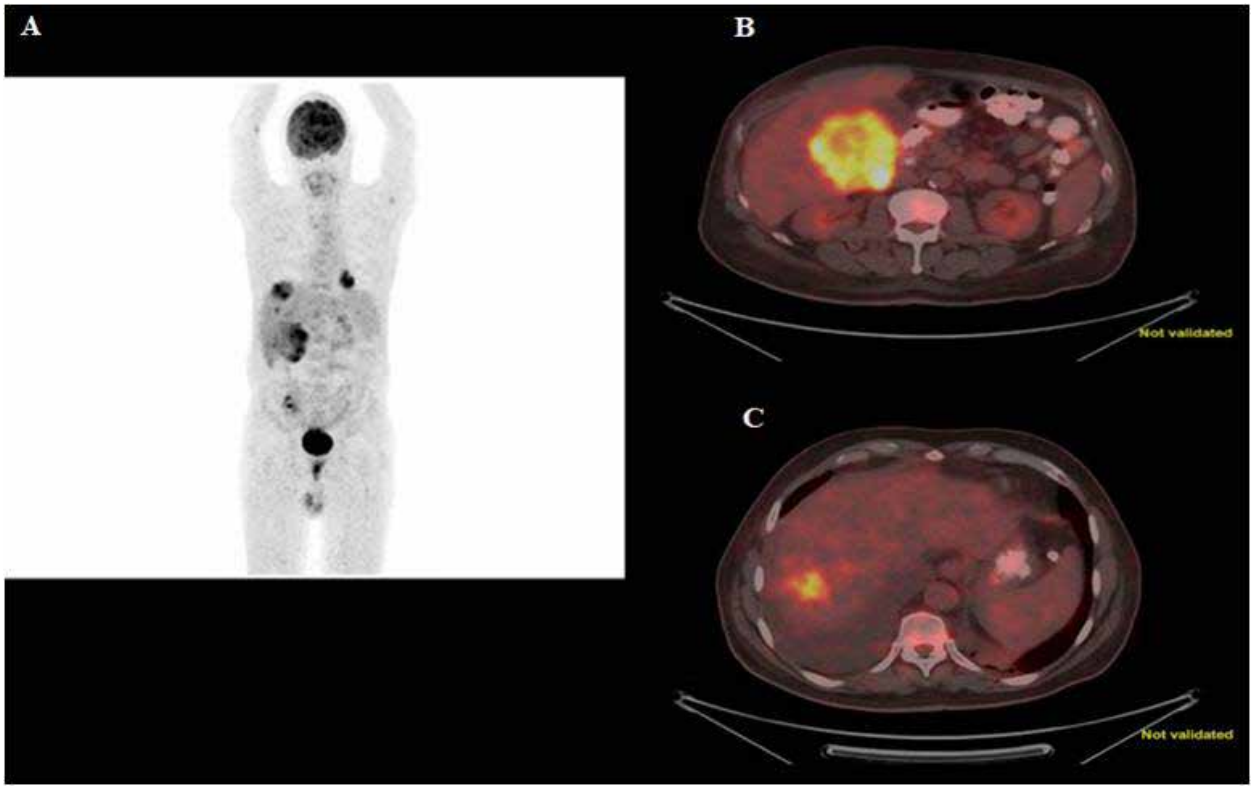

Figure 3: Metastatic disease in the liver is observed in positron emission tomography/computed tomography (PET/CT) images **(A-C)**.

The patient received 4 cycles of chemotherapy with a combination of cisplatin and etoposide. Three months after the initial suspicion of the diagnosis, the patient exhibited signs of excessive fluid retention and showed symptoms of both left- and right-sided cardiac failure. The patient had normal liver and renal parameters and a B-type natriuretic peptide (BNP) of 2647 pg/ml (normal <300 pg/mL). Upon re-evaluation, the patient presented with worsening dyspnea, significant peripheral edema and ascites, indicating a provisional diagnosis of biventricular failure. A follow-up TTE showed a further increase in the size of the right ventricular (RV) cavity, with severe tricuspid regurgitation persisting. The RV systolic function was markedly reduced, and the RV systolic pressure was elevated to 60 mmHg, indicating significant pulmonary hypertension. The LV systolic function remained within normal limits, but there was a slight increase in the severity of mitral regurgitation. The aortic regurgitation remained moderate, and the pulmonary valve regurgitation showed no significant changes. This constellation of clinical presentation is consistent with predominantly right ventricular failure. This is supported by the normal LV systolic function, the normal BNP levels, and further RV systolic dysfunction and RV enlargement.

The patient was hospitalized and after the signs of congestion were relieved with intravenous diuretic therapy, he was maintained on a treatment regimen consisting of a daily dose of metoprolol succinate 25 mg, spironolactone 25 mg and furosemide 40 mg orally. Despite these measures, the patient's symptoms persisted, and given the severity of his condition, including progressive RV enlargement, RV systolic dysfunction and severe symptoms of right heart failure, he was evaluated for potential valve-replacement surgery. However, valve-replacement surgery was not performed due to the patient's anticipated limited survival duration and the patient's reluctance to undergo the operative procedure.

DISCUSSION

In this report, a 56-year-old male case with CHD, in whom all four heart valves were affected and whose suspicion of neuroendocrine carcinoma first emerged after echocardiographic examination, is presented. In further examinations based on this suspicion, it was determined that the patient had a metastatic neuroendocrine carcinoma that had metastasized to the liver, lung and bone.

CHD is seen in 50% of patients with carcinoid syndrome and is the main cause of morbidity and mortality. The pathophysiology of CHD is still poorly understood; however, the disease is believed to be caused by chronic exposure to excessive circulating vasoactive substances produced by neuroendocrine tumors. The advancement of

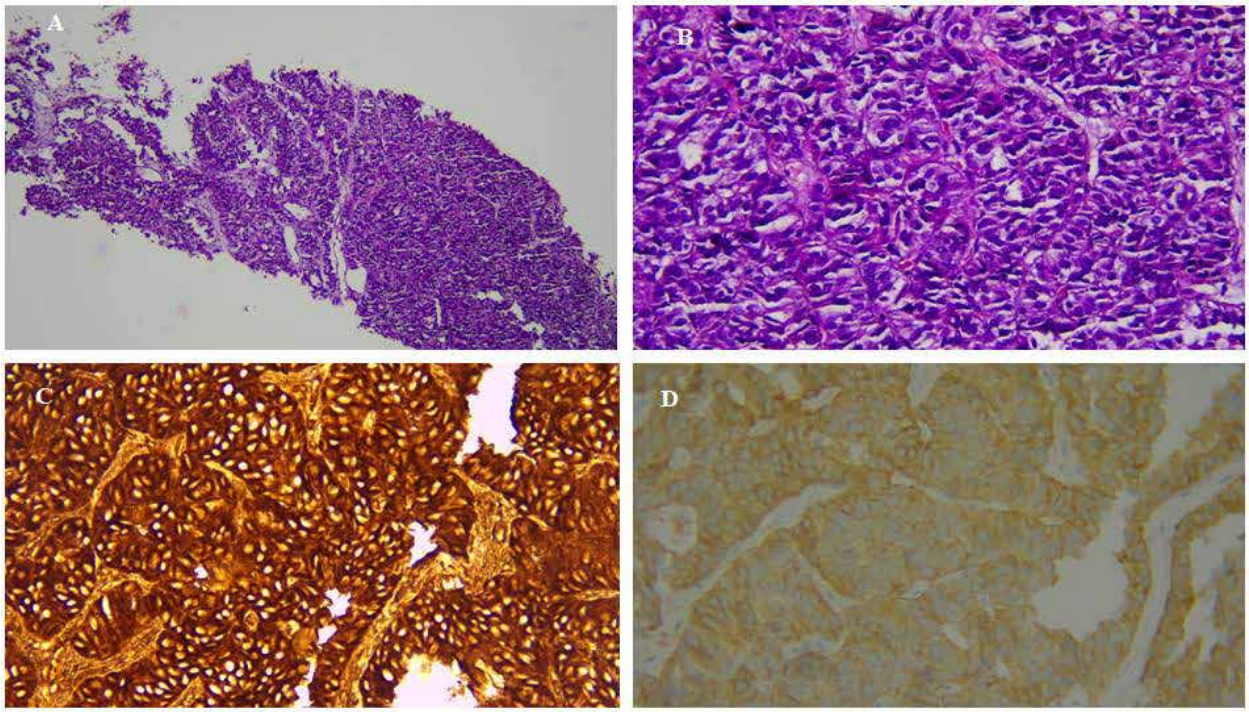

Figure 4: In the liver biopsy sample, tumor cells showing irregular solid islands, rosette disposition and palisade arrangement are observed. x100. **(A)** At high magnification; some of the tumor cells consist of atypical cells with large cytoplasm, prominent nucleoli, and coarse chromatin. x400; **(B)** Chromogranin and synaptophysin applied by immunohistochemical method show diffuse positive staining in tumor cells. x400 **(C, D)**.

cardiac imaging modalities, antitumor treatment and cardiac surgery, has improved the prognosis of patients with CHD[3].

Pathogenesis and Pathophysiology

The pathogenesis of CHD is multifactorial. Carcinoid tumors produce various vasoactive substances, including serotonin, histamine, bradykinin, prostaglandins and other fibroblast proliferative factors like transforming growth factor-beta (TGF-β) and tachykinins (neurokinin A, substance P, neuropeptide K). These peptides cause the deposition of plaques on the endocardial surfaces of valve leaflets, subvalvular apparatus and cardiac chambers[3]. The resulting fibrotic lesions lead to thickening, retraction and reduced mobility of the valve leaflets, primarily affecting the tricuspid and pulmonary valves. The key role of serotonin in forming these plaques is supported by the high levels of serum serotonin and its metabolite 5-HIAA observed in patients with CHD[4].

In this case, the pathophysiology involved the deposition of fibrous plaques primarily on the tricuspid and pulmonary valves, leading to severe tricuspid regurgitation and moderate pulmonary regurgitation. Additionally, the mitral and aortic valves were affected, showing moderate to severe mitral regurgitation and moderate aortic regurgitation, respectively.

Clinical Presentation and Diagnosis

CHD typically presents with symptoms of right heart failure, including fatigue, peripheral edema, ascites and hepatomegaly. Echocardiography is the primary diagnostic tool, revealing thickened and immobile valve leaflets with regurgitation. Similar to our case presentation, the characteristic "dagger-shaped" Doppler signal of tricuspid regurgitation is a hallmark of CHD[3]. Left-sided involvement is rare and usually occurs in patients with bronchial carcinoids or extensive liver metastasis, leading to elevated levels of circulating vasoactive substances[5]. In the presence of liver metastasis, vasoactive substances can directly access the heart through the systemic venous circulation, bypassing inactivation processes, and thereby contributing to the development of the disease primarily affecting the right side of the heart. This preference is attributed to the lungs' inactivation of vasoactive substances and serotonin degradation to 5-HIAA, which reduces serotonin levels capable of inducing fibrosis in the left heart. Additionally, left-sided valve pathology may occur in patients with an intracardiac shunt, such as a patent foramen ovale or atrial septal defect.

In this case, the patient presented with symptoms of chest pain, loss of appetite, indigestion and significant weight loss. Upon echocardiographic examination, no evidence of intracardiac shunting was identified in our case.

Management

The management of CHD involves controlling carcinoid syndrome symptoms with somatostatin analogs such as octreotide or lanreotide, which inhibit the release of serotonin and other vasoactive substances. For patients with severe valvular disease and heart failure, surgical intervention may be necessary[6]. Indications for valve surgery include symptomatic right heart failure, progressive right ventricular enlargement, or right ventricular systolic dysfunction in asymptomatic patients. In patients undergoing hepatic resection for metastases, concurrent cardiac surgery may be indicated to reduce the risk of perioperative complications due to increased hepatic venous pressure[3].

For the patient in this case, conservative management was chosen due to advanced metastatic disease, limited life expectancy and the patient's reluctance to undergo surgery. The patient was managed with diuretics and supportive measures to control symptoms of fluid retention and heart failure. Despite the severe valvular disease, the decision against surgery was influenced by the patient's overall poor prognosis and high surgical risk.

Prognosis

The prognosis of patients with CHD is generally poor, with a median survival of less than two years from the onset of heart failure symptoms. Early diagnosis and intervention can improve outcomes, but the overall prognosis remains guarded due to the progressive nature of the disease and the presence of metastatic neuroendocrine carcinomas[3]. Cardiac surgery, while beneficial for symptom relief and improving quality of life, carries high perioperative risks, particularly in patients with extensive metastatic disease and poor functional status.

In this case, the prognosis was significantly impacted by the patient's advanced metastatic disease and severe valvular involvement. The patient's survival and quality of life were managed through conservative measures, focusing on symptom control rather than curative intent, given the high risk associated with surgical intervention and the limited expected benefit.

The combined positivity of chromogranin A and synaptophysin expression is stated to be the most reliable stain combination in the diagnosis of neuroendocrine carcinomas[7]. In our case, the tumor cells stained positively for both synaptophysin and chromogranin using the immunohistochemical method which supported the diagnosis of neuroendocrine carcinoma.

In this clinical case, the integration of echocardiographic imaging and a 24-hour urine 5-HIAA level yielded valuable insights, unequivocally guiding the accurate diagnosis, a confirmation subsequently supported by histological examination.

CONCLUSION

Neuroendocrine carcinomas are aggressive and chemosensitive tumors with a poor prognosis. Therefore, early diagnosis and treatment initiated without wasting time affect survival. Symptoms and findings that will lead to the diagnosis immediately are very important. Chief among these findings are the findings on the echocardiogram that suggest the disease. In this case, it is important for clinicians to increase their awareness.

ACKNOWLEDGMENTS

None

Conflicts of interest: The authors declare that there is no conflict of interest.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Informed consent: The patient's legal representative provided written informed consent for the publication of this case report and any associated images.

REFERENCES

1. Shinn BJ, Tafe LJ, Vanichakarn P. A case of carcinoid syndrome due to malignant metastatic carcinoid tumor with carcinoid heart disease ınvolving four cardiac valves. Am J Case Rep 2018; 19:284-8.
2. Mattig I, Franke MR, Pschowski R, Brand A, Stangl K, Knebel F, *et al*. Prevalence, one-year-incidence and predictors of carcinoid heart disease. Cardiovasc Ultrasound 2023; 21(1):18.
3. Sabet A, Haghighiabyaneh M, Rajyaguru C, Raisinghani A, Kupsky D, DeMaria AN. Carcinoid heart disease. Structural Heart 2020; 4(2):78-86.
4. Robiolio PA, Rigolin VH, Wilson JS, Harrison JK, Sanders LL, Bashore TM, *et al*. Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. Circulation 1995; 92(4):790-5.
5. Jahagirdar V, Kamal A, Steeds R, Ayuk J. Metastatic small bowel neuroendocrine tumour with bilateral carcinoid heart disease. BMJ Case Rep 2016; 2016:bcr2015213693.
6. Lichtenauer M, Pichler T, Eder S, Mirna M, Magnes T, Wernly B, *et al*. Carcinoid heart disease involving the left heart: a case report and biomarker analysis. ESC Heart Fail 2019; 6(1):222-7.
7. Öberg K, Hellman P, Ferolla P, Papotti M; ESMO Guidelines Working Group. Neuroendocrine bronchial and thymic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23 Suppl 7:vii120-3.

Case Report

Listeria monocytogenes meningitis in an immunocompetent adult: A case report

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Kuwait Medical Journal 2026; 58 (3): 216 - 219

ABSTRACT

Listeriosis is a rare infectious disease caused by *Listeria monocytogenes* (*L. monocytogenes*). Patients with immunosuppression are at increased risk of developing invasive diseases, particularly meningitis. We describe a case of meningitis caused by *L. monocytogenes* in an immunocompetent 34-year-old adult. The patient received treatment with intravenous ampicillin and made a full recovery. *Listeria* meningitis should be suspected in immunocompetent adults with bacterial meningitis who fail to respond to empirical antibiotic treatment. Otherwise, if timely diagnosis and treatment are not performed, serious complications may develop or result in death.

KEY WORDS: immunocompetent, listeriosis, meningitis

INTRODUCTION

Listeriosis is an infectious disease caused by *L.monocytogenes*. It is a rare disease with an annual incidence ranging from 3 to 6 per million[1]. Listeriosis is well recognised to occur in particular at-risk groups such as pregnant women, elderly, immunocompromised people and newborns[2]. We aimed to present a case of *Listeria* meningitis in a young patient without immunodeficiency or another risk factor.

CASE REPORT

A 34-year-old male patient with no history of chronic illness presented to our hospital with a sudden onset of incoherent speech and confusion. For the three days preceding admission, he had fever and headache. There was no recent history of travel or contact with sick individuals. The patient was conscious on physical examination but had limited orientation and cooperation. His body temperature was 38.6 °C, blood pressure was 77/149 mmHg, respiratory rate was 26 breaths per minute, and heart rate was 115 beats per minute. The patient had neck stiffness. Other physical examination findings were normal. Laboratory investigations revealed a leukocyte count of 20,030/mm^3 [86% polymorphonuclear leukocytes (PMN)], C-reactive protein at 247 mg/L, and an erythrocyte sedimentation rate of 32 mm/h. Cranial computed tomography (CT) scan showed no abnormalities. For further evaluation, a lumbar puncture (LP) was performed. Cerebrospinal fluid (CSF) analysis revealed a leukocyte count of 160/mm^3 (60% lymphocytes), protein concentration of 193 mg/dL, and glucose level of 10 mg/dL (simultaneous blood glucose level was 145 mg/dL) (Table 1). Gram staining of the CSF sample showed no bacteria. The patient was diagnosed with suspected bacterial meningitis and admitted to our clinic. After obtaining blood cultures, empirical intravenous (IV) treatment with ceftriaxone (2 g every 12 hours), vancomycin (1 g every 8 hours), and dexamethasone (0.15 mg/kg every 6 hours) was started. On the following day, a preliminary evaluation of the CSF culture revealed the growth of gram-positive bacilli (Figures 1 and 2), prompting the addition of IV ampicillin (2 g every 4 hours) to the existing regimen. Tests for serum anti-HIV, rapid plasma reagin and

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Table 1: CSF findings during disease follow-up

Variables	At admission	14th day	21st day
Leukocytes (n/mm³) (normal range, 0-10)	160	60	16
Neutrophils (%)	40	60	-
Lymphocytes (%)	60	40	-
Protein (mg/dL) (normal range, 15-45)	193	22	-
Glucose (mg/dL) (normal range, 40-70)	10	62	-
Simultaneous blood glucose (mg/dL)	145	130	-

Brucella agglutination were negative. On the fourth day of follow-up, the patient developed diplopia. Repeat cranial imaging showed no pathology on CT, but indicated findings consistent with increased intracranial pressure on MRI. The neurology team evaluated the patient and considered the possibility of sixth cranial nerve palsy. It was decided to continue and gradually taper the dexamethasone treatment. On the fourth day of antibiotic therapy, CSF culture identification using the VITEK 2 Compact (Biomerieux, France) system reported growth of *Listeria* species, leading to the discontinuation of ceftriaxone and vancomycin. The system failed to identify the isolate at the species level due to the limited scope of its database and insufficient discriminatory power between *Listeria* species. By the end of the first week of treatment, the patient's diplopia resolved. After completing the second week of treatment, all symptoms and signs of the disease regressed, and a control LP was performed. CSF analysis showed a leukocyte count of 60/mm³ (60% PMN), protein level of 22 mg/dL and glucose level of 62 mg/dL (simultaneous blood glucose was 130 mg/dL). No bacteria were seen on Gram stain of the CSF sample, and there was no growth in the CSF culture.

During the second week of treatment, results from the bacterial isolate sent to the Microbiology Reference Laboratory identified the CSF culture isolate as *Listeria monocytogenes* using MALDI-TOF MS (BRUKER, Microflex). Antibiotic susceptibility testing using the Gradient Strip test method and evaluated according to EUCAST 2023 Standards showed sensitivity to ampicillin, meropenem and trimethoprim-sulfamethoxazole. No growth was detected in blood cultures. After completing the third week of treatment, a control LP was performed, revealing a leukocyte count of 16/mm³. Due to the limited amount of CSF obtained, only cell count analysis was conducted. The patient, having completed three weeks of ampicillin and dexamethasone therapy, was discharged in good health. Further advanced laboratory investigations during the hospital stay and subsequent outpatient follow-ups revealed no immunological abnormalities.

DISCUSSION

Listeria monocytogenes is widely found in nature. The primary route of transmission is believed to be through the consumption of contaminated food. Ready-to-eat foods and dairy products have been particularly associated with *Listeria* infections[2]. In our case, the route of transmission could not be determined, but it is thought to be foodborne due to its common mode of transmission. Listeriosis display in two forms: invasive and non-invasive. The most common clinical forms of invasive listeriosis are bacteremia and central nervous system involvement, with high mortality rates despite treatment. In immunocompetent young individuals,

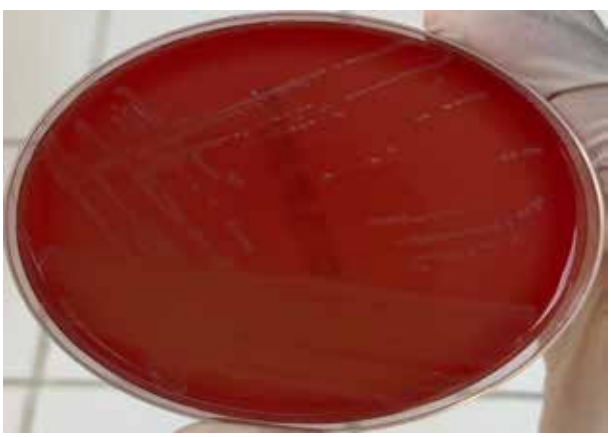

Figure 1: Growth of gram-positive bacilli on 5% sheep blood agar

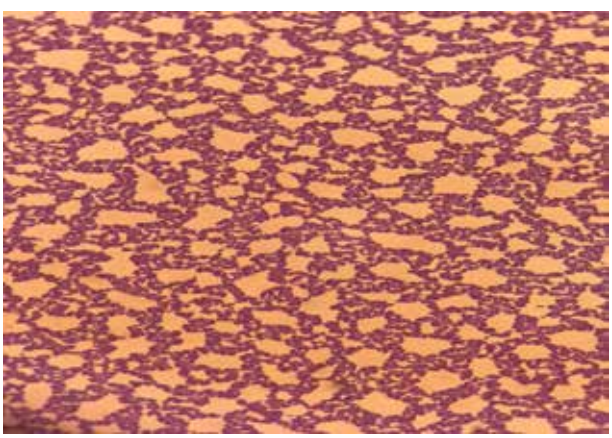

Figure 2: Gram stain (100X) showing gram-positive bacilli

listeriosis typically presents as a self-limiting febrile gastroenteritis[1,2]. Patients at high risk for invasive *Listeria* infections include those with cancer, pregnant women, organ transplant recipients, individuals with immunodeficiency syndromes, and those receiving corticosteroids or immunosuppressive therapy. Another predisposing factor is age, with elderly adults and neonates being at higher risk. As far as we know, our patient did not have any underlying disease or risk factor that could cause immunodeficiency.

The clinical features and CSF findings of *Listeria* meningitis are similar to those of community-acquired bacterial meningitis caused by more common etiological agents[3]. *Listeria* is a non-tuberculous bacterium that causes lymphocyte predominance in the CSF in the absence of antibiotic use. In a study of 257 patients with *Listeria* meningitis or meningoencephalitis, almost all patients had elevated CSF protein concentrations, and 39% had decreased CSF glucose concentrations[2]. Microorganisms are often not seen on Gram stain of CSF, and the definitive diagnosis is made by isolating *L. monocytogenes* in CSF culture[1]. In Turkey, the sensitivity of microscopy and culture in identifying bacteria is limited due to the widespread use of antibiotics before hospital admission. The CSF findings in our case were consistent with the literature, and the patient was diagnosed with bacterial meningitis at presentation. The causative agent was identified as *L. monocytogenes* following its growth in CSF culture.

Empirical treatment for community-acquired bacterial meningitis in adults under 50 years old is a combination of third-generation cephalosporin and vancomycin. *Listeria monocytogenes* is naturally resistant to third-generation cephalosporins, and vancomycin has limited antimicrobial activity against *L. monocytogenes*[4,5]. In the treatment of *Listeria* meningitis, it is recommended to add gentamicin, a bactericidal agent, to ampicillin to achieve a synergistic effect[1]. A multinational, multicenter study, including Turkey, found no superiority of combination therapy with ampicillin and aminoglycoside over ampicillin monotherapy[6]. In our case, the empirically started ceftriaxone and vancomycin were discontinued on the fourth day once the causative agent was identified, and ampicillin therapy was completed for three weeks.

The use of dexamethasone as an adjunctive agent in treatment is not recommended due to a lack of proven benefit[1]. However, some studies tend to reevaluate dexamethasone treatment due to its effects on inflammation and edema[7]. In our case, dexamethasone treatment started for bacterial meningitis was continued even after *L. monocytogenes* was identified, due to increased intracranial pressure in the patient. The dexamethasone dose was gradually tapered and discontinued in the third week, as the patient was thought to have responded to the treatment. Our immunocompetent 34-year-old patient was successfully treated with ampicillin. The preliminary evaluation of the CSF culture showing gram-positive bacilli growth a day after presentation prevented significant delays in treatment, contributing to the successful management of the disease. However, this is not always the case, and delays in treatment can occur, especially in patients not in high-risk groups, due to diagnostic difficulties. The disease can result in death or neurological sequelae[8].

CONCLUSION

Our case shows that *Listeria* meningitis can occur in young, immunocompetent individuals, albeit rarely, and that the agent should be kept in mind because *Listeria* is resistant to third-generation cephalosporin and vancomycin combination therapy, which is the empirical treatment of bacterial meningitis.

ACKNOWLEDGMENTS

Author contributions: All authors contributed to the conception of the idea, drafting and approval of the final version of the manuscript. Merve Aytekin wrote the manuscript and Canan Eryildiz prepared the figures. All authors read and approved the final manuscript.

Conflict of interest: The authors declare no conflicts of interests.

Funding: The authors have no funding or financial relationships to disclose.

Consent: A written informed consent was obtained from the patient.

REFERENCES

1. Charlier C, Perrodeau É, Leclercq A, Cazenave B, Pilmis B, Henry B, *et al*. Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study. The Lancet Infectious Diseases 2017; 17(5):510-9.
2. Mylonakis E, Hohmann EL, Calderwood SB. Central Nervous System Infection with Listeria monocytogenes: 33 Years' Experience at a General Hospital and Review of 776 Episodes from the Literature. Medicine 1998; 77(5):313-36.
3. Brouwer MC, van de Beek D, Heckenberg SG, Spanjaard L, de Gans J. Community-acquired Listeria monocytogenes meningitis in adults. Clinical Infectious Diseases 2006; 43(10):1233-8.
4. Van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in treatment of bacterial meningitis. The Lancet 2012; 380(9854):1693-702.
5. Sinner SW, Tunkel AR. Antimicrobial agents in the treatment of bacterial meningitis. Infectious Disease Clinics 2004; 18(3):581-602.

6. Arslan F, Meynet E, Sunbul M, Sipahi OR, Kurtaran B, Kaya S, *et al*. The clinical features, diagnosis, treatment, and prognosis of neuroinvasive listeriosis: a multinational study. European Journal of Clinical Microbiology & Infectious Diseases 2015; 34:1213-21.
7. Thønnings S, Knudsen JD, Schønheyder HC, Søgaard M, Arpi M, Gradel KO, *et al*. Antibiotic treatment and mortality in patients with Listeria monocytogenes meningitis or bacteraemia. Clinical Microbiology and Infection 2016; 22(8):725-30.
8. Amaya-Villar R, García-Cabrera E, Sulleiro-Igual E, Fernández-Viladrich P, Fontanals-Aymerich D, Catalán-Alonso P, *et al*. Three-year multicenter surveillance of community-acquired Listeria monocytogenes meningitis in adults. BMC Infectious Diseases 2010; 10:1-8.

Brief Communication

Narrative consent in psychiatry: integrating coherence and authorship of the self into capacity assessment

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Kuwait Medical Journal 2026; 58 (3): 220 - 222

ABSTRACT

Background: Capacity and consent assessments in psychiatry rely primarily on cognitive criteria such as understanding, appreciation, reasoning and the ability to express a choice. These criteria are essential but insufficient for capturing the disruptions of selfhood characteristic of many psychiatric disorders.
Objective: To propose a narrative consent model that supplements cognitive assessments with an evaluation of the coherence, continuity and authorship of a patient's life-narrative
Methods: Conceptual analysis drawing on philosophy of personal identity, narrative theory and psychiatric ethics, with attention to cultural considerations relevant to Middle Eastern clinical practice
Results: Narrative consent reframes decisional capacity as both a cognitive and narrative achievement. It helps distinguish refusals that reflect transient, pathology-driven identities from those that express stable, diachronic values. The model offers practical clinical questions and aligns with relational and temporal dimensions of autonomy in Middle Eastern contexts.
Conclusion: A narrative consent model provides a more comprehensive and culturally sensitive framework for psychiatric decision-making. It offers an original contribution by operationalizing narrative identity theory into a clinically applicable consent assessment tool.

KEY WORDS: autonomy, capacity, consent, medical ethics, Middle East, narrative identity, psychiatry

INTRODUCTION

Capacity and consent assessments are central to psychiatric practice and legal decision-making. Widely used frameworks, including the MacArthur Competence Assessment Tool, evaluate four cognitive abilities: understanding, appreciation, reasoning and the ability to express a choice[1,2]. These criteria reflect a rationalist conception of autonomy that prioritizes momentary cognitive performance.

However, psychiatric disorders often disrupt not only cognition but the deeper narrative structure through which persons interpret their lives, values and futures. Philosophical work on personal identity suggests that autonomy is not merely a snapshot of cognitive functioning but a narrative achievement: persons act as agents by authoring a coherent story of who they are and who they aspire to be[3,4]. When this narrative structure is fragmented, constricted or replaced by pathology-driven identities, cognitive criteria alone may misrepresent a patient's true decisional capacity.

This paper proposes a narrative consent model that supplements cognitive criteria with an assessment of whether a patient's decision reflects a coherent, diachronic and self-authored life-narrative. The model is particularly relevant in Middle Eastern contexts, where identity is relational, temporality is morally significant, and decisions are embedded in family and community narratives.

Methods: Conceptual and Ethical Approach

This paper employs a conceptual methodology grounded in:

- philosophical theories of personal identity (Schechtman, Ricoeur)[3,4]
- relational and narrative accounts of autonomy (Mackenzie, Christman)[5]

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- psychiatric ethics literature on values, personhood and mental disorder[6-11]
- cross-cultural perspectives on autonomy and decision-making in Middle Eastern societies[12]

The aim is not to generate empirical data but to develop a normative framework that can guide clinical practice.

Narrative Disruption in Psychiatric Illness

Psychosis and Fragmented Narratives

Psychotic disorders often involve a breakdown in the coherence of the self-narrative. Delusions may impose alien storylines, while disorganized thought disrupts temporal and causal structure. A patient refusing treatment because "I am being controlled by external forces" may demonstrate intact reasoning within the delusional narrative but lacks authorship over that narrative[6,9].

Mania and Radical Revaluation

Mania can produce abrupt, extreme shifts in values—grandiosity, impulsivity and expansive goals—that are inconsistent with the patient's long-standing commitments. Decisions made in mania may be cognitively articulate yet narratively unmoored from the patient's diachronic identity[7].

Severe Depression and Narrative Constriction

Depression often constricts the self-narrative, eliminating future possibilities and eroding agency. A refusal of treatment may appear reasoned but reflects a pathology-driven collapse of the narrative horizon rather than stable values[8].

Limitations of Cognitive Capacity Models

Cognitive tests can misclassify two common clinical situations:

- False positives: A patient in mania or psychosis may articulate reasons that satisfy cognitive criteria but express a transient, pathology-generated self[6,7].
- False negatives: A patient with chronic mental illness may make a decision that appears unusual but is consistent with their long-standing values and life-story[9-11].

A narrative lens helps clinicians distinguish between decisions authored by the patient and those authored by the illness.

The Narrative Consent Model

Core Claim

A patient has decisional capacity when their choice is:

- cognitively intelligible
- narratively coherent with their diachronic self
- authored by the patient rather than by pathology

Three Narrative Criteria

- Coherence: Does the decision fit within a minimally structured, intelligible self-story?
- Continuity: Is the decision aligned with enduring values and commitments?
- Authorship: Is the narrative genuinely the patient's own, or generated by symptoms?

Clinical Operationalization

Clinicians can incorporate narrative assessment through structured questions:

- "How does this decision fit with the kind of person you see yourself as?"
- "Has this value been important to you over time?"
- "Would you have made a similar decision before this illness episode?"
- "Does this choice reflect your long-term commitments or something that feels new or imposed?"

These questions contextualize cognitive testing within the patient's lived identity.

Cultural Relevance in Middle Eastern Psychiatry

Middle Eastern societies emphasize relational identity, family continuity and moral narratives grounded in religion and tradition. A narrative consent model aligns with these cultural realities[12]:

- Relational autonomy: Decisions are embedded in family and community narratives.
- Temporal identity: Islamic and regional ethical traditions emphasize continuity of character and intention.
- Moral authorship: Distinguishing self-authored values from externally imposed influences resonates with cultural understandings of responsibility.

Thus, narrative consent offers a culturally sensitive alternative to purely individualistic, cognitive models.

Relevance to Kuwait's Mental-Health Landscape

These initiatives emphasize:

- patient-centred care,
- culturally grounded clinical practice,
- family involvement in treatment,
- respect for patient dignity and autonomy within a culturally sensitive framework.

Kuwait's regulatory environment, including the Ministry of Health's guidelines on clinical ethics and human-subjects protection, underscores the importance of consent processes that are both ethically robust and culturally appropriate. A narrative consent model aligns with these priorities by offering a framework that:

- respects the patient's cultural and familial context,
- supports clinicians in distinguishing authentic preferences from pathology-driven shifts in identity,

- enhances the ethical quality of consent in psychiatric care by integrating narrative, relational and cognitive dimensions.

Given Kuwait's commitment to culturally responsive mental-health services, narrative consent provides a timely and contextually relevant approach that complements existing policy goals and clinical practices.

DISCUSSION

Narrative consent does not replace cognitive criteria; it supplements them. It helps clinicians avoid over-valuing momentary reasoning and under-valuing the patient's enduring identity. It also provides a richer understanding of autonomy in psychiatric contexts, where the self is often destabilized[3-5].

Challenges include training clinicians in narrative interviewing, avoiding paternalistic misuse and ensuring transparency in narrative judgments. Future research should explore structured narrative assessment tools and empirical validation.

CONCLUSION

A narrative consent model reframes decisional capacity as both a cognitive and narrative achievement. By evaluating coherence, continuity and authorship of the patient's life-story, clinicians can better distinguish authentic decisions from pathology-driven ones. This approach is philosophically grounded, clinically useful, and culturally resonant in Middle Eastern psychiatric practice. It offers an original contribution to psychiatric ethics and capacity assessment.

ACKNOWLEDGMENTS

None.

Conflict of Interest: The author declares no conflict of interest.

Funding: No external funding was received for this work.

REFERENCES

1. Grisso T, Appelbaum PS. Assessing Competence to Consent to Treatment. Oxford University Press; 1998.
2. Appelbaum PS. Assessment of patients' competence to consent to treatment. N Engl J Med 2007; 357(18):1834-40.
3. Schechtman M. The Constitution of Selves. Cornell University Press; 1996.
4. Ricoeur P. Oneself as Another. University of Chicago Press; 1992.
5. Mackenzie C, Stoljar N, editors. Relational Autonomy: Feminist Perspectives on Autonomy, Agency, and the Social Self. Oxford University Press; 2000.
6. Charland LC. Is Mr. Spock mentally competent? Philos Psychiatry Psychol 1998; 5(1):67-81.
7. Fulford KWM. Moral Theory and Medical Practice. Cambridge University Press; 1989.
8. Sadler JZ. Values and Psychiatric Diagnosis. Oxford University Press; 2005.
9. Bolton D, Hill J. Mind, Meaning, and Mental Disorder. Oxford University Press; 2004.
10. Tan DJ, Hope T, Stewart A. Competence to refuse treatment in anorexia nervosa. Int J Law Psychiatry 2003; 26(6):697-707.
11. Owen GS, Freyenhagen F, Richardson G, Hotopf M. Mental capacity and decisional autonomy. Inquiry 2009; 52(1):79-107.
12. Al-Krenawi A, Graham JR. Mental health practice in Arab countries. Curr Opin Psychiatry 2000; 13(5):517-20.

Brief Communication

Preserving human intelligence in medicine: why scientific conferences must remain live, interactive, and human-led

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Kuwait Medical Journal 2026; 58 (3): 223 - 225

ABSTRACT

The rapid integration of artificial intelligence (AI) into clinical practice and scientific communication has introduced new efficiencies but also new vulnerabilities. One emerging concern is the increasing use of AI to mediate, summarize or participate in scientific conferences. This perspective argues that scientific meetings must remain fundamentally live, interactive and human-led. Delegating core intellectual functions to AI risks diminishing clinical judgment, weakening scientific creativity and eroding the professional culture that sustains high-quality care. Drawing on evidence from cognitive psychology, communication science and studies of automation, this article outlines the irreplaceable cognitive, ethical and developmental value of live scientific exchange. It proposes a balanced path in which AI supports—but never substitutes—the human intelligence that conferences are designed to cultivate.

KEY WORDS: artificial intelligence; clinical reasoning; medical conferences; professional identity; scientific communication

INTRODUCTION

Artificial intelligence is increasingly embedded in clinical practice, research and medical education. While these tools offer efficiency, they also introduce new risks, particularly when used to mediate scientific conferences. Automated note-taking, AI-generated debate positions, algorithmic question-generation and virtual attendance by AI "delegates" are now marketed as productivity tools. These developments raise a fundamental question: what becomes of medicine when clinicians outsource the intellectual labour that conferences were designed to cultivate?

Scientific meetings have historically served as crucibles for clinical judgment, scientific creativity and ethical deliberation. This perspective argues that conferences must remain fundamentally live, interactive and human-centered. Delegating core intellectual functions to AI risks the gradual marginalization of human intelligence and the erosion of the professional culture that sustains high-quality care.

The Irreplaceable Cognitive Value of Live Scientific Exchange

Live debate strengthens clinical judgment

Clinical reasoning is a dynamic process involving uncertainty, disagreement and the weighing of competing interpretations. Research in cognitive psychology demonstrates that argumentative dialogue improves diagnostic accuracy, particularly when clinicians must justify their reasoning to peers[1,2]. Exposure to dissenting views reduces premature closure and mitigates cognitive bias—two contributors to diagnostic error.

AI-generated summaries cannot replicate this process. They present conclusions without the struggle that produced them. When clinicians rely on algorithmic distillation rather than engaging directly with debate, they lose opportunities to refine the judgment that underpins safe practice.

Creativity emerges from human friction, not algorithmic coherence

Innovation in medicine rarely arises from linear information transfer. Studies of scientific discovery

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show that breakthroughs often emerge from informal interactions, unexpected questions and interdisciplinary collisions[3]. Conferences provide precisely these conditions: spontaneous conversations, contested ideas and the productive discomfort of intellectual disagreement.

AI systems, by contrast, optimize for coherence and predictability. They smooth over conflict and generate the "most likely" answer. A conference mediated by AI risks becoming a space of homogenized thought-efficient, but intellectually sterile.

Professional identity is formed through participation, not delegation

For trainees, conferences are formative. They learn how to defend a position under scrutiny, challenge senior colleagues respectfully, present uncertainty honestly, and respond to critique. Participation in scholarly communities predicts long-term academic engagement and leadership[4,5].

If AI tools attend, summarize or speak on behalf of clinicians, these developmental experiences disappear. Delegated intelligence produces delegated professionals-clinicians who outsource the very skills that define expertise.

The Risks of AI-Mediated Conferences

Cognitive atrophy

When clinicians rely on AI to digest complex material, their ability to analyze, synthesize and critique weakens. Research on automation in aviation and other high-stakes fields shows that over-reliance on decision-support systems leads to skill degradation, reduced vigilance and poorer performance when systems fail[6,7]. Medicine is not immune to these dynamics.

Homogenization of scientific discourse

Large language models are trained on overlapping corpora and tend to converge on similar formulations. If AI tools generate questions, abstracts or debate positions, conferences risk becoming echo chambers. Intellectual diversity-a key driver of scientific progress-is diminished.

Loss of professional agency

When AI intermediates scientific exchange, clinicians become passive recipients rather than active contributors. This shift mirrors patterns seen in other industries where automation reduces autonomy and engagement.

Erosion of ethical deliberation

Many conference debates involve moral complexity: end-of-life care, resource allocation, public health ethics. These discussions require empathy, lived experience and moral imagination. AI can model arguments, but it cannot care. Ethical deliberation without human presence becomes procedural rather than moral.

What Live Conferences Provide that AI cannot

Embodied presence

Nonverbal cues, emotional tone and the social dynamics of a room shape understanding. Research in communication science shows that in-person interaction enhances trust, comprehension and collaborative problem-solving[8]. These elements are essential for navigating scientific uncertainty.

Spontaneity

Unscripted moments—a question from the back row, a hallway conversation—often generate the most meaningful insights. These cannot be automated.

Accountability

Speaking in front of peers carries a weight that AI-mediated participation lacks. It encourages rigor, humility and responsibility.

Community

Medicine is a communal profession. Shared experiences build solidarity, mentorship and collective responsibility. These are essential for clinician well-being and retention.

A Balanced Path Forward: AI as tool, not delegate

This perspective does not argue against AI. Used appropriately, AI can support literature searches, enhance accessibility, assist with note-taking, provide translation and help clinicians review material after the event. But AI must remain a tool, not a proxy. The core intellectual labour—debating, questioning, imagining, challenging—must remain human.

CONCLUSION

Scientific conferences are more than information exchanges. They are arenas of human intelligence, where clinicians and researchers test ideas, confront uncertainty and cultivate the judgment that defines the profession. If AI replaces human participation—even in the name of efficiency—clinicians risk becoming well-informed but intellectually diminished, technologically empowered but professionally disempowered.

To preserve the integrity of medicine, conferences must remain live, interactive and fundamentally human. AI may assist, but it must never attend, argue or think on our behalf. The future of medicine

depends not on the delegation of intelligence, but on the cultivation of human intellect, creativity and moral agency.

REFERENCES

1. Klein JG. Five pitfalls in decisions about diagnosis and prescribing. BMJ 2005; 330:781-3.
2. Mamede S, van Gog T, Moura AS, de Faria RMD, Peixoto JM, Rikers RM, *et al*. Reflection as a strategy to foster medical students 'diagnostic reasoning: a randomised controlled trial. Med Educ 2020; 54:365-73.
3. Uzzi B, Mukherjee S, Stringer M, Jones B. Atypical combinations and scientific impact. Science 2013; 342:468-72.
4. Wenger-Trayner E, Fenton-O'Creevy M, Hutchinson S, Kubiak C, Wenger-Trayner B. Learning in Landscapes of Practice. London: Routledge; 2015.
5. Gruppen LD, Irby DM, Durning SJ, Maggio LA. Conceptualising learning environments in the health professions. Acad Med 2019; 94:969-74.
6. Parasuraman R, Riley V. Humans and automation: use, misuse, disuse, abuse. Hum Factors 1997; 39:230-53.
7. Casner SM, Hutchins EL, Norman DA. The challenges of partially automated driving. Commun ACM 2016; 59:70-7.
8. Burgoon JK, Guerrero LK, Floyd K. Nonverbal Communication. New York: Routledge; 2016.

Letter to the Editor

Time-of-day as a missing clinical variable: a call for routine documentation

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Kuwait Medical Journal 2026; 58 (3): 226

Dear Editor,

A growing body of evidence indicates that many commonly used clinical biomarkers are influenced by circadian rhythms, resulting in measurable time-of-day–dependent variability[1,2]. Despite this, the timing of laboratory sample collection is rarely recorded or standardized in routine clinical practice.

This omission may represent an under-recognized source of variability in biomarker interpretation. For parameters such as circulating immune cells (e.g., neutrophils and lymphocytes), hormones and metabolic markers, diurnal fluctuations may influence threshold-based classification and risk stratification[1,3]. For instance, serum cortisol and high-sensitivity troponin exhibit diurnal variations that may affect diagnostic thresholds for adrenal insufficiency and myocardial injury, respectively. As a result, clinically meaningful differences may arise not only from underlying disease processes, but also from the time at which measurements are obtained.

At the system level, failure to account for temporal variation may affect the comparability of data across patients, institutions and healthcare settings. In large-scale and multi-center studies, unrecorded differences in sampling time may introduce systematic bias, potentially influencing epidemiological analyses and health policy decisions[3]. In healthcare systems where electronic health records are still being implemented or optimized, adding a timestamp for phlebotomy represents a low-cost, high-yield intervention that does not require advanced infrastructure.

While morning fasting samples are commonly used, the exact hour of sampling (e.g., 7:00 AM vs. 10:00 AM) may still yield clinically relevant differences for several analytes. Therefore, precise documentation, rather than approximate timing, is essential.

A simple and feasible solution would be the routine documentation of sampling time as part of standard laboratory reporting. Additionally, partial standardization of blood sampling schedules—particularly for time-sensitive biomarkers—may improve consistency and interpretability of clinical data. Integration of temporal variables into electronic health records may further support more accurate analysis and facilitate future research[4].

Incorporating time of day as a standard clinical variable represents a low-cost, high-impact step toward improving biomarker reliability and strengthening both clinical and public health decision-making.

REFERENCES

1. Scheiermann C, Kunisaki Y, Frenette PS. Circadian control of the immune system. Nat Rev Immunol 2013; 13(3):190-8.
2. Dallmann R, Okyar A, Lévi F. Dosing-time makes the poison: circadian regulation and pharmacotherapy. Trends Mol Med 2016; 22(5):430-45.
3. Fishbein AB, Knutson KL, Zee PC. Circadian disruption and human health. J Clin Invest 2021; 131(19):e148286.
4. Ballesta A, Innominato PF, Dallmann R, Rand DA, Lévi FA. Systems chronotherapeutics. Pharmacol Rev 2017; 69(2):161-99.

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Letter to the Editor

Unveiling new perspectives on hypercalcemia and Vitamin D: exploring the complexities of high Serum 25 (OH) Vitamin D levels

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Kuwait Medical Journal 2026; 58 (3): 227 - 228

Dear Editor,

We are writing in response to the recently published article[1] titled "Evaluation of hypercalcemia frequency with very high serum 25 (OH) Vitamin D levels" by Aslihan Calim and Canan Alkim. We commend the authors for their research on this important topic. However, we would like to present some new and original points that we believe are worth considering.

Firstly, while the study provides valuable insights into the frequency of hypercalcemia[2] in patients with high serum 25 (OH) Vitamin D levels, it would be beneficial to explore the underlying mechanisms that contribute to this phenomenon. Understanding the physiological processes involved in the regulation of calcium homeostasis in the presence of excessive Vitamin D could shed light on potential therapeutic interventions or preventive measures. Secondly, the article mentions the distribution of patients with Vitamin D intoxication by years in the hospital from 2014 to 2020. It would be interesting to investigate whether there has been a significant increase in the number of cases over time. This could be indicative of changing trends in Vitamin D supplementation practices or other factors that contribute to the observed hypercalcemia[2]. Furthermore, it would be valuable to explore the potential impact of Vitamin D supplementation guidelines on the prevalence of hypercalcemia[3]. The article does not provide information on the dosage or duration of Vitamin D supplementation in the study participants. Investigating whether there is a correlation between the dosage of Vitamin D and the occurrence of hypercalcemia[4,5] could help inform future guidelines and recommendations. It would significantly help in framing better public health policies in the region.

In addition, it would be worthwhile to consider the role of other factors that may influence the development of hypercalcemia in individuals with high serum 25 (OH) Vitamin D levels. For instance, the study does not mention the participants' dietary calcium intake or their exposure to sunlight, both of which can affect calcium metabolism[6,7]. Exploring these variables could provide a more comprehensive understanding of the relationship between Vitamin D levels and hypercalcemia. Moreover, the article primarily focuses on the frequency of hypercalcemia in patients with very high serum 25 (OH) Vitamin D levels. However, it would be interesting to investigate the potential clinical implications of this finding. Does the presence of hypercalcemia in these individuals lead to specific symptoms or complications? Understanding the clinical significance of hypercalcemia in the context of high Vitamin D levels could help guide clinical management and patient care. Lastly, the study provides demographic information about the participants, including gender, age and calcium status. However, it would be beneficial to explore whether there are any significant differences in the frequency of hypercalcemia based on these demographic factors[8]. This could help identify vulnerable populations or individuals who may be at a higher risk of developing hypercalcemia in the presence of high Vitamin D levels.

All in all, we appreciate the authors' efforts in evaluating the frequency of hypercalcemia in patients with very high serum 25 (OH) Vitamin D levels.

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However, we believe that further exploration of the underlying mechanisms, investigation of changing trends over time, consideration of Vitamin D supplementation guidelines, examination of other influencing factors, assessment of clinical implications, and analysis of demographic differences would enhance the significance and applicability of the study findings. We hope that these suggestions will be taken into account for future research in this field by medical practitioners and researchers.

REFERENCES

1. Calim A, Alkim C. Evaluation of hypercalcemia frequency with very high serum 25 (OH) Vitamin D levels. Kuwait Medical Journal 2023 [Article in Press].
2. Tebben PJ, Singh RJ, Kumar R. Vitamin D-mediated hypercalcemia: mechanisms, diagnosis, and treatment. Endocr Rev 2016; 37(5):521-47.
3. Rizzoli R. Vitamin D supplementation: upper limit for safety revisited? Aging Clin Exp Res 2021; 33(1):19-24.
4. Araki T, Holick MF, Alfonso BD, Charlap E, Romero CM, Rizk D, *et al*. Vitamin D intoxication with severe hypercalcemia due to manufacturing and labeling errors of two dietary supplements made in the United States. J Clin Endocrinol Metab 2011; 96(12):3603-8.
5. Mio K, Haruhara K, Shimizu A, Oshiro K, Kawai R, Ikeda M, *et al*. Hypercalcemia worsened after vitamin D supplementation in a sarcoidosis patient: A case report. Medicine (Baltimore) 2022; 101(40):e30883.
6. Kopiczko A. Assessment of intake of calcium and vitamin D and sun exposure in the context of osteoporosis risk in a study conducted on perimenopausal women. Prz Menopauzalny 2014; 13(2):79-83.
7. Kopiczko A. Determinants of bone health in adults Polish women: The influence of physical activity, nutrition, sun exposure and biological factors. PLoS One 2020; 15(9):e0238127.
8. Mousseaux C, Dupont A, Rafat C, Ekpe K, Ghrenassia E, Kerhuel L, *et al*. Epidemiology, clinical features, and management of severe hypercalcemia in critically ill patients. Ann Intensive Care 2019; 9(1):133.

Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2026; 58 (3): 229 - 231

Epidemiology and clinical profile of inflammatory bowel disease in Kuwait: a nationwide tertiary care (SEEF-IBD) study

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BMC Gastroenterol. 2026 Jun 29. doi: 10.1186/s12876-026-05056-1. Online ahead of print.

INTRODUCTION

The prevalence of inflammatory bowel disease (IBD) continues to rise globally, with notable shifts in its epidemiological patterns. However, data on characteristics of IBD in Kuwait remain limited. This study aimed to evaluate the demographic and clinical characteristics of IBD in Kuwait.

METHODS

We conducted a retrospective cross-sectional study across all 7 tertiary centers in Kuwait. Data was retrieved between November 2025 and December 2025. The primary objective of this study was to report the demographics patterns and phenotypes of IBD in Kuwait. Secondary outcomes were treatment patterns, history of IBD-related surgeries and extraintestinal manifestations (EIM).

RESULTS

A total of 1,944 patients with IBD were included, of whom CD was slightly more common than UC (1,002; 51.5% vs. 894; 46%). Among CD patients, ileocolonic disease (L3) was the predominant phenotype (516; 51.5%), and penetrating disease (B3) accounted for 363 (36.2%). Proportion of male, smoker and younger (< 30 years old) patients was higher in patients with penetrating disease ($p < 0.001$). In UC, left-sided disease (E2: 390; 43.6%) was the dominant phenotype. Biologics were prescribed in 846 (43.5%) patients. A history of IBD-related surgery was reported in 418 patients (21.5%). EIM were present in 719 patients (37%).

CONCLUSIONS

This study provides a comprehensive characterization of the demographic patterns of IBD in Kuwait, highlighting a higher prevalence of CD, particularly penetrating phenotypes among younger male patients. These findings reflect the evolving burden of IBD in the Middle East and reinforce the importance of timely diagnosis and ensuring access to effective, targeted therapies.

A structured point-of-care ultrasound protocol for peripheral nerve assessment in the interventional pain medicine clinic: a technical note

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J Ultrasound. 2026 Jul 24. doi: 10.1007/s40477-026-01195-z. Online ahead of print.

PURPOSE
Peripheral nerve ultrasound in the pain medicine clinic remains largely non-standardized. The purpose of this technical note is to propose a structured point-of-care ultrasound protocol for systematic peripheral nerve evaluation in the interventional pain medicine setting.

METHODS
The Peripheral Nerve Assessment Protocol (PNAP) was developed based on the existing peripheral nerve ultrasound literature, established point-of-care ultrasound models, and clinical experience in interventional pain medicine. The protocol targets 10 nerves across four anatomical regions using a four-step assessment sequence: static survey, dynamic provocation, Doppler interrogation, and contralateral comparison.

RESULTS
Sonographic diagnostic criteria and a three-tier clinical decision framework are presented to guide same-visit treatment planning. The protocol integrates diagnostic assessment with procedural decision-making within a single clinical encounter.

CONCLUSION
The PNAP provides a reproducible methodology for peripheral nerve assessment in the interventional pain medicine clinic that may serve as a foundation for future validation studies.

Healthcare providers' perceptions of fibromyalgia management in Kuwait: a descriptive comparative study

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BMC Health Serv Res. 2026 May 11. doi: 10.1186/s12913-026-14587-y. Online ahead of print.

BACKGROUND
Fibromyalgia (FM) is a complex chronic pain condition that poses diagnostic and management challenges worldwide. In Kuwait, limited awareness, cultural perceptions, and systemic barriers may affect the quality of FM care. This study examined healthcare practitioners' perceptions, diagnostic strategies, and management approaches to identify gaps in rehabilitation services.

METHODS
A descriptive comparative study was conducted among 112 healthcare practitioners from public and

private sectors. Data was collected using a survey instrument adapted from existing sources and validated within the present study to assess perceptions, diagnostic methods, treatment strategies, and barriers to FM management. Descriptive statistics and Pearson chi-square tests were used to assess associations between demographics, training, specialization, and clinical decision-making.

RESULTS

Of the participants, 35.7% reported experience treating FM. Most were rehabilitation professionals (60.7%), female (82.1%), and trained in Kuwait (81.3%). Significant differences in FM management were found based on education, specialization, and years of experience ($p < 0.05$). Practitioners demonstrated variable confidence in diagnosing and treating FM, with reliance on traditional diagnostic criteria despite international updates. Notable gaps were observed in rehabilitation services, multidisciplinary collaboration, and adherence to evidence-based guidelines.

CONCLUSION

FM care in Kuwait is limited by educational gaps, inconsistent diagnostic practices, and insufficient multidisciplinary collaboration. Strengthening continuous education, adopting updated guidelines, and enhancing coordination between physicians, rehabilitation specialists, and mental health professionals are essential. System-wide interventions could improve FM diagnosis, management, and patient outcomes. Future research should involve larger, longitudinal studies to address evolving challenges in FM care.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2026; 58 (3): 232 - 241

International Conference on **Medical & Health Science**
Ireland, Dublin
Sep 1, 2026
Organized by: Research fora
Email: info@researchfora.com

International Conference on **Medical Health Science, Pharmacology & Biotechnology**
United States, New York
Sep 1, 2026
Organized by: ISSRD
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International Conference on **Medical and Biosciences**
Berlin, Germany
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Email: info@researchworld.org

International Conference on Recent Advances in **Medical and Health Sciences**
United Arab Emirates, Abu Dhabi
Sep 2, 2026
Organized by: Academics world
Email: info@academicsworld.org

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Germany, Munich
Sep 3, 2026
Organized by: WRFER
Email: contact.wrfer@gmail.com

International Conference on **Medical and Biological Engineering**
United Kingdom, Edinburgh
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Organized by: Techno conferences
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3rd Kuwait Conference on **Pediatric Haematology & Oncology**
Kuwait, Four Seasons Hotel
Sep 4-5, 2026
Organized by: Ministry of Health
Website: https://3kcpho.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
China, Beijing
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Organized by: ISETE
Email: info.iseteconference@gmail.com

International **Cancer** Conference
United Kingdom, Reading
Sep 5, 2026
Organized by: Biofora
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International Conference on **Hygiene and Medical Ethics**
New Zealand, Napier
Sep 5, 2026
Organized by: Research Era
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International Conference on **Medical, Biological and Pharmaceutical Sciences**
Saudi Arabia, Mecca
Sep 6, 2026
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International Conference on **Medical and Biosciences**
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Sep 7, 2026
Organized by: Research world
Email: info@researchworld.org

3rd Edition of Unite Explores **Cancer** Conference
Belgium, Brussels
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Organized by: Unite Scientific Explores
Email: uniteexplores.cancer@gmail.com

International Conference on **Medical Ethics and Professionalism**
Switzerland, Bern
Sep 8, 2026
Organized by: Sciencefora
Email: info.sciencefora@gmail.com

International Conference on latest **Medical Research and Development**
Australia, Melbourne, Victoria
Sep 10, 2026
Organized by: Universal Research Cluster
Email: info.universalconference@gmail.com

International **Cancer** Conference
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International Conference on **Medical, Biological and Pharmaceutical Sciences**
Qatar, Al Wakrah
Sep 11, 2026
Organized by: iPharma conferences
Email: info.ipharmaconferences@gmail.com

International Conference on **Healthcare Innovation and Medical Sciences**
Spain, Seville
Sep 12, 2026
Organized by: Biofora
Email: papers.biofora@gmail.com

World Conference on **Bioethics, Medical Ethics and Health Law**
Netherlands, Amsterdam
Sep 13, 2026
Organized by: Science Guru
Email: info.scienceguru@gmail.com

International Conferences on Advances in **Nursing Science, Medical and Health Care**
China, Beijing
Sep 15, 2026
Organized by: Theires
Email: info@theires.org

International **Cancer** Conference
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Sep 16, 2026
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International Conference on **Medical Fitness and Corrective Exercise**
Switzerland, Geneva
Sep 17, 2026
Organized by: Academic Research Network
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International Symposium on the **Autonomic Nervous System**
Tajikistan, Dushanbe
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Organized by: Canadian Association for Scientific Research and Publication
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Organized by: Flexz conference
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World Conference on **Bioethics, Medical Ethics and Health Law**
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International Conference on **Medical and Biological Engineering**
France, Marseille
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WHO-Facts Sheet

1. Chronic Obstructive Pulmonary Disease
2. Ebola disease
3. Infertility
4. Oral health
5. Post-traumatic stress disorder

Compiled and edited by
Vineetha E Mammen

Kuwait Medical Journal 2026; 58 (3): 242 - 252

1. Chronic Obstructive Pulmonary Disease

KEY FACTS

- Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, causing 3.4 million deaths in 2023, approximately 6% of all global deaths (1).
- Nearly 90% of COPD deaths in those under 70 years of age occur in low- and middle-income countries (LMIC).
- COPD is the seventh leading cause of poor health worldwide (measured by disability-adjusted life years).
- Tobacco smoking accounts for over 70% of COPD cases in high-income countries. In LMIC tobacco smoking accounts for 30–40% of COPD cases, and household air pollution is a major risk factor.

Overview

Chronic obstructive pulmonary disease (COPD) is a common lung disease causing restricted airflow and breathing problems. It is sometimes called emphysema or chronic bronchitis. In people with COPD, the lungs can get damaged or clogged with phlegm. Symptoms include cough, sometimes with phlegm, difficulty breathing, wheezing and tiredness.

Smoking and air pollution are the most common causes of COPD. People with COPD are at higher risk of other health problems. COPD is not curable but symptoms can improve if one avoids smoking and exposure to air pollution and gets vaccines to prevent infections. It can also be treated with medicines, oxygen and pulmonary rehabilitation.

Symptoms

The most common symptoms of COPD are difficulty breathing, chronic cough (sometimes with phlegm) and feeling tired. COPD symptoms can get worse quickly. These are called flare-ups. These usually last for a few days and often require additional medicine.

People with COPD also have a higher risk for other health problems. These include:

- lung infections, like the flu or pneumonia
- lung cancer
- heart problems
- weak muscles and brittle bones
- depression and anxiety.

Common symptoms of COPD develop from mid-life onwards. As COPD progresses, people find it more difficult to carry out their normal daily activities, often due to breathlessness. There may be a considerable financial burden due to limitation of workplace and home productivity, and costs of medical treatment.

COPD is sometimes called emphysema or chronic bronchitis. Emphysema usually refers to destruction of the tiny air sacs at the end of the airways in the lungs. Chronic bronchitis refers to a chronic cough with the production of phlegm resulting from inflammation in the airways. COPD and asthma share common symptoms (cough, wheeze and difficulty breathing) and people may have both conditions.

Causes

Several processes can cause the airways to become narrow and lead to COPD. There may be destruction of parts of the lung, mucus blocking the airways, and inflammation and swelling of the airway lining.

COPD develops gradually over time, often resulting from a combination of risk factors:

- tobacco exposure from active smoking or passive exposure to second-hand smoke;
- occupational exposure to dusts, fumes or chemicals;
- indoor air pollution: biomass fuel (wood, animal

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dung, crop residue) or coal is frequently used for cooking and heating in low- and middle-income countries with high levels of smoke exposure;
- early life events such as poor growth in utero, prematurity, and frequent or severe respiratory infections in childhood that prevent maximum lung growth;
- asthma in childhood; and
- a rare genetic condition called alpha-1 antitrypsin deficiency, which can cause COPD at a young age.

COPD should be suspected if a person has typical symptoms, and the diagnosis confirmed by a breathing test called spirometry, which measures how the lungs are working. In low- and middle-income countries, spirometry is often not available and so the diagnosis may be missed.

Treatment

COPD isn't curable, but it can get better by not smoking, avoiding air pollution and getting vaccines. It can be treated with medicines, oxygen and pulmonary rehabilitation.

There are several treatments available for COPD. Inhaled medicines that open and reduce swelling in the airways are the main treatments. Bronchodilator inhalers are the most important medicines for treating COPD. They relax the airways to keep them open. Short-acting bronchodilators start to work in seconds and can last for 4–6 hours. These are often used during flare-ups. Long-acting bronchodilators take longer to start working but last longer. These are taken daily and can be combined with inhaled steroids.

Other treatments may also be used:
- Steroid pills and antibiotics are often used to treat flare-ups.
- Oxygen is used for people who have had COPD for a long time or have severe COPD.
- Pulmonary rehabilitation teaches exercises to improve your breathing and ability to exercise.
- Surgery may improve symptoms for some people with severe COPD.

Some inhalers open the airways and may be given regularly to prevent or reduce symptoms, and to relieve symptoms during acute flare-ups. Inhaled corticosteroids are sometimes given in combination with these to reduce inflammation in the lungs.

Inhalers must be taken using the correct technique, and in some cases with a spacer device to help deliver the medication into the airways more effectively. Access to inhalers is limited in many low- and middle-income countries; in 2023 salbutamol inhalers were generally available in public primary health care facilities in less than two-thirds of low- and low-middle income countries.

Flare-ups are often caused by a respiratory infection, and people may be given an antibiotic or steroid tablets in addition to inhaled or nebulised treatment as needed.

Living with COPD

Lifestyle changes can help improve symptoms of COPD. Quit smoking or vaping. This is the most important thing to do. Even if you have been smoking for many years, quitting can still help. Avoid second-hand smoke or smoke from indoor cooking fires. Stay physically active.

Protect yourself from lung infections:
- Get a flu vaccine every year.
- Get the pneumonia vaccine.
- Get all available COVID-19 vaccines and make sure you have had the latest boosters.

People living with COPD must be given information about their condition, treatment and self-care to help them to stay as active and healthy as possible.

WHO response

COPD is included in the WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases (NCDs) and the United Nations 2030 Agenda for Sustainable Development.

WHO is taking action to extend diagnosis of and treatment for COPD in a number of ways. The WHO Package of Essential Noncommunicable Disease Interventions (PEN) was developed to help improve NCD management in primary health care in low-resource settings. PEN includes protocols for the assessment, diagnosis and management of chronic respiratory diseases (asthma and chronic obstructive pulmonary disease), and modules on healthy lifestyle counselling, including tobacco cessation and self-care.

WHO is currently developing new guidelines for the diagnosis and management of COPD in primary care. Rehabilitation 2030 is a strategic approach to prioritize and strengthen rehabilitation services in health systems. Pulmonary rehabilitation for COPD is included in the Package of Interventions for Rehabilitation, developed as part of this WHO initiative.

Reducing tobacco smoke exposure is important for both primary prevention of COPD and disease management. The Framework Convention on Tobacco Control is enabling progress in this area as are WHO initiatives such as MPOWER and mTobacco Cessation. Further prevention activities include the WHO Clean Household Energy Solutions Toolkit (CHEST) to promote clean and safe interventions in the home and facilitate the design of policies that promote the adoption of clean household energy at local, programmatic and national levels.

The Global Alliance against Chronic Respiratory Diseases (GARD) contributes to WHO's work to prevent and control chronic respiratory diseases. GARD is a voluntary alliance of national and international organizations and agencies from many countries committed to the vision of a world where all people breathe freely.

REFERENCES

1 Global Burden of Disease Collaborative Network. Global Burden of Disease 2023: Findings from the GBD 2023 Study. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2025.

2. Ebola disease

KEY FACTS

- Ebola disease is a severe, often fatal illness in humans.
- Three different viruses are known to cause large Ebola disease outbreaks: Ebola virus, Sudan virus and Bundibugyo virus.
- The average Ebola disease case fatality rate is around 50%. Case fatality rates have varied from 25–90% in past outbreaks.
- Early intensive supportive care with rehydration and the treatment of symptoms improves survival.
- Approved vaccines and treatments are only available for one of the viruses (Ebola virus) and are under development for the others.
- Outbreak control relies on a package of interventions including intensive supportive care of patients, infection prevention and control, disease surveillance and contact tracing, laboratory services, safe and dignified burials, vaccination if relevant, and social mobilization.

Overview

Ebola disease (EBOD) is a rare but severe illness in humans (1). It is often fatal. Ebola disease is caused by viruses that belong to the Orthoebolavirus genus of the filoviridae family (2). Six species of Orthoebolaviruses have been identified to date, with three known to cause large outbreaks:

- Ebola virus (EBOV) causing Ebola virus disease (EVD)
- Sudan virus (SUDV) causing Sudan virus disease (SVD)
- Bundibugyo virus (BDBV) causing Bundibugyo virus disease (BVD).

Ebola disease first occurred in 1976 in two simultaneous outbreaks: one outbreak was of Sudan virus disease in Nzara in what is now South Sudan, and the other outbreak was of Ebola virus disease in Yambuku, in what is now the Democratic Republic of the Congo. The latter occurred in a village near the Ebola River, from which the disease takes its name.

While there are licensed vaccines and therapeutics for Ebola virus disease, there is no approved vaccine or treatment for other Ebola diseases, such as SVD or BVD. Candidate products are in development. Early intensive supportive care including rehydration and treatment of specific symptoms, can improve survival. Seeking early care can be lifesaving.

Transmission

It is thought that fruit bats of the Pteropodidae family are natural hosts of the Orthoebolavirus. The virus can get into the human population when people have close contact with the blood, secretions, organs or other bodily fluids of infected animals such as fruit bats, chimpanzees, gorillas, monkeys, forest antelope or porcupines found ill or dead or in the rainforest.

People can get infected with the virus from another person by direct contact (through broken skin or mucous membranes) with:

- the blood or body fluids of a person who is sick with or has died from Ebola disease; and
- objects or surfaces that have been contaminated with body fluids (like blood, feces, vomit) from a person sick with the disease or who has died from the disease.

People cannot transmit the disease before they have symptoms, and they remain infectious as long as their blood contains the virus. Health and care workers have frequently been infected while treating patients with Ebola disease. This occurs through close contact with patients when infection control precautions are not strictly practiced. Burial ceremonies that involve direct contact with the body of a person who has died can also contribute to the transmission of Ebola disease.

Symptoms

The incubation period or interval from infection to onset of symptoms varies from 2 to 21 days. The symptoms of Ebola disease can be sudden and include fever, fatigue, malaise, muscle pain, headache and sore throat. These are followed by vomiting, diarrhoea, abdominal pain rash, and symptoms of impaired kidney and liver functions. It is important for health and care workers to be on the lookout for these symptoms.

Despite a perception that bleeding is a common symptom, this is less frequent and can occur later in the disease. Some patients may develop internal and external bleeding, including blood in vomit and faeces, bleeding from the nose, gums and vagina. Bleeding at

the sites where needles have punctured the skin can also occur. The impact on the central nervous system can result in confusion, irritability and aggression.

Diagnosis

It can be difficult to clinically distinguish Ebola disease from other infectious diseases such as malaria, typhoid fever, shigellosis, meningitis and other viral haemorrhagic fevers because symptoms at early stage of the disease are similar.

Confirmation that the person has an Orthoebolavirus infection is made using the following diagnostic methods:

- reverse transcriptase polymerase chain reaction (RT-PCR) assay
- antibody-capture enzyme-linked immunosorbent assay (ELISA)
- antigen-capture detection tests
- virus isolation by cell culture.

Samples collected from patients are an extreme biohazard risk; laboratory testing on non-inactivated samples should be conducted under maximum biological containment conditions. All non-inactivated biological specimens should be packaged using the triple packaging system when transported nationally and internationally See Diagnostic testing for Ebola and Marburg diseases.

Treatment

Over the years, WHO and partners have developed guidance and training that outline how to provide the best possible care for patients and increase their chance of survival, whether or not specific treatments are being used. Called optimized supportive care, this covers the relevant tests to administer, how to manage pain, nutrition and co-infections (such as malaria), and other approaches that put the patient on the best path to recovery. For Ebola virus disease, WHO made strong recommendations for treatment with mAb114 (ansuvimabTM) or REGN-EB3 (InmazebTM) that are both monoclonal antibodies. For other Ebola diseases, such as SVD or BVD, there are no approved therapeutics, but candidate products are under development and a CORE protocol for clinical trials is available.

Vaccines

For Ebola virus disease:

- Two vaccines are approved: Ervebo (Merck & Co.) and Zabdeno and Mvabea (Janssen Pharmaceutica). Ervebo vaccine is recommended as part of outbreak response, see SAGE recommendations of July 2024.
- In case of a confirmed Ebola virus disease outbreak, Ervebo vaccines can be accessed through the International Coordinating Group on vaccine provision.
- For preventive vaccination of health and care workers, request of Ervebo vaccines can be made through Gavi Preventive Ebola vaccination.

For other Ebola diseases, such as SVD:

- Several candidate vaccines are at different stages of development.
- As part of outbreak response, a CORE protocol to evaluate the safety, tolerability, immunogenicity, and efficacy of vaccine candidates is available.

Prevention and control

Community engagement is key to successfully controlling any outbreak. Outbreak control relies on using a range of interventions, such as clinical care, surveillance and contact tracing, laboratory services, infection prevention and control in health facilities, safe and dignified burials, vaccination (only for Ebola virus disease) and social mobilization.

Raising awareness of risk factors and protective measures that individuals can take is an effective way to reduce human transmission. Risk reduction messaging should focus on several factors:

- Reduce the risk of wildlife-to-human transmission from contact with infected fruit bats or monkeys/apes and the consumption of their raw meat.
- Reduce the risk of human-to-human transmission arising from direct or close contact with infected people, particularly with their body fluids. Close physical contact with Ebola patients should be avoided. Patients should be isolated in a designated treatment centre for early care and to avoid transmission at home.
- Communities should be well informed, both about the disease itself and how to control the outbreak. This is done best when they are involved in the response and there is open discussion.
- Outbreak containment measures include safe and dignified burial of the deceased, identifying people who may have been in contact with someone infected with Ebola disease and monitoring their health for 21 days, separating the healthy from the sick to prevent further spread and providing care to confirmed patients. Maintaining good hygiene and a clean environment are also important.

Controlling infection in health-care settings

Health and care workers should always take standard precautions when caring for patients, regardless of their presumed diagnosis. These include basic hand hygiene, respiratory hygiene, use of personal protective equipment (to block splashes or other contact with infected materials), safe injection practices and safe and dignified burial practices.

Health and care workers caring for patients with suspected or confirmed Ebola disease should apply extra infection control measures to prevent contact with the patients' blood and body fluids and contaminated surfaces or materials such as clothing and bedding. Infection prevention and control guideline for Ebola and Marburg diseases.

Laboratory workers are also at risk. Samples taken from humans and animals for investigation of Orthoebolavirus infection should be handled by trained staff and processed in suitably equipped laboratories.

Care for survivors

All survivors, their partners and families should be shown respect, dignity and compassion. WHO does not recommend isolation of recovered patients whose blood has tested negative for Orthoebolavirus. Survivors might suffer from both clinical and psychological sequelae. WHO encourages affected countries to consider the establishment of care programme to alleviate sequelae, support to community reintegration, counselling and biological testing.

Orthoebolaviruses are known to persist in immune-privileged sites in some people who have recovered. These sites include the testicles, the inside of the eye and the brain. Relapse-symptomatic illness in the absence of re-infection in someone who has recovered from Ebola disease is rare but has been documented. Reasons for this phenomenon are not yet fully understood.

Ebola virus transmission via infected semen has been documented up to fifteen months after clinical recovery. To mitigate the risk of this transmission, a semen testing programme should be implemented to:

- offer counselling to male survivors and their sexual partners to inform them of the potential risk and support them adhering to safer sex practices (including condom provision and good hand and personal hygiene);
- offer monthly semen testing until they have had two consecutive negative test results; and
- after two consecutive negative tests, survivors can safely resume normal sexual practices with minimized risk of virus transmission.

In the absence of a semen testing programme, male survivors should follow safer sex practices for 12 months. Orthoebolavirus may persist in the placenta, amniotic fluid and fetus of women infected while pregnant, and in the breast milk of breastfeeding women who are infected with the virus. Survivor care programmes should encompass care for pregnant and breastfeeding women after their recovery.

WHO response

WHO works with countries to prevent Ebola outbreaks by maintaining surveillance and supporting at-risk countries to develop preparedness plans. The following document provides overall guidance for control of Ebola and Marburg virus outbreaks: Ebola and Marburg virus disease epidemics: preparedness, alert, control, and evaluation

When an outbreak is detected, WHO responds by supporting outbreak response, disease detection, community engagement, contact tracing, vaccination, vaccine and treatment trials, case management, laboratory services, infection control, logistics, and training and assistance with safe and dignified burial practices.

REFERENCES

1. International Classification of Disease, ICD-11, 2024 : International Classification of Diseases (ICD)
2. International Committee on Virus Taxonomy, ICTV : https://ictv.global/report/chapter/filoviridae/filoviridae/orthoebolavirus

3. Infertility

KEY FACTS

- Infertility affects millions of people – and has an impact on their families and communities. Estimates suggest that approximately one in every six people of reproductive age worldwide experience infertility in their lifetime.
- In the male reproductive system, infertility is most commonly caused by problems in the ejection of semen, absence or low levels of sperm, or abnormal shape (morphology) and movement (motility) of the sperm.
- In the female reproductive system, infertility may be caused by a range of abnormalities of the ovaries, uterus, fallopian tubes, and the endocrine system, among others.
- Infertility can be primary or secondary. Primary infertility is when a pregnancy has never been achieved by a person, and secondary infertility is when at least one prior pregnancy has been achieved.
- Fertility care encompasses the prevention, diagnosis and treatment of infertility. Equal and equitable access to fertility care remains a challenge in most countries; particularly in low and middle-income countries. Fertility care is rarely prioritized in national universal health coverage benefit packages.

Overview

Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. Infertility may occur due to male, female or unexplained factors. Some causes of infertility are preventable. Treatment of infertility often involves in-vitro fertilization (IVF) and other types of medically assisted reproduction.

What causes infertility?

Infertility may be caused by a number of different factors, in either the male or female reproductive systems. However, it is sometimes not possible to explain the causes of infertility.

In the female reproductive system, infertility may be caused by:

- tubal disorders such as blocked fallopian tubes, which are in turn caused by untreated sexually transmitted infections (STIs) or complications of unsafe abortion, postpartum sepsis or abdominal/ pelvic surgery;
- uterine disorders which could be inflammatory in nature (such as such endometriosis), congenital in nature (such as septate uterus), or benign in nature (such as fibroids);
- disorders of the ovaries, such as polycystic ovarian syndrome and other follicular disorders;
- disorders of the endocrine system causing imbalances of reproductive hormones. The endocrine system includes hypothalamus and the pituitary glands. Examples of common disorders affecting this system include pituitary cancers and hypopituitarism.

The relative importance of these causes of female infertility may differ from country to country, for example due to differences in the background prevalence of STIs, or differing ages of populations studied.

In the male reproductive system, infertility may be caused by:

- obstruction of the reproductive tract causing dysfunctionalities in the ejection of semen. This blockage can occur in the tubes that carry semen (such as ejaculatory ducts and seminal vesicles). Blockages are commonly due to injuries or infections of the genital tract;
- hormonal disorders leading to abnormalities in hormones produced by the pituitary gland, hypothalamus and testicles – hormones such as testosterone regulate sperm production. Example of disorders that result in hormonal imbalance include pituitary or testicular cancers;
- testicular failure to produce sperm, for example due to varicoceles or medical treatments that impair sperm-producing cells (such as chemotherapy); and
- abnormal sperm function and quality. Conditions or situations that cause abnormal shape (morphology) and movement (motility) of the sperm negatively affect fertility. For example, the use of anabolic steroids can cause abnormal semen parameters such sperm count and shape (1).

Lifestyle factors such as smoking, excessive alcohol intake and obesity can affect fertility. In addition, exposure to environmental pollutants and toxins can be directly toxic to gametes (eggs and sperm), resulting in their decreased numbers and poor quality (1,2).

Why addressing infertility is important?

Every human being has a right to the enjoyment of the highest attainable standard of physical and mental health. Individuals and couples have the right to decide the number, timing and spacing of their children. Infertility can negate the realization of these essential human rights (3).

A wide variety of people, including heterosexual couples, same-sex partners, older persons, individuals who are not in sexual relationships and those with certain medical conditions, such as some HIV sero-discordant couples and cancer survivors, may require infertility management and fertility care services. Inequities and disparities in access to fertility care services adversely affect the poor, unmarried, uneducated, unemployed and other marginalized populations.

Addressing infertility can also mitigate gender inequality. Although both women and men can experience infertility, women in a relationship with a man are often perceived to suffer from infertility, regardless of whether they are infertile or not. Infertility has significant negative social impacts on the lives of infertile couples and particularly women, who frequently experience violence, divorce, social stigma, emotional stress, depression, anxiety and low self-esteem.

In some settings, fear of infertility can deter women and men from using contraception if they feel socially pressured to prove their fertility at an early age because of a high social value of childbearing. In such situations, education and awareness-raising interventions to address understanding of the prevalence and determinants of fertility and infertility is essential.

Addressing challenges

Availability, access, and quality of interventions to address infertility remain a challenge in most countries. Diagnosis and treatment of infertility is often not prioritized in national population and

development policies and reproductive health strategies and are rarely covered through public health financing. Moreover, a lack of trained personnel and the necessary equipment and infrastructure, and the currently high costs of treatment medicines, are major barriers even for countries that are actively addressing the needs of people with infertility. While assisted reproduction technologies (ART) have been available for more than three decades, with millions of children born worldwide from ART interventions such as in vitro fertilization (IVF), these technologies are still largely unavailable, inaccessible and unaffordable in many parts of the world, particularly in low and middle-income countries (LMIC).

Government policies could mitigate the many inequities in access to safe and effective fertility care. To effectively address infertility, health policies need to recognize that infertility is a disease that can often be prevented, thereby mitigating the need for costly and poorly accessible treatments. Incorporating fertility awareness in national comprehensive sexuality education programmes, promoting healthy lifestyles to reduce behavioural risks, including prevention, diagnosis and early treatment of STIs, preventing complications of unsafe abortion, postpartum sepsis and abdominal/pelvic surgery, and addressing environmental toxins associated with infertility, are policy and programmatic interventions that all governments can implement.

In addition, enabling laws and policies that regulate third party reproduction and ART are essential to ensure universal access without discrimination and to protect and promote the human rights of all parties involved. Once fertility policies are in place, it is essential to ensure that their implementation is monitored, and the quality of services is continually improved.

WHO response

WHO recognizes that the provision of high-quality services for family-planning, including fertility care services, is one of the core elements of reproductive health. Recognizing the importance and impact of infertility on people's quality of life and well-being, WHO is committed to addressing infertility and fertility care by:

- collaborating with partners to conduct global epidemiological and etiological research into infertility;
- engaging and facilitating policy dialogue with countries worldwide to frame infertility within an enabling legal and policy environment;
- supporting the generation of data on the burden of infertility to inform resource allocation and provision of services;
- developing guidelines on the prevention, diagnosis and treatment of male and female infertility, as part of the global norms and standards of quality care related to fertility care;
- continually revising and updating other normative products, including the WHO laboratory manual for the examination and processing of human semen;
- collaborating with relevant stakeholders including academic centres, ministries of health, other UN organizations, non-state actors (NSAs) and other partners to strengthen political commitment, availability and health system capacity to deliver fertility care globally; and
- providing country-level technical support to member states to develop or strengthen implementation of national fertility policies and services.

REFERENCES

1. Gore AC, Chappell VA, Fenton SE, et al. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocrine Reviews 2015;36(6):E1-E150. doi: 10.1210/er.2015-1010
2. Segal TR, Giudice LC. Before the beginning: environmental exposures and reproductive and obstetrical outcomes. Fertility and Sterility 2019;112(4):613-21.
3. Zegers-Hochschild F, Dickens BM, Dughman-Manzur S. Human rights to in vitro fertilization. International Journal of Gynecology & Obstetrics 2013;123(1):86-89.

4.Oral health

KEY FACTS

- Oral diseases, while largely preventable, pose a major health burden for many countries and affect people throughout their lifetime, causing pain, discomfort, disfigurement and even death.
- It is estimated that oral diseases affect nearly 3.7 billion people.
- Untreated dental caries (tooth decay) in permanent teeth is the most common health condition according to the Global Burden of Disease 2021.
- Prevention and treatment for oral health conditions is expensive and usually not part of national universal health coverage (UHC) benefit packages.
- Most low- and middle-income countries do not have sufficient services available to prevent and treat oral health conditions.
- Oral diseases are caused by a range of modifiable risk factors common to many noncommunicable diseases (NCDs), including sugar consumption, tobacco use, alcohol use and poor hygiene, and their underlying social and commercial determinants.

Overview

Most oral health conditions are largely preventable and can be treated in their early stages. Most cases are dental caries (tooth decay), periodontal diseases, tooth loss and oral cancers. Other oral conditions of public health importance are orofacial clefts, noma (severe gangrenous disease starting in the mouth mostly affecting children) and oro-dental trauma.

Prevalence of the main oral diseases continues to increase globally with growing urbanization and changes in living conditions. This is primarily due to inadequate exposure to fluoride (in the water supply and oral hygiene products such as toothpaste), availability and affordability of food with high sugar content and poor access to oral health care services in the community. Marketing of food and beverages high in sugar, as well as tobacco and alcohol, have led to a growing consumption of products that contribute to oral health conditions and other NCDs.

Dental caries (tooth decay)

Dental caries results when plaque forms on the surface of a tooth and converts the free sugars (all sugars added to foods by the manufacturer, cook or consumer, plus sugars naturally present in honey, syrups and fruit juices) contained in foods and drinks into acids that destroy the tooth over time. A continued high intake of free sugars, inadequate exposure to fluoride and a lack of removal of plaque by toothbrushing can lead to caries, pain and sometimes tooth loss and infection.

Periodontal (gum) disease

Periodontal disease affects the tissues that both surround and support the teeth. The disease is characterized by bleeding or swollen gums (gingivitis), pain and sometimes bad breath. In its more severe form, the gum can come away from the tooth and supporting bone, causing teeth to become loose and sometimes fall out. Severe periodontal diseases are estimated to affect more than 1 billion cases worldwide. The main risk factors for periodontal disease are poor oral hygiene and tobacco use.

Edentulism (total tooth loss)

Losing teeth is generally the end point of a lifelong history of oral disease, mainly advanced dental caries and severe periodontal disease, but can also be due to trauma and other causes. The estimated global average prevalence of complete tooth loss is almost 7% among people aged 20 years or older. For people aged 60 years or older, a much higher global prevalence of 23% has been estimated. Losing teeth can be psychologically traumatic, socially damaging and functionally limiting.

Oral cancer

Oral cancer includes cancers of the lip, other parts of the mouth and the oropharynx and combined rank as the 13th most common cancer worldwide. The global incidence of cancers of the lip and oral cavity is estimated to be 389 846 new cases and 188 438 deaths in 2022 (1). Oral cancer is more common in men and in older people, more deadly in men compared to women and it varies strongly by socio-economic circumstances.

Tobacco, alcohol and areca nut (betel quid) use are among the leading causes of oral cancer. In North America and Europe, human papillomavirus infections are responsible for a growing percentage of oral cancers among young people.

Oro-dental trauma

Oro-dental trauma results from injury to the teeth, mouth and oral cavity. Latest estimates show that 1 billion people are affected, with a prevalence of around 20% for children up to 12 years old. Oro-dental trauma can be caused by oral factors such as lack of alignment of teeth and environmental factors (such as unsafe playgrounds, risk-taking behaviour, road accidents and violence). Treatment is costly and lengthy and sometimes can even lead to tooth loss, resulting in complications for facial and psychological development and quality of life.

Noma

Noma is a severe gangrenous disease of the mouth and the face. It mostly affects children aged 2–6 years suffering from malnutrition, affected by infectious disease, living in extreme poverty with poor oral hygiene or with weakened immune systems.

Noma is mostly found in sub-Saharan Africa, although cases have also been reported in Latin America and Asia. Noma starts as a soft tissue lesion (a sore) of the gums. It then develops into an acute necrotizing gingivitis that progresses rapidly, destroying the soft tissues and further progressing to involve the hard tissues and skin of the face.

According to latest estimates (from 1998) there are 140 000 new cases of noma annually. Without treatment, noma is fatal in 90% of cases. Survivors suffer from severe facial disfigurement, have difficulty speaking and eating, endure social stigma, and require complex surgery and rehabilitation. Where noma is detected at an early stage, its progression can be rapidly halted through basic hygiene, antibiotics and improved nutrition.

Cleft lip and palate

Orofacial clefts, the most common of craniofacial birth defects, have a global prevalence of between 1

in 1000–1500 births, with wide variation in different studies and populations (2). Genetic predisposition is a major cause. However, poor maternal nutrition, tobacco consumption, alcohol and obesity during pregnancy also play a role. In low-income settings, there is a high mortality rate in the neonatal period. If lip and palate clefts are properly treated by surgery, complete rehabilitation is possible.

Risk factors

Most oral diseases and conditions share modifiable risk factors such as tobacco use, alcohol consumption and an unhealthy diet high in free sugars that are common to other NCDs including cardiovascular disease, cancer, chronic respiratory disease and diabetes.

In addition, diabetes has been linked in a reciprocal way with the development and progression of periodontal disease. There is also a causal link between the high consumption of sugar and diabetes, obesity and dental caries.

Oral health inequalities

Oral diseases disproportionately affect the poor and socially disadvantaged members of society. There is a very strong and consistent association between socioeconomic status (income, occupation and educational level) and the prevalence and severity of oral diseases. This association exists from early childhood to older age and across populations in high-, middle- and low-income countries.

Prevention

The burden of oral diseases and other noncommunicable diseases can be reduced through public health interventions by addressing common risk factors. These include:

- promoting a well-balanced diet low in free sugars and high in fruit and vegetables, and favouring water as the main drink;
- stopping use of all forms of tobacco, including chewing of areca nuts;
- reducing alcohol consumption; and
- encouraging use of protective equipment when doing sports and travelling on bicycles and motorcycles (to reduce the risk of facial injuries).

Adequate exposure to fluoride is an essential factor in the prevention of dental caries. Twice-daily tooth brushing with fluoride-containing toothpaste (1000 to 1500 ppm) should be encouraged.

Access to oral health services

Unequal distribution of oral health professionals and a lack of appropriate health facilities to meet population needs in most countries means that access to primary oral health services is often low. Out-of-pocket costs for oral health care can be major barriers to accessing care. Paying for necessary oral health care is among the leading reasons for catastrophic health expenditures, resulting in an increased risk of impoverishment and economic hardship.

WHO response

The World Health Assembly approved a Resolution on oral health in 2021 at the Seventy-fourth World Health Assembly. The Resolution recommends a shift from the traditional curative approach towards a preventive approach that includes promotion of oral health within the family, schools and workplaces, and includes timely, comprehensive and inclusive care within the primary health-care system. The Resolution affirms that oral health should be firmly embedded within the NCD agenda and that oral health-care interventions should be included in national universal health coverage benefit packages.

In response to the mandate outlined in the resolution, the Secretariat developed the Global strategy on oral health, adopted in May 2022 (decision WHA75.11), and included the Global oral health action plan 2023–2030 (GOHAP) in the report on NCDs, noted by the Seventy-sixth World Health Assembly in 2023 (WHA76.9). The GOHAP includes a range of actions for Member States, the WHO Secretariat, international partners, civil society organizations and the private sector.

In 2024, as an outcome of the first ever WHO Global Oral Health Meeting that took place 26–29 November in Bangkok, Thailand, the Bangkok Declaration – No Health Without Oral Health was adopted. This Declaration advocates for elevating oral diseases as a global public health priority. The Bangkok Declaration reiterates Member States' commitment to the landmark 2021 resolution on oral health, which advances the prevention and control of oral diseases as part of the NCD, UHC and environmental agendas. It emphasizes the need to strengthen health systems through primary health care approaches, ensuring that environmental sustainability and climate resilience are central components.

REFERENCES

1. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today
2. Salari N, Darvishi N, Heydari M, Bokaee S, Darvishi F, Mohammadi M. Global prevalence of cleft palate, cleft lip and cleft palate and lip: A comprehensive systematic review and meta-analysis. J Stomatol Oral Maxillofac

Surg. 2021;S2468-7855(21)00118X. doi:10.1016/j.jormas.2021.05.008.

5. Post-traumatic stress disorder

KEY FACTS

- An estimated 3.9% of the world population has had post-traumatic stress disorder (PTSD) at some stage in their lives.
- Most people exposed to potentially traumatic events do not develop PTSD.
- Feeling supported by family, friends or other people following the potentially traumatic event can reduce the risk of developing PTSD.
- More women are affected by PTSD than men.
- There are effective treatments for PTSD.

Overview

Many people feel extreme fear during or after witnessing or experiencing potentially traumatic events, such as war, accidents, natural disasters or sexual violence. Most people exposed to such events will experience distress but will recover naturally with time. Some people continue to experience a range of mental health conditions that can persist for months or even years, including PTSD, depressive disorders, anxiety disorders and substance use disorders.

Around 70% of people globally will experience a potentially traumatic event during their lifetime (1), But only a minority (5.6%) will go on to develop PTSD (2). An estimated 3.9% of the world population has experienced PTSD at some point in their lives (2). The likelihood of developing PTSD varies depending on the type of traumatic event experienced. For example, rates of PTSD are more than three times (15.3%) higher among people exposed to violent conflict or war (3). PTSD rates are especially high following sexual violence (1).

Up to 40% of people with PTSD recover within one year (1). There are many effective treatments for PTSD, yet only 1 in 4 people with PTSD in low- and middle-income countries (LMICs) report seeking any form of treatment (2). Barriers to care include lack of awareness that PTSD can be treated, lack of availability of mental health services, social stigma and lack of trained mental health care providers.

Symptoms and patterns

Experiencing distress or other mental health difficulties after a potentially traumatic event is common but does not mean someone is experiencing PTSD. Someone experiences PTSD when they have symptoms re-experiencing the event, avoid reminders of the event and experience symptoms of heightened arousal that cause significant distress, and interfere with daily activities and family, social, school or working life.

Re-experiencing symptoms

People with PTSD have repeated and unwanted recollections of the traumatic event(s), which make them feel as if the event(s) is happening all over again. These memories are accompanied by intense fear or horror. They may be experienced as images, sounds (e.g. gunfire), smells (e.g. the odour of an assailant) or other sensations. These recollections might occur through intrusive memories, nightmares, or, in severe cases, flashbacks. During flashbacks, the person might momentarily believe and act as if they were back at the time of the event, experiencing it again.

Avoidance symptoms

People with PTSD avoid situations, activities, thoughts or memories that remind them of the traumatic event(s). They may even avoid talking about the event(s) with their family or health care providers. People usually use these strategies to try to avoid distressing recollections. Yet avoidance strategies may inadvertently intensify re-experiencing symptoms over time and thus perpetuate the presence of PTSD.

Hyperarousal symptoms

People with PTSD may experience a heightened sense of danger, even when they are not actually at risk. This can involve them being much more vigilant than usual, for example constantly scanning their surroundings for potential threats or feeling the need to sit with their back against a wall in public places. They may be more easily startled or jumpy, reacting with excessive fear to sudden movements or loud noises.

Symptoms of PTSD typically begin immediately after or within one month of a traumatic event. In younger children, symptoms are often behavioural and can include re-enacting the traumatic event during play or in drawings. Children often unjustly blame themselves for what happened. The experience of PTSD can also vary across cultures. For instance, in some cultures, it may be more acceptable to express anger about the event, making this a more prominent experience. In other cultures, people with PTSD may more commonly have physical complaints with unclear causes, such as headaches or gastrointestinal symptoms.

People with PTSD may also have depressive disorder, anxiety disorders and substance use disorders as well as suicidal thoughts and behaviours. Many of the effects of PTSD (such as physical tension or harmful use of alcohol) are also known risk factors for physical diseases such as cardiovascular disease.

Contributing factors

PTSD, like other mental health conditions, results from interacting social, psychological and biological factors. Anyone can experience PTSD after a potentially traumatic event, but people who have previously experienced traumatic events are more susceptible. Women are more likely to experience PTSD than men. Other factors, including a family history of mental health conditions, younger age, and lower levels of education, can also increase the likelihood of developing PTSD after a potentially traumatic experience.

The nature of the event experienced can also affect the chances of developing PTSD. For example, experiencing ongoing or repeated potentially traumatic events, developing a serious physical injury during the event(s), or witnessing harm to others can all increase risk. Receiving social support following potentially traumatic events can reduce the risk for PTSD.

Treatment

There are many effective treatments for people with PTSD. Evidence-based psychological interventions are the first choice treatments and can be delivered to individuals or groups, in person or online. Some may also be accessed through self-help manuals, websites and apps. Psychological interventions can help people learn new ways of thinking and coping that may reduce their symptoms. They can help people manage difficult situations and address the events, people or places that trigger their traumatic memories.

The psychological interventions with the most evidence for effective treatment of PTSD are those based on cognitive behavioural therapy with a trauma focus and eye movement desensitization and reprocessing (EMDR). Many of these involve exposure techniques, in which the person is asked to recall, narrate or imagine the traumatic event(s) so that they are exposed to their memories within a safe and supportive environment. Psychological interventions for PTSD may also include real or imagined exposure to triggers that may evoke traumatic memories.

Self-care

Self-care can have an important role in supporting treatment for PTSD. To help manage symptoms and promote overall well-being, a person can:

- continue normal daily routines as far as possible;
- connect with and talk to trusted people about what happened but only when the person feels ready to do so;
- avoid or cut down on alcohol and illicit drugs that can make symptoms worse;
- exercise regularly, even if it's just a short walk;
- maintain or develop healthy sleeping habits; and
- learn stress management, which may include breathing techniques and progressive muscle relaxation.

WHO response

WHO's Comprehensive mental health action plan 2013–2030 highlights the actions required to provide appropriate interventions for people with mental health conditions, including people exposed to potentially traumatic events and experiencing PTSD.

PTSD is included in the priority conditions covered by WHO's mhGAP Programme, which includes guidelines for managing PTSD. This programme aims to help countries increase services for people with mental, neurological and substance use disorders in non-specialized settings in LMICs and is being implemented in more than 100 countries.

WHO responds to the mental health needs of people exposed to conflict and natural disasters in a range of countries and, with the United Nations High Commissioner for Refugees, has published an mhGAP Humanitarian Intervention Guide, which includes a module on managing PTSD in non-specialized health care settings during emergencies.

REFERENCES

1. Kessler RC, Aguilar-Gaxiola S, Alonso J, Benjet C, Bromet EJ, Cardoso G, et al. Trauma and PTSD in the WHO world mental health surveys. Eur J Psychotraumatol. 2017;8(sup5):1353383. doi:10.1080/20008198.2017.1353383.
2. Koenen KC, Ratanatharathorn A, Ng L, McLaughlin KA, Bromet EJ, Stein DJ, et al. Posttraumatic stress disorder in the World Mental Health Surveys. Psychol Med. 2017 Oct;47(13):2260–74. doi:10.1017/S0033291717000708.
3. Charlson F, van Ommeren M, Flaxman A, Cornett J, Whiteford H, Saxena S. New WHO prevalence estimates of mental disorders in conflict settings: a systematic review and meta-analysis. Lancet. 2019. 394(10194):240–248. doi:10.1016/S0140-6736(19)30934-1.