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## LITERATURE REVIEW

# Is Lipohypertrophy Merely a Cosmetic Defect? The Impact of Lipohypertrophy on Treatment and Lives of Patients with Diabetes — A Literature Review

*a literature review*

## HIGHLIGHTS

- ▶ Lipohypertrophy (LH) is a common, often-overlooked complication of insulin therapy with consequences far beyond cosmetics.
- ▶ Injection at LH sites reduces insulin absorption and increases glycemic variability, worsening HbA1c.

- ▶ LH is associated with recurrent hypoglycemia, diabetic ketoacidosis, and impaired CGM / insulin-pump accuracy.
- ▶ Psychological burden — diabetic distress and depression — is higher in patients with extensive LH.
- ▶ Site rotation, single-use shorter needles, structured education, and skin inspection are key preventive strategies.

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## ABSTRACT

**BACKGROUND:** Lipohypertrophy (LH) is a common complication of diabetes, regardless of its type, in which tissue exposed to insulin leads to hypertrophy of adipocytes and fibrosis. Despite appearing as only a visual problem, it has many negative consequences that pose a threat to patients' health, lives, and quality of life.

**AIM:** In this article we present the multiple dimensions affected by this complication, as well as the potential benefits associated with the treatment of LH.

**METHODS:** A narrative review was conducted using the medical databases PubMed, Google Scholar, and ScienceDirect, with a focus on the impact of insulin-induced LH on the health and daily functioning of patients with diabetes.

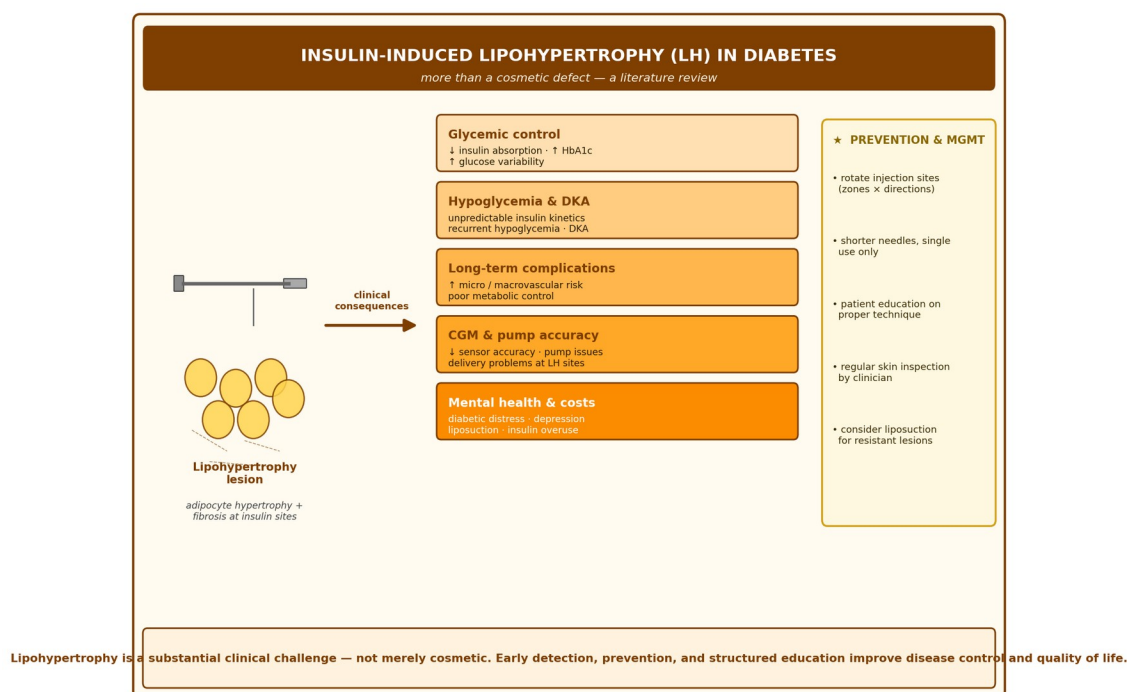
**RESULTS:** The following aspects were analyzed: the impact of LH on glycemic control, risks associated with glycemic variability, long-term complications, quality of life, effects on the management of

comorbidities, mental health, and treatment-related costs. Each of these domains was found to be significantly impaired or complicated by the presence of LH. Furthermore, improvements in patient health outcomes were observed in cases where regression of LH lesions was achieved.

**CONCLUSION:** The entirety of the reviewed literature indicates that LH constitutes a substantial clinical challenge. Early detection, prevention, and effective management are essential for improving disease control and enhancing the quality of life for patients with diabetes.

**KEYWORDS** Diabetes; complications of diabetes; lipodystrophy; glycemic control; diabetic distress; hypoglycemia

## GRAPHICAL ABSTRACT



**Figure 1.** Schematic overview of insulin-induced lipohypertrophy — pathology (adipocyte hypertrophy and fibrosis at injection sites), main clinical consequences (glycemic control, hypoglycemia/DKA, long-term complications, CGM/pump accuracy, mental health and costs), and the key preventive and management strategies.

## PLAIN LANGUAGE SUMMARY

Lipohypertrophy (LH) is a thickened, rubbery lump under the skin that often develops in people with diabetes when they inject insulin repeatedly into the same place. Although these lumps can look like only a cosmetic issue, this review shows they have important medical consequences. Injecting into an LH lump means insulin is absorbed unpredictably, so blood-sugar control becomes harder — patients may experience unexpected highs, low blood sugar (hypoglycemia), and even life-threatening diabetic ketoacidosis. LH can also reduce the accuracy of continuous glucose monitors and insulin pumps. People with extensive LH are more likely to experience diabetic distress and depression, and their treatment is more expensive due to higher insulin use and additional medical care. The good news is that LH can largely be prevented: by rotating injection sites carefully, using shorter single-use needles, learning the proper injection technique, and having the skin checked regularly by a nurse or doctor.



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## 1. INTRODUCTION

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Diabetes mellitus is a disease affecting an increasing number of individuals each year, which consequently leads to a growing prevalence of its associated complications. One of the most common cutaneous complications of insulin therapy is lipohypertrophy (LH), the pathogenesis of which is still not clearly understood. It is believed to be influenced by inflammatory processes as well as the anabolic effects of insulin, which promote adipocyte hypertrophy and fibrosis in areas exposed to this medicine. This results in the formation of nodules and localized overgrowth of adipose tissue, often plain to see.

In many cases, the aesthetic aspect constitutes the primary motivation for patients to seek treatment for LH. In a study investigating the use of liposuction as a treatment modality for LH (Mangan et al., 2023), cosmetic concerns were reported as the reason for intervention by 100% of patients undergoing the procedure. Health-related considerations were cited less frequently, highlighting the extent to which LH may contribute to body image concerns, potentially leading patients to opt for unnecessary surgical interventions.

However, the question remains: is LH merely a visual problem? Existing review articles on this topic most commonly focus on its impact on glycemic control. Nevertheless, the available literature also includes studies addressing a wider spectrum of issues associated with LH. The present article aims to review the current literature on the impact of this complication. We wanted to show various aspects of LH in patients' lives, as well as to demonstrate how reducing the occurrence of LH may improve patient outcomes and overall quality of life.

## 2. METHODS

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### 2.1 Materials and Methods

Based on the available literature from the medical databases PubMed, Google Scholar, and ScienceDirect, using keywords such as “lipohypertrophy and diabetes”, “lipohypertrophy and effect,” and “lipohypertrophy and glycemic variability,” a total of 20 studies were selected based on their abstracts. These studies provided data on various aspects of the impact LH has on the lives of patients with diabetes and were subsequently included in the analysis. The review focused primarily on the main subject of the study; therefore, articles addressing the diagnosis and treatment of lipohypertrophy were excluded.

### 2.2 AI

In this article ChatGPT (OpenAI) was used to assist with the translation and linguistic editing of the text. The final version was reviewed and revised by the authors.

## 3. RESULTS AND DISCUSSION

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### 3.1 Impact of LH on Disease Control

The most well-established impact of LH on the lives of patients with diabetes mellitus is its interference with glycemic control and the reduced efficacy of insulin therapy. Numerous studies have documented the effect of LH on insulin absorption and distribution. This phenomenon has been recognized for decades, dating back to the era when porcine insulins were still in use. The introduction of recombinant human and analog insulins raised hopes for improvement; however, while these formulations have reduced the incidence, they have not eliminated the development of LH.

A 2024 meta-analysis (Mader et al., 2024) synthesizing findings from 37 studies examining the impact of LH on disease control demonstrated that insulin administration into LH-affected areas results in less

predictable and slower absorption, often necessitating higher insulin doses to achieve the same therapeutic effect as injections into unaffected tissue. Patients with LH were also shown to exhibit higher glycemic variability, increased frequency of hypoglycemic events, including unexpected hypoglycemia, and higher mean glycated hemoglobin (HbA1c) levels. Such instability in glycemic control and frequent deviations from target glucose ranges may accelerate the development of diabetes-related complications and significantly impair quality of life.

A study conducted in China (Ji et al., 2017) illustrates the importance of this issue. Data from this study indicate that patients with LH had HbA1c levels approximately 0.5% higher while requiring up to an additional 1/3 more insulin IU/kg/day compared to individuals without this complication. This represents a substantial increase in insulin consumption with relatively limited therapeutic benefit. Moreover, the escalation of insulin doses driven by LH may further intensify the progression of this complication, creating a self-perpetuating issue that should be actively addressed in clinical practice.

In another study (Gupta et al., 2018), the effects of insulin administration into LH-affected versus unaffected tissue were supported by data from continuous glucose monitoring (CGM) systems. When patients administered insulin into the affected tissue over a 7-day period, the mean glucose level was  $224.8 \pm 76.19$  mg/dL, with a coefficient of variation of 33.9%. After switching the injection site to unaffected tissue for the subsequent 7 days, these parameters improved to  $165.40 \pm 49.56$  mg/dL and 29.96%, respectively. These findings highlight the substantial intra-individual differences that can result solely from changing the injection site and underscore the importance of preventing insulin administration into pathologically altered tissue in order to optimize treatment outcomes.

### 3.2 More Frequent Episodes of Hypoglycemia

The study by Strollo et al. (Strollo et al., 2016) focused on the impact of LH on hypoglycemia. The authors demonstrated a strong association between LH and unexplained hypoglycemic episodes as well as glycemic variability. As many as 74.2% of patients with LH experienced glucose fluctuations or hypoglycemia, compared to only 1.8% in the group without this complication. The risk of hypoglycemia increased up to 4.38 times more when LH coexisted with factors such as low socioeconomic status, social isolation, poor metabolic control, diabetes-related complications, or improper injection technique. In their conclusions, the authors suggest that all patients presenting with unexplained hypoglycemia should be gently examined for the presence of LH, as it may represent an underrecognized and sometimes difficult to detect cause. Additionally, the study demonstrated a significantly increased correlation between LH and the occurrence of diabetes-related complications, including diabetic retinopathy, nephropathy, peripheral arterial disease, sensory-motor and autonomic neuropathy.

The study by Boon and Saeed (Boon and Saeed, 2015) provides a broader perspective on the clinical consequences of hypoglycemia. It describes a case of a patient experiencing frequent and severe hypoglycemic episodes, most likely caused by repeated insulin administration solely into the skin of the abdomen over many years without proper rotation of injection sites. This led to the development of a large area of LH. During one hypoglycemic episode, the patient fell and sustained a head injury. Following the incident, he presented with left-sided hemiparesis and a reduced score on the Glasgow Coma Scale. A CT scan of the head revealed a right-sided subdural hematoma with mass effect, necessitating urgent neurosurgical intervention to save the patient's life. This highlights the critical importance of preventing hypoglycemia, as each episode carries a risk of serious injury or life-threatening consequences. Impaired concentration, visual disturbances, motor incoordination, and loss of consciousness during hypoglycemia can all contribute to dangerous accidents and trauma.

A study conducted by an Italian research group (Grassi et al., 2014) demonstrated the beneficial impact of patient education and the reduction of lipodystrophic lesions in individuals with diabetes mellitus. Over a relatively short follow-up period of just three months, the study reported a mean decrease in HbA1c of 0.58%, a reduction in fasting glucose levels by an average of 14 mg/dL, and a decrease in daily insulin requirements by 2.0 IU. Additionally, patients reported improvements in their injection technique, as well as increased awareness and motivation to adhere to proper insulin administration practices. These findings emphasize the critical importance of patient education and show how relatively simple interventions can lead to rapid and meaningful improvements in glycemic control.

### 3.3 Problems Caused by LH Across Different Age Groups

The impact of LH on treatment outcomes has been confirmed across various patient populations, each with individual clinical challenges; however, all groups consistently demonstrate that the presence of LH is associated with poorer disease control. In a study conducted at the University Hospital of Messina involving children with type 1 diabetes mellitus (Lombardo et al., 2022), LH was associated with a higher standard deviation of blood glucose levels and increased glycemic variability, as reflected by a higher coefficient of variation. Notably, the effect of LH on glycemic variability was more pronounced in younger patients. The authors suggest that this may be caused by the smaller body surface area in children, which limits the availability of injection sites and reduces the ability to adequately rotate them, thereby increasing the likelihood of repeated injections into the same or nearby areas. This represents an important issue, as the early development of LH in pediatric patients may lead to long-term adverse consequences that can persist throughout their lives.

In a study conducted across eight Italian diabetes clinics (Gentile et al., 2021), the impact of LH on glycemic management in patients with type 2 diabetes mellitus was evaluated by comparing groups below and above 65 years of age. In older individuals, glycemic control is frequently complicated by comorbidities such as chronic kidney disease, neoplasms, and use of medications that influence blood glucose levels. Age-related skin changes, including reduced elasticity and thinning, are also observed. These factors affect both glycemic control and increase susceptibility to cutaneous complications of diabetes. This may explain the higher prevalence of LH observed in the older group compared to younger participants in the study. Furthermore, the association between LH and more frequent episodes of hypoglycemia (both severe and non-severe), increased glycemic variability, and higher HbA1c levels was found to be more pronounced in older individuals than in younger patients. In this population, LH was also correlated with a higher incidence of cardiovascular complications and end-stage renal disease requiring dialysis. Hypoglycemia, increased glycemic variability, and elevated HbA1c are all factors that may promote the development of diabetes-related complications and pose a significant risk to life, particularly in older adults.

### 3.4 Contributing to the Development of Chronic Diseases

The relationship between LH and treatment-related challenges has also been investigated in patients requiring dialysis in a multicenter Italian study (Gentile et al., 2019). Dialysis in patients with diabetes significantly complicates glycemic management. This difficulty is associated with increased glycemic variability and a higher frequency of hypoglycemic episodes due to alterations in insulin clearance in individuals with end-stage renal disease. The study demonstrated that, in addition to the previously described challenges affecting all dialysis patients, those with LH, when compared to those without, exhibited higher HbA1c levels, greater glycemic variability, and more frequent hypoglycemic events. These findings underscore the importance of implementing effective preventive strategies against LH in patients undergoing dialysis, as its presence may accelerate the progression of complications and further deteriorate quality of life in a population whose overall well-being is already significantly compromised.

In another study (Kirac et al., 2023), LH was identified as an independent risk factor for increased cardiovascular risk and the development of atherosclerosis. The authors suggest several potential mechanisms underlying this association. LH negatively affects diabetes control and glycemic stability, which in itself may elevate cardiovascular risk in patients. However, the authors emphasize that LH remained an independent factor, and a possible explanation lies in the role of inflammation within the altered tissue, which shares common pathogenic pathways with cardiovascular diseases. Moreover, LH promotes the need for higher insulin doses due to impaired absorption, which may increasingly stimulate the mitogen-activated protein kinase (MAPK) signaling pathway regulated by extracellular signals, thereby contributing to the development and progression of atherosclerosis.

In a multicenter study conducted between 2016 and 2020 (Gentile et al., 2021), the impact of health education regarding proper insulin administration techniques was evaluated. Additionally, during follow-up visits, patients were educated about the harmful effects of smoking and the importance of managing coexisting cardiovascular conditions. At baseline, the group with LH presented significantly worse metabolic parameters; however, with appropriate education, these parameters improved substantially and became comparable to those observed in patients without LH. Improvements were noted in parameters of glycemic control, including a significant reduction in the frequency of hypoglycemic episodes and glycemic variability. Furthermore, patient adherence to antihypertensive, lipid-lowering, and aspirin therapies improved, which was associated with lower mean arterial blood pressure and improved lipid profile parameters. Many patients also quit smoking during the study period. By the end of the study, the number of patients with LH had significantly decreased, and indicators such as the 10-year cardiovascular risk score (I-10-y RS) and NYHA class were notably reduced.

Two studies identified in medical databases (Holstein et al., 2021; Smith et al., 2021) suggest a potential association between LH and an increased risk of developing diabetic ketoacidosis (DKA) in patients with diabetes mellitus. Failure to rotate insulin injection sites and repeated administration into areas affected by LH reduces insulin absorption and impairs its pharmacodynamic effect, leading to chronic hyperglycemia and, consequently, the development of ketoacidosis. Although there is a lack of direct evidence in the current literature establishing a causal relationship between LH and DKA, an indirect effect appears highly plausible. Reducing the prevalence of this complication could therefore potentially decrease the incidence of this life-threatening condition.

### **3.5 Influence of LH on New Technologies in Diabetes Care**

Another possible implication of LH may involve its impact on the performance of modern diabetes technologies. In a study by Karlin et al. (2016), contrary to the initial hypotheses, no significant difference was observed in the duration of infusion set function between sites affected by LH and unaffected tissue. There was also no evidence of more frequent malfunctions or a need to replace insulin pump infusion sets. However, the authors suggest that differences in insulin pharmacokinetics in altered tissue may have been masked by other factors influencing glycemic control. Moreover, it was observed that when infusion sets were placed in unaffected tissue, glycemic excursions tended to be more rapid compared to cases where the infusion set was inserted into LH-affected areas. A possible explanation for this phenomenon is the formation of insulin depots within the pathologically altered tissue, which may slow the rate of glucose increase. This effect, however, should not be interpreted as beneficial, as it is also associated with a higher frequency of hypoglycemic episodes, which may be severe, unpredictable, and potentially life-threatening.

In a multicenter study investigating the impact of LH on the performance of continuous glucose monitoring (CGM) systems (De Salvo et al., 2015), it was shown that sensors placed in affected areas exhibited similar or slightly higher accuracy compared to those inserted into unaffected tissue. The median

absolute relative difference (ARD) in LH sites reached a mean value of 10.0%, compared to 11.0% in healthy tissue. According to this study, LH does not significantly affect CGM performance. However, the authors emphasize the need for further research on this topic and raise the question of whether repeated mechanical irritation of tissues by CGM sensors could itself promote the development of LH, potentially representing an additional source of this cutaneous complication of diabetes.

### 3.6 Psychiatric Consequences of LH

An important aspect of this condition is the psychological well-being of patients. Quality of life and satisfaction with therapy directly influence motivation, adherence, and treatment outcomes. In a study examining the impact of disease-related factors on the mental health of patients with type 1 diabetes (Al-Ozairi et al., 2024), several determinants of increased diabetes-related distress and depressive symptoms were identified. Among the factors associated with greater psychiatric burden were female sex, higher levels of HbA1c, obesity, physical inactivity, the presence of microvascular complications, and lipohypertrophy. It has also been demonstrated (Hernar et al., 2017) that patients with more than one area of LH exhibit higher levels of depressive symptoms, lower satisfaction with therapeutic outcomes, higher administered insulin doses, and more frequent suboptimal insulin administration. Another study (Ciechanowski et al., 2000) highlights that diabetes-related distress and depressive symptoms may lead to serious health consequences, including low self-esteem, reduced motivation for treatment adherence, worsening disease control, and, consequently, accelerated progression of cardiovascular diseases and even increased mortality risk. These studies emphasize the importance of examining injection sites when a deterioration in the patient's mental condition or motivation for treatment is observed.

### 3.7 Financial Aspect

Another study (Sandro Gentile et al., 2022) addresses an additional important dimension of LH impact, namely, economic burden. Based on data such as healthcare reimbursement rates, hospitalization costs, the price of insulin required to meet increased demand, and loss of income due to absenteeism among patients and their caregivers, the authors estimated the financial impact associated with this complication. Patients with LH were divided into two groups: an intervention group that received intensive training in proper insulin administration techniques, and a control group that received only basic education. Over an 18-month follow-up period, the intervention group demonstrated a marked reduction in hypoglycemic episodes, which translated into an 83.08% decrease in costs related to severe hypoglycemia and a 92.7% reduction in costs associated with symptomatic hypoglycemia. In contrast, costs in the control group remained unchanged. Additionally, a 24% reduction in daily insulin requirements was observed in the intervention group, compared to a 4% reduction in the control group, corresponding to annual savings of €123.26 versus €2.20. These findings indicate that effective prevention and management of LH may represent a significant opportunity for cost reduction, benefiting both patients and public healthcare systems while simultaneously improving clinical outcomes.

The previously mentioned study from China (Ji et al., 2017) also highlights the issue of increased healthcare system costs, estimating them at approximately USD 297 million annually. This corresponds to around 22% of the insulin market in China, attributable solely to the increased insulin demand induced by LH.

Similarly, an article by an Italian research group (Gentile et al., 2024) addresses the economic burden associated with this complication. The most effective approach to LH is prevention, as once the condition develops, achieving its regression is challenging. Spontaneous regression or improvement with supportive manual therapies is often prolonged and yields unsatisfactory results. In many cases, the only effective treatment is liposuction: a costly procedure that is typically not reimbursed by public healthcare systems. The authors emphasize that the cost of patient education and appropriate preventive strategies for LH is usually

funded by the healthcare system and may be more than one hundred times lower than the cost of private liposuction. Therefore, preventing the development of LH may result in substantial financial savings for patients.

**Table 1.** Key clinical consequences of lipohypertrophy (LH).

Domain	Key Findings
<b>Glycemic control</b>	↑ HbA1c, ↑ time-out-of-range, ↑ insulin dose needed
<b>Hypoglycemia / DKA</b>	Unpredictable absorption, more severe hypoglycemic episodes, DKA case reports
<b>Long-term complications</b>	↑ risk of micro- and macrovascular complications
<b>CGM and insulin pumps</b>	Lower sensor accuracy, pump-site malabsorption
<b>Mental health</b>	↑ diabetic distress, ↑ depressive symptoms
<b>Economic burden</b>	↑ insulin use, additional medical / cosmetic interventions

#### 4. CONCLUSION

This article presents numerous examples of the negative impact of lipohypertrophy on the lives of patients with diabetes mellitus, demonstrating that it is not merely a cosmetic concern. The implications of this complication extend to everyday functioning, difficulties in achieving adequate disease control, challenges in managing comorbid conditions, and an increased risk of long-term complications. It affects not only the patient's physical well-being but also their mental health. This is a very important aspect of this condition, as the patient must cope on their own with managing diabetes every day.

LH is a preventable complication of diabetes, and its occurrence can be effectively reduced through proper patient education and regular examination of insulin injection sites, which, unfortunately, are often neglected in clinical practice. As highlighted in this article, LH represents a significant issue from both the patient's perspective and that of the healthcare system as a whole. Reducing the number of people with this complication could result in significant savings for the healthcare system, lowering the amount of insulin patients use and the incidence of complications, both acute and long-term.

Preventing LH requires active engagement from patients and healthcare professionals; however, current efforts remain insufficient. Strengthening preventive strategies could substantially reduce the burden of this complication and help avoid many of its associated adverse outcomes.

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## 5. DISCLOSURE

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### 5.1. Author Contributions

Conceptualization: Alicja Graczyk. Methodology: Alicja Graczyk, Michał Hajt, Natalia Grabowska. Resources: Dastin Misiaszek, Weronika Martynowska, Piotr Ciecierski, Natalia Grabowska. Writing – rough preparation: Alicja Graczyk, Michał Hajt, Dastin Misiaszek, Anna Wolszczak, Piotr Ciecierski, Jakub Motor, Weronika Martynowska. Writing – review and editing: Alicja Graczyk, Weronika Martynowska, Jakub Motor, Natalia Grabowska. Supervision: Alicja Graczyk. All authors have read and agreed with the published version of the manuscript.

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### 5.4. Informed Consent Statement

Not applicable.

### 5.5. Conflict of Interest Statement

The authors declare no conflict of interest.

### 5.6. Data Availability Statement

Not applicable.

### 5.7. Acknowledgements

Not applicable.

### 5.8. Declaration of Generative AI Use

In preparing this work, the authors used ChatGPT (OpenAI) for the purpose of improving the grammar and writing style of the English version. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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