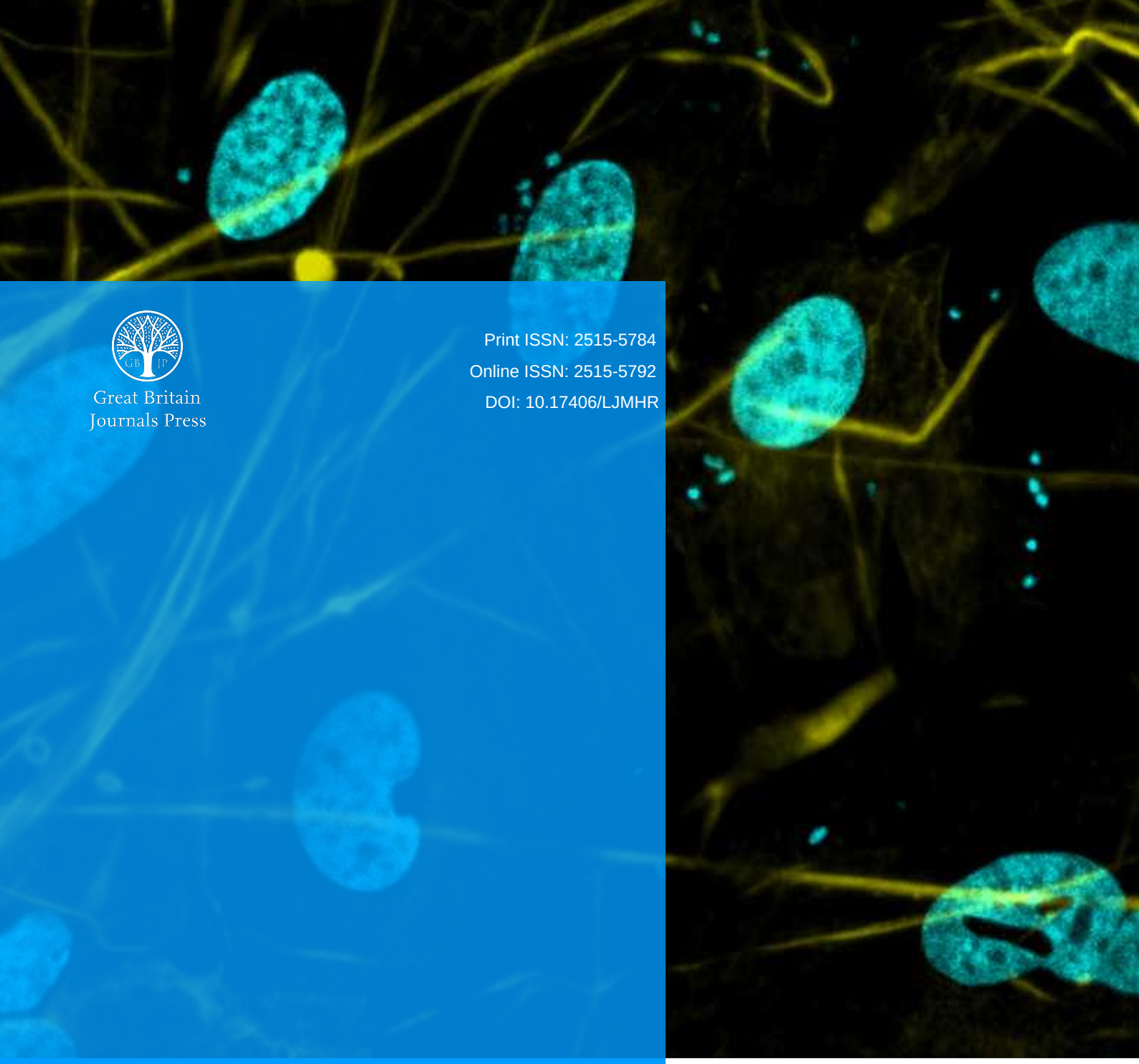

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Diabetic Foot: A Multidisciplinary Approach to Limb Preservation

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ABSTRACT

Diabetic foot is a major chronic complication of diabetes mellitus and represents a leading cause of hospitalisation, infection and non- traumatic lower limb amputation worldwide. The pathogenesis is multifactorial primarily involving peripheral neuropathy, peripheral arterial disease, impaired immunity and poor glycemic control which together predispose patients to ulceration and delayed wound healing. This review of literature aims to summarise current evidence regarding epidemiology, risk factors clinical evaluation and treatment strategies for diabetic foot disease. The literature consistently demonstrates that early identification of at-risk patients through routine screening and structured risk stratification significantly reduces ulcer occurrence. Management of established diabetic foot ulcers requires a multi-disciplinary approach combining glycemic control, infection management using culture guided antimicrobial therapy, regular wound debridement, appropriate wound dressings and appropriate offloading techniques.In patients with associated ischaemia, timely vascular assessment followed by endovascular or surgical revascularisation is critical for limb salvage. Advanced adjunctive therapies including negative pressure wound therapy, bioengineered skin substitutes and growth factor- based treatments have shown beneficial outcomes in selected cases. Overall, comprehensive preventive programs and standardised multidisciplinary treatment protocols remain essential for reducing amputation rates and improving functional outcomes in patients with diabetic foot disease.

Index Terms: diabetic foot • ulcer • management • treatment • peripheral vascular disease

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REVIEW

Diabetic Foot: A Multidisciplinary Approach to Limb Preservation

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Abstract

Diabetic foot is a major chronic complication of diabetes mellitus and represents a leading cause of hospitalisation, infection and non- traumatic lower limb amputation worldwide. The pathogenesis is multifactorial primarily involving peripheral neuropathy, peripheral arterial disease, impaired immunity and poor glycemic control which together predispose patients to ulceration and delayed wound healing. This review of literature aims to summarise current evidence regarding epidemiology, risk factors clinical evaluation and treatment strategies for diabetic foot disease. The literature consistently demonstrates that early identification of at-risk patients through routine screening and structured risk stratification significantly reduces ulcer occurrence. Management of established diabetic foot ulcers requires a multi-disciplinary approach combining glycemic control, infection management using culture guided antimicrobial therapy, regular wound debridement, appropriate wound dressings and appropriate offloading techniques.In patients with associated ischaemia, timely vascular assessment followed by endovascular or surgical revascularisation is critical for limb salvage. Advanced adjunctive therapies including negative pressure wound therapy, bioengineered skin substitutes and growth factor- based treatments have shown beneficial outcomes in selected cases. Overall, comprehensive preventive programs and standardised multidisciplinary treatment protocols remain essential for reducing amputation rates and improving functional outcomes in patients with diabetic foot disease.

Keywords: *diabetic foot, ulcer, management, treatment, peripheral vascular disease*

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1 Introduction

Diabetes remains a major global health challenge, driving significant morbidity, mortality, and economic strain. Among its many complications, diabetic foot also represents one of the most debilitating outcomes, with diabetes and serving as the leading cause of non-traumatic lower limb amputation worldwide.[1,2]

WHO defines diabetic foot as Infection, ulceration or destruction of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular diseases in the lower limb.[1,2] Diabetic foot ulcers emerge from a complex interaction of peripheral neuropathy, peripheral arterial disease, and impaired wound healing, usually exacerbated by infection.[1,2] Beyond localised tissue damage, diabetic foot ulceration reflects widespread systemic vascular disease and increases risk of cardiovascular morbidity and early mortality. Major lower limb amputations carry a grave prognosis with post-amputation five year mortality exceeding 50% in patients with diabetes.[1,2]

In India, diabetic foot disease represents a particularly significant public health burden, with an estimated 40,000 amputations performed annually. A large proportion of these amputations are neuropathic in origin and complicated by secondary infection, many of which are potentially preventable.[2]

Several factors predict poor outcomes in individuals with diabetic foot ulcer, including severity, prolonged duration, infection, peripheral arterial disease, neuropathy, chronic kidney disease, cardiovascular disease, smoking, and male gender.[1,2] These variables influence healing rates, recurrence, and likelihood of progression to major amputation or death[1,2]. In India sociocultural factors such as barefoot walking, low socioeconomic status, illiteracy, delayed healthcare seeking and reliance on alternative systems of medicine further contribute to late presentation and poor outcomes[2].

Effective management of diabetic foot ulcers and their associated complications requires a comprehensive, evidence-based approach[1,2]. Core components of treatment include appropriate pressure offloading, prompt and adequate control of infection, timely revascularisation (when indicated), surgical assessment (where necessary), optimisation of glycemic control and systematic management of coexisting medical conditions[1,2]. Given the multifactorial pathophysiology of diabetic foot disease, improved clinical outcomes are more likely when care

is delivered through a coordinated, multidisciplinary team approach involving interprofessional collaboration[1,2].

2 REVIEW OF LITERATURE

2.1 Burden of Diabetic Foot Disease

Hyperglycaemia is associated with various complications, both microvascular- including nephropathy, neuropathy, and retinopathy and macrovascular complications such as coronary artery disease, stroke, and peripheral arterial disease[1,2]. Among these, diabetic foot disease represents one of the most severe and disabling complications. Diabetes is a leading cause of non-traumatic lower-extremity amputations, with non-healing foot ulcers frequently preceding limb loss[1,2,10].The lifetime risk of developing a foot ulcer in individuals with diabetes ranges between 15% and 20% [1,2,3]. With 15% of these ulcers progressing to foot or limb amputation [1-3]. Population-based studies report an annual incidence of diabetic foot ulcers ranging from 0.5% to 3%, while prevalence varies between 2% and 10% [[1-3]. Approximately 45–60% of diabetic foot ulcers are neuropathic, while nearly 45% exhibit combined neuropathic and ischemic components [1,2,3]. Infection is implicated in nearly half of lower-limb amputations in diabetic patients [1,2,3].

2.2 Risk Factors

Diabetic foot ulcers arise from an interaction of multiple factors. With peripheral neuropathy comes a loss of sensation, which allows repeated trauma to go unnoticed. Motor neuropathy causes muscle imbalance and foot deformities, resulting in abnormal plantar pressure and callus formation, while autonomic neuropathy reduces sweating, causing dry and fissured skin[1,2].Arterial insufficiency further complicates neuropathic ulcers by impairing tissue perfusion and delaying wound healing. Mechanical stress at the wound site plays a significant role in ulcer persistence [1,2,4]. Additional risk factors include poor glycemic control, long duration of diabetes, trauma, inappropriate footwear, callus formation, history of previous ulceration or amputation, advancingage, visual impairment, chronic kidney diseaseand poor nutritional status[1,2,10]. Infections contribute to chronicity by furtherworsening wound healing leading to a non healing ulcer. Interestingly, a deficiency of Vitamin D is an emerging risk factor for diabetic foot infection [1,2,5].

2.3 Classification of Wounds

The Red–Yellow–Black wound classification system by Marion Laboratories categorizes wounds based on the following characteristics [1,2]:

- **Necrotic tissue:** Black or dark green in colour, which may be dry or infected
- **Sloughy tissue:** A yellow, glutinous tissue composed of wound exudate and debris, often mistaken for infection.
- **Granulating tissue:** Red, vascular tissue indicating active healing
- **Epithelializing tissue:** Pink in colour, indicating epithelium growing over the wound by keratinocyte migration from wound margins

The presence of devitalised tissue or critical colonisation prevents chronic wounds from healing [1,2,6] hence, necessitates removal through debridement of tissue. However, debridement may be contraindicated in purely arterial ulcers [1,2,3,11]. With regular excision of necrotic tissue and surrounding callus we are likely to see accelerated wound healing and an increased likelihood of complete secondary closure [1,2,3].

Wound classification system[11]

Stages	Description
Stage A	No infection or ischemia
Stage B	Infection present
Stage C	Ischemia present
Stage D	Infection and ischemia present
Grading	
Grade 0	Epithelialized wound
Grade 1	Superficial wound
Grade 2	Wound penetrates to tendon or capsule
Grade 3	Wound penetrates to bone or joint

2.4 Grading of Diabetic Foot Ulcers

Wound grading is performed using Wagner's classification or the University of Texas wound classification system [1,2]. It includes wound depth, infection, and ischemia. To adequately treat am ulcer, a thorough wound assessment is necessary including documentation of the ulcer location, size, depth, wound margins, base, drainage, colour, odour, pain, and progression [1,2].

2.5 Microbiology of Diabetic Foot Infections

Hyperglycaemia, impaired immune response, neuropathy, and peripheral arterial disease predispose patients to diabetic foot infections [1,2,7].

Diabetic foot infections may involve aerobic, anaerobic, or fungal organisms. With both mono-microbial and poly-microbial infections being quite common [1-3]. Organisms that most commonly infect diabetic foot ulcers include *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*,[1,2,3,44] with both gram positive and gram negative bacteria showing a similar predominance. Due to theregional variability in microbial patterns, culture-guided antibiotic therapy is required for adequate resolution[1,2].

3 DISCUSSION

Diabetic foot disease remains one of the most feared and debilitating complications of diabetes mellitus. It is associated with prolonged hospitalisations, substantial financial burden, repeated surgical interventions, and a persistent risk of limb loss, all of which significantly affect the physical and psychological well-being of patients. The possibility of amputation and the subsequent experience of phantom limb pain further contribute to emotional distress and reduced quality of life. Consequently, diabetic foot disease continues to pose a major challenge for patients, caregivers, and healthcare systems[1,2].

Clinically, the diabetic foot is characterised by a classical triad of **neuropathy, ischaemia, and infection** with each component contributing to ulcer formation, progression, and poor healing outcomes. These factors rarely act in isolation; instead, their coexistence creates a complex pathological environment that predisposes the foot to breakdown and chronic infection. Preventive strategies therefore are the most effective means of reducing morbidity[1,2,27].

Pathogenesis

The development of diabetic foot ulcers is multifactorial, with peripheral neuropathy and ischemia serving as the primary underlying mechanisms. Continuous weight-bearing and shear forces exacerbate tissue damage, leading to progressive ulceration. Charcot arthropathy represents an advanced manifestation of neuropathy, resulting from a combination of motor, sensory, and autonomic dysfunction, ultimately causing joint instability, altered foot architecture, and increased risk of ulceration[1,2].

Peripheral vascular disease further compromises wound healing by reducing tissue perfusion. Although atherosclerosis in diabetic patients resembles that seen in non-diabetics, it tends to be more diffuse, occurs earlier, and progresses more rapidly. In diabetic individuals, distal vessels below the knee are more commonly involved, while pedal arteries may remain relatively spared. The coexistence of ischemia and neuropathy significantly increases the risk of ulceration and limb loss[1,2,31].

3.1 Infection and Osteomyelitis

Infection in the diabetic foot is a limb-threatening condition due to the unique anatomical characteristics of the foot, including multiple intercommunicating compartments that facilitate rapid spread. The absence of pain due to neuropathy allows continued ambulation, further propagating infection. Soft tissue structures such as fascia, tendons, and muscle sheaths provide little resistance to infection, and the presence of hyperglycemia and ischaemia impairs host defense mechanisms[1,2].

Osteomyelitis commonly develops as a result of contiguous spread from deep soft tissue infections and is frequently associated with chronic or longstanding ulcers. Diagnosis can be challenging and requires careful clinical evaluation, supported by imaging and microbiological studies. Probing to bone remains a useful bedside test, while magnetic resonance imaging offers high sensitivity and specificity for detecting bone involvement. Definitive diagnosis requires bone biopsy for culture and histopathology[1,2,39].

3.2 Classification and Assessment

Accurate classification of diabetic foot ulcers is essential for guiding management. Diabetic foot lesions are broadly categorized into neuropathic and neuroischemic types, each requiring distinct therapeutic strategies. The University of Texas Wound Classification System is widely accepted due to its ability to incorporate depth, infection, and ischemia [1,2,https://pmc.ncbi.nlm.nih.gov/articles/PMC2878694/].

3.3 Examination of the Feet

Assessment of the feet is a fundamental component of routine physical examination, particularly in individuals with diabetes. Inspection should focus on identifying features suggestive of neuropathy, including xerosis, fissuring, structural deformities, callus formation, altered foot architecture, ulceration, dilated superficial veins, and nail abnormalities. The interdigital spaces must be examined carefully, as lesions in these areas may be easily overlooked[1,2]. Clinical signs indicative of significant ischemia include loss of hair over the dorsum of the foot and the presence of dependent rubor[1,2]. Palpation: To assess temperature differences, noting areas of unusual warmth or coolness. Peripheral arterial pulses must be evaluated systematically. The dorsalis pedis artery is palpated lateral to the tendon of extensor hallucis longus, while the posterior tibial artery is felt posterior and inferior to the medial malleolus[1,2]. Examination should also include palpation and auscultation of the femoral artery to detect bruits. The plantar surface should be assessed for bony prominences, areas of increased pressure, or callosities that may predispose to ulcer formation[1,2]. Evaluation for sensory neuropathy can be performed using Semmes–Weinstein monofilaments or biothesiometry. In resource-limited settings, simpler bedside methods—such as testing light touch with cotton wool, assessing pinprick sensation, and evaluating vibration perception using a 128 Hz tuning fork—are acceptable alternatives. The primary objective of sensory testing is to determine the presence of loss of protective sensation (LOPS), which significantly increases the risk of ulceration[1,2]. A handheld Doppler device may be employed to verify arterial flow and further assess vascular status. When combined with a sphygmomanometer, measurement of ankle and brachial systolic pressures allows calculation of the ankle–brachial index (ABI). Under normal circumstances, ankle systolic pressure slightly exceeds brachial pressure, yielding an ABI greater than 1. An ABI value below 0.9, particularly when accompanied by diminished or absent pulses, is indicative of peripheral arterial disease. Conversely, palpable pulses with an ABI above 1 generally exclude significant ischemia [1,https://pmc.ncbi.nlm.nih.gov/articles/PMC2878694/,24].

3.4 Revascularization

Individuals presenting with significant peripheral ischaemia need re-establishment of arterial perfusion, as sufficient blood supply is critical for effective wound healing and eradication of infection. In cases of inadequate circulation tissue repair gets compromised the likelihood of limb loss drastically increases. Bypass surgery continues to be a well-recognised intervention for ischemic lower extremities, with durable long-term outcomes reported. Limb salvage rates of nearly 90% at 10 years have been documented following lower extremity bypass procedures [1,2,22,23]. In cases where arterial disease involves multiple segments, revascularization should target each level of obstruction to restore adequate distal blood flow and enhance the probability of limb preservation. Percutaneous transluminal angioplasty is particularly appropriate for discrete, short-segment stenotic lesions. Conversely, when disease is extensive—characterised by multiple occlusions, lesions longer than 15 cm, or infra-popliteal vessel involvement—bypass surgery is generally regarded as the treatment of choice. [1,2].

3.5 Prevention

Timely identification of individuals at risk for ulceration plays a crucial role in preventing the development of diabetic foot lesions. An effective screening method includes- annual foot examinations for all patients with diabetes to initiate early intervention[1,2].Patient education forms the cornerstone of prevention strategies. Individuals

should be counselled about strict glycemic control, use of appropriate footwear, avoiding foot trauma and routine self-inspection of the feet[1,2].

Preventive strategies may be categorised into three levels:

• **Primary prevention:** Identification of high-risk feet and provision of guidance regarding protective or therapeutic footwear.

• **Secondary prevention:** Early management of minor foot problems, including callus care, treatment of nail disorders, and appropriate handling of blisters or superficial lesions.

• **Tertiary prevention:** Early referral to specialised centers for advanced or complicated foot lesions [1,2].

Improved limb salvage rates and reduction in amputation incidence can be achieved through structured training of primary care physicians and paramedical staff in diabetic foot management. The "Step by Step" program, implemented by the World Diabetes Foundation, represents one such initiative [1,2].

Continuous patient education and long-term follow-up are essential for all individuals suffering with diabetes, especially diabetic foot ulcers. Such patients should be advised to limit excessive mechanical stress on the affected limb and adopt activity modifications when necessary[1,2].A comprehensive understanding of diabetic foot pathology, systematic foot examination, appropriate classification of ulcers, multidisciplinary management, and implementation of preventive measures collectively contribute to improved limb preservation and reduced amputation rates among individuals with diabetes[1,2].

4 Conclusion

Diabetic foot disease remains a major and largely preventable cause of morbidity among individuals with diabetes mellitus and continues to contribute for a significant proportion of hospitalisation and non-traumatic lower-limb amputations worldwide. This literature review consistently demonstrates that diabetic foot complications arise from the interaction of peripheral neuropathy, peripheral arterial disease, infection, foot deformities and poor glycaemic control; additionally delayed presentation and inadequate preventive care further exacerbates disease severity and adversely affect clinical outcomes.

Evidence strongly supports the effectiveness of preventive strategies including routine foot screening, risk stratification, patient education, use of appropriate footwear and early referral to specialised diabetic foot clinics. Multidisciplinary care models involving surgeons, diabetologists, podiatrists, vascular specialists and wound care teams have been shown to significantly reduce ulcer recurrence and amputation rates. In terms of treatment, the literature highlights that successful management requires a structured stepwise approach consisting of optimal glycaemic control, aggressive infection management using culture-guided antimicrobial therapy, regular wound debridement, appropriate wound dressings and effective off-loading techniques such as total contact casting or customised orthotic devices. In patients with ischaemic limbs, timely vascular assessment and revascularisation procedures, either endovascular or surgical, play a crucial role in improving limb salvage. Advanced wound-care modalities, including negative pressure wound therapy, growth factor-based therapies, and skin substitutes have demonstrated promising adjunctive benefits in selected cases. In summary, diabetic foot disease is largely preventable and treatable when addressed through early detection, standardised treatment protocols and coordinated multidisciplinary care. Strengthening preventive services, ensuring timely surgical and vascular interventions and expanding access to comprehensive diabetic foot management programs remain essential steps in reducing the burden of amputations and improving long-term patient outcomes[1,2].

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The Paradox of Airway Closure: From Protection to Pathology

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ABSTRACT

Airway closure, first recognized by Laennec and later quantified in studies by Dollfuss, Hedenstierna and Hughes, represents a physiological phenomenon with far-reaching clinical consequences. While often overlooked in critical care, its role in promoting atelectasis, impaired gas exchange, and ventilator-induced lung injury is well established. The present narrative review revisits the fundamental physiology of airway closure, its exacerbation in anaesthesia and obesity, and its near-universality in mechanically ventilated ARDS patients. A reinterpretation of pleural pressure data from landmark studies, suggests that airway closure may be far more prevalent than currently appreciated. Strategies such as optimal PEEP and avoidance of high oxygen fractions are discussed, with emphasis on the urgent need for better integration of airway closure physiology into clinical practice. This article re-examines how positive airway pressure in combination with elevated intrathoracic pressure — the inevitable companion of positive pressure ventilation — underlies many of the adverse effects attributed to modern mechanical ventilation. By contrast, negative pressure ventilation, long abandoned, may offer physiological advantages worth reconsidering. The question we must now ask is: could a return to negative extra-thoracic pressure — or a hybrid model — prevent the very complications we have come to accept as inevitable?

Index Terms: Mechanical Ventilation • Positive Pressure Ventilation • Negative Pressure Ventilation • Airway Resistance • Airway Closure • Atelectasis • Ventilator Induced Lung Injury • Pleural Pressure • Intra-thoracic pressure

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NARRATIVE REVIEW

The Paradox of Airway Closure: From Protection to Pathology

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Abstract

Airway closure, first recognized by Laennec and later quantified in studies by Dollfuss, Hedenstierna and Hughes, represents a physiological phenomenon with far-reaching clinical consequences. While often overlooked in critical care, its role in promoting atelectasis, impaired gas exchange, and ventilator-induced lung injury is well established. The present narrative review revisits the fundamental physiology of airway closure, its exacerbation in anaesthesia and obesity, and its near-universality in mechanically ventilated ARDS patients. A reinterpretation of pleural pressure data from landmark studies, suggests that airway closure may be far more prevalent than currently appreciated. Strategies such as optimal PEEP and avoidance of high oxygen fractions are discussed, with emphasis on the urgent need for better integration of airway closure physiology into clinical practice. This article re-examines how positive airway pressure in combination with elevated intrathoracic pressure — the inevitable companion of positive pressure ventilation — underlies many of the adverse effects attributed to modern mechanical ventilation. By contrast, negative pressure ventilation, long abandoned, may offer physiological advantages worth reconsidering. The question we must now ask is: could a return to negative extra-thoracic pressure — or a hybrid model — prevent the very complications we have come to accept as inevitable?

Keywords: *Mechanical Ventilation, Positive Pressure Ventilation, Negative Pressure Ventilation, Airway Resistance, Airway Closure, Atelectasis, Ventilator Induced Lung Injury, Pleural Pressure, Intra-thoracic pressure*

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1 Introduction

Despite decades of technical progress in mechanical ventilation, an important mechanical consequence of positive pressure ventilation (PPV) remains insufficiently appreciated: the rise in pleural pressure (P_{pl}) and intrathoracic pressure (P_{it}) that inevitably accompanies the application of positive airway pressure (P_{aw}) within a thorax that does not actively expand. This increase in surrounding tissue pressure may compress the lung parenchyma and the small peripheral airways, particularly in dependent regions or in lungs with reduced compliance.

The present article is not intended as a comprehensive review of airway closure or ventilator-induced lung injury (VILI). Rather, it focuses on a specific mechanical interpretation: that airway closure, atelectasis, hyperinflation, and related complications during PPV are closely linked to lung tissue compression caused by elevated pleural and intrathoracic pressure. This perspective differs from the common emphasis on transpulmonary pressure alone, suggesting that reductions in transpulmonary pressure by themselves are insufficient to explain or prevent atelectasis during positive-pressure ventilation.

The transition from negative pressure ventilation (NPV) to PPV in the mid-20th century was driven largely by practical advantages—airway access, emergency applicability, and ease of use—rather than by controlled physiological comparison. As a result, the mechanical differences between inflating the lung by raising P_{aw} and inflating it by lowering P_{pl} may have remained underappreciated. The present review reconsiders airway closure in that light.

TRIBUTE TO PROFESSOR HEDENSTIERNA

The ideas presented in this paper have been profoundly influenced by the pioneering work of Göran Hedenstierna, whose studies from the 1970s onward laid much of the foundation for our current understanding of airway closure, atelectasis, and the effects of oxygen and pressure on lung mechanics.

Those who met Göran (JPM) may recall his persistent warning against the routine use of high oxygen concentrations during PPV. He repeatedly emphasized the relationship between inspired oxygen fraction and the development of atelectasis. At the time, however, few of us fully understood the mechanism he proposed, and clinical practice changed little—we continued to increase the oxygen concentration to 100% before intubation and before terminating PPV and proceeding to extubation.

When I (JvE) revisited his 1976 paper on airway closure [1], I realized how far ahead of his time he had been. He recognized that airway closure is not merely a pathological phenomenon, but a physiological mechanism that protects the lung at low volumes. His meticulous experiments demonstrated how anaesthesia, PPV, and high oxygen concentrations disturb this delicate balance and thereby promote atelectasis.

"This concept is increasingly reflected in contemporary lung-protective strategies, which recommend avoiding unnecessarily high inspired oxygen fractions. During maintenance, weaning, and immediately prior to extubation, FiO_2 may often be limited to approximately 0.4 whenever clinically feasible, whereas higher FiO_2 values, up to approximately 0.8, may be appropriate during induction and airway management [2]."

In addition, positive pressure ventilation differs fundamentally from spontaneous breathing and NPV in its hemodynamic effects. The increase in intrathoracic pressure reduces venous return and cardiac preload, may impair cardiac output, and can transiently affect organ perfusion, for example by reducing urine output. At the same time, it decreases left ventricular afterload while increasing right ventricular afterload through elevated pulmonary vascular resistance.

In May 2021, I wrote to Professor Hedenstierna to share my reflections on the contemporary implications of his work, unaware that my letter would reach him only weeks before his passing. I am convinced that, had our paths crossed earlier, we would have found substantial common ground.

This paper therefore stands, in part, as a continuation of his line of reasoning—exploring how P_{pl}, P_{it}, and airway closure interact to shape both ventilation and perfusion. His scientific legacy remains a source of insight for those who seek to understand and preserve the lung's intrinsic physiology rather than override it.

2 Mechanical Framework

The lung parenchyma is mechanically interposed between the pleural space and the conducting airways (Figure 1). P_{pl} acts on the external surface of the lung, whereas P_{aw} is transmitted through the bronchial tree into the alveolar space. Both therefore contribute to the pressure environment surrounding the small intraparenchymal airways, particularly the terminal and respiratory bronchioles—highly compliant, collapsible structures of submillimeter diameter that supply individual acini.

For this reason, lung tissue compression cannot be understood from transpulmonary pressure alone. Transpulmonary pressure (P_{tp}), defined as alveolar pressure (P_{alv}) minus P_{pl} (in contrast to the very commonly used definition: $P_L = P_{aw}$ minus P_{pl}. The two definitions are only equivalent in the absence of airway closure.), describes distending pressure across the lung, but does not by itself describe the absolute pressure acting on the parenchyma. A useful approximation of the compressive load on the parenchyma is the mean of P_{aw} and P_{pl}:

$$P_{it} \approx (P_{aw} + P_{pl})/2. \tag{1}$$

When P_{aw} and P_{pl} rise simultaneously, P_{tp} may remain unchanged while the absolute pressure surrounding the parenchyma increases. Under such conditions, small compliant airways embedded in lung tissue may narrow or close, especially in gravity-dependent regions, where the weight of the overlying lung tissue increases local compressive forces, an effect that may be further enhanced in the presence of edema. This distinction helps explain why PPV and NPV cannot be considered mechanically equivalent even at similar P_{tp}'s.

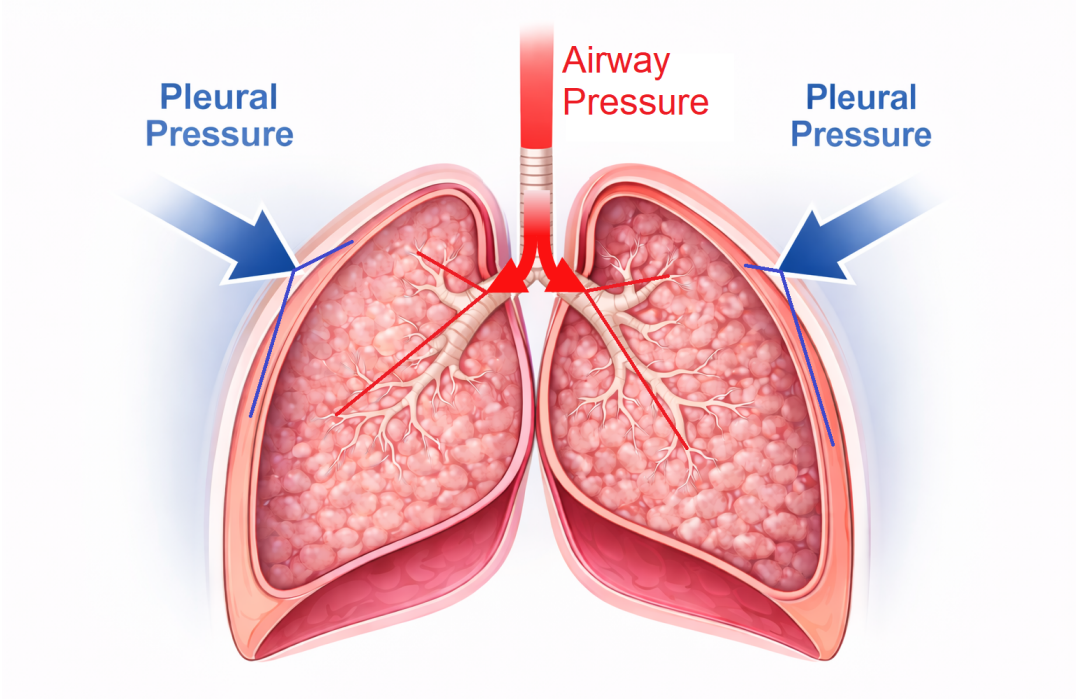

Figure 1. Pressures acting on the lung parenchyma during positive and negative pressure ventilation, the parenchyma is sandwiched between pleural space and the main airways. During positive pressure ventilation, airway pressure is elevated above atmospheric pressure and pleural pressure rises in parallel. During negative pressure ventilation, pleural pressure is reduced below atmospheric pressure (i.e., becomes more negative), while airway pressure remains at atmospheric level. Airway pressure is transmitted throughout the bronchial tree into the alveolar space and therefore contributes directly to the mechanical compression experienced by the lung tissue.

3 Physiological Airway Closure

Airway closure is a well-established physiological phenomenon. In patients with small airway disease, peripheral airway closure becomes evident during forced expiration, as demonstrated by expiratory CT imaging, in which air trapping and mosaic attenuation are recognized as indirect markers of small-airway closure [3]. Milic-Emili, in his 2007 review [4], recalled that René Laennec had already described "trapped air" in the excised lung around 1820. Dollfuss et al. [5] demonstrated that expiration below functional residual capacity (FRC) initiates airway closure, and Hughes et al. [6] confirmed this in the excised dog lung. According to these classical observations, closure of the feeding airway occurs when local trans-airway pressure falls below a threshold of about 2–2.5 cmH_2O.

This mechanism protects the alveolus against complete collapse: the small airway closes before the alveolar unit itself is fully compressed. In the healthy spontaneously breathing subject, such closure is common and usually transient and reversible. Excluded units are readily reintegrated during the next inspiration or spontaneous sigh, preserving ventilation–perfusion matching and lung volume stability.

Because P_{pl} becomes less negative toward the dependent regions of the lung, closure begins in the dependent lung and progresses upward as P_{it} rises or lung volume falls. This gravitational dependence is reflected in the classic concepts of closing volume and closing capacity [7].

This gravitational sequence is also directly reflected in the lower, leftward limb of the pressure–volume relationship. As lung volume decreases below FRC, progressively more dependent airways reach their closing threshold, resulting in a gradual loss of ventilated units over a pressure range that corresponds to the vertical P_{pl} gradient. The residual volume thus represents the lung volume at which airway closure has extended throughout the lung. At still lower pressures, this volume remains trapped (as noticed by Laennec), since the closed airways prevent further emptying.

COMPRESSIVE LOAD DURING INSPIRATION: WHY PPV MAY TURN PHYSIOLOGY INTO PATHOLOGY

Figure 2. illustrates the simulated compressive load on lung parenchyma by PPV and NPV, both applied with an identical driving pressure of 10 cmH_2O and zero end-expiratory pressure. Although resulting volume changes may be (they are not! See below under "Experimental support from isolated lungs") comparable, the underlying pressure environment differs fundamentally.

The simulation shown in Figure **??** is based on a simplified lumped-parameter model of the respiratory system, consisting of a single-compartment lung enclosed within a compliant chest wall. Both lung and chest wall compliances were assumed to be linear and equal (150 mL/cmH_2O), with a functional residual capacity (FRC) of 2.4 L and a pleural pressure of -6 cmH_2O at FRC.

The model was not intended to represent regional heterogeneity or complex lung mechanics, but rather to illustrate the effect of different pressure application modes on the mechanical environment of the lung. In particular, the simulation highlights how airway pressure contributes to parenchymal compression during PPV, whereas NPV alters the surrounding pressure without increasing airway pressure.

In the absence of PEEP or negative end-expiratory pressure (NEEP), expiratory curves for PPV and NPV are nearly superimposed. However, when PEEP or NEEP is introduced, the curves diverge, reflecting differences in the pressure environment during both inflation and deflation.

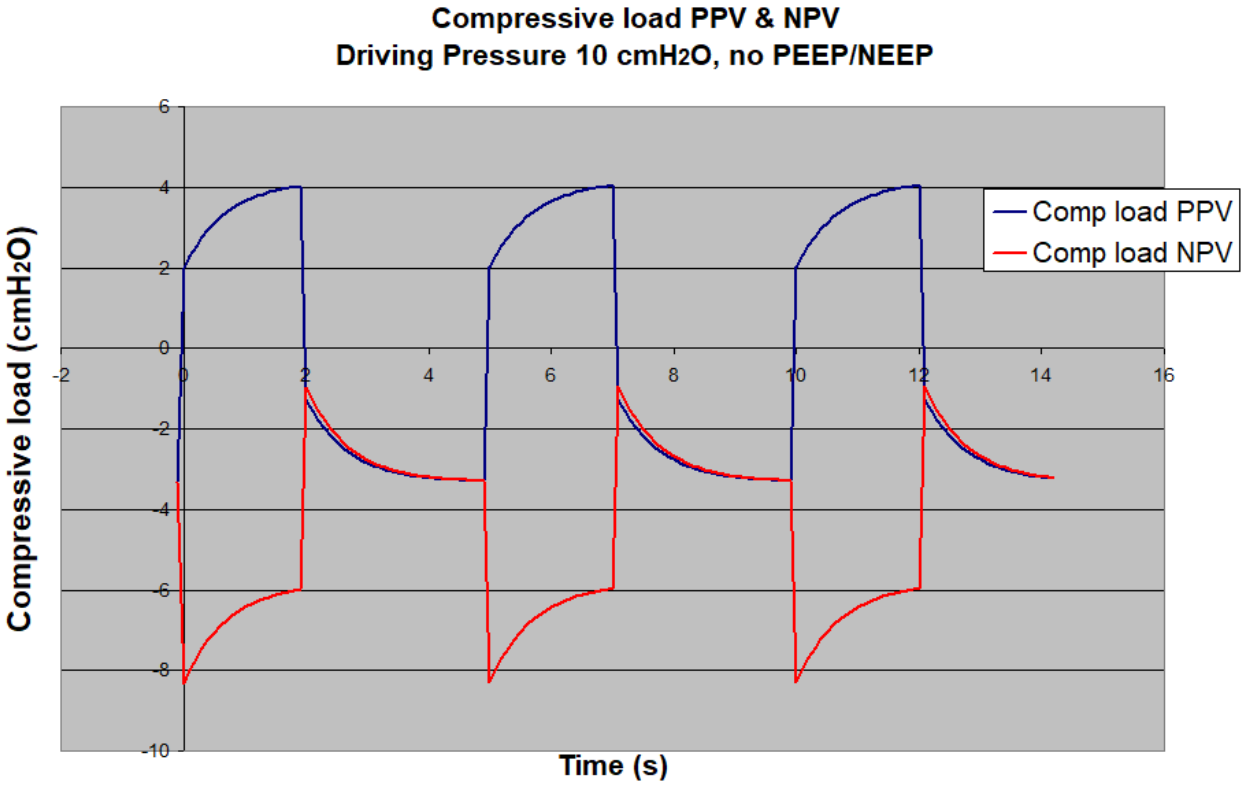

Figure 2. Compressive load on parenchyma during mechanical ventilation. The load is depicted during both NPV and PPV, with a driving pressure of 10 cmH_2O (≈ 10 mbar). Here no PEEP (NEEP for NPV) is applied, that is why the expiration curves are identical (the slight differences are due to the simulation process: $\Delta t \to 0$ would make them coincide perfectly). PEEP will shift the curve upward for PPV and down for NPV and make this equivalence disappear.

Compressive load is approximated as the mean P_{it}, here defined as $(P_{aw} + P_{pl})/2$. During inspiration with NPV, P_{pl} becomes more negative, reducing this mean pressure and thereby decreasing tissue compression. In contrast, during PPV, P_{aw} rises above atmospheric pressure and P_{pl} increases accordingly, resulting in an increase in compressive load during inspiration.

This difference has major consequences for small peripheral airways. Under physiological conditions, airway closure during expiration is typically transient and reversible. However, under PPV—particularly in dependent regions—closed airways may fail to reopen during the subsequent inspiration, because the rise in P_{aw} is accompanied by an increase in surrounding tissue pressure.

Airway hysteresis, partly related to surface tension and adhesive forces at the airway walls, ongoing gas absorption, and the absence of sufficiently negative P_{pl} interact to stabilize airway closure. Hysteresis implies that reopening requires higher distending pressures than those present at end-expiration, while ongoing gas absorption further reduces the volume of isolated acini, particularly at high inspired oxygen fractions. In the absence of sufficiently negative P_{pl} to relieve surrounding tissue compression, these regions may remain closed despite apparently adequate transpulmonary pressure. Thus, a normally protective physiological mechanism may evolve into a pathological state characterized by persistent exclusion of peripheral lung units, impaired recruitment, and progressive atelectasis.

From a clinical perspective, this has important implications for the interpretation of P_{es} measurements. In routine practice, transpulmonary pressure is estimated as P_{aw} - P_{es}, assuming that P_{aw} is transmitted to the alveoli. However, this assumption no longer holds once peripheral airway closure occurs e.g. during expiration. At the moment of closure, alveolar pressure in the affected units equals the P_{aw} at which flow ceases locally, after which these units become mechanically uncoupled from the airway opening. Subsequent decreases in P_{aw} are therefore not transmitted to these regions. As a result, a transpulmonary pressure calculated from P_{aw} and P_{es} may not reflect the local mechanical conditions within closed or excluded lung units. Airway opening pressure (AOP), typically assessed during inspiration, provides information on reopening but does not capture the alveolar pressure at which closure occurred during expiration.

This mechanism helps explain why airway closure is frequently observed in anaesthetized and mechanically ventilated patients, particularly in conditions associated with elevated P_{pl}, such as obesity, ARDS, reduced chest wall compliance, pneumoperitoneum, and Trendelenburg positioning.

It should be emphasized that this expression represents a global or mean approximation of the pressure acting on the lung parenchyma. While P_{aw} is relatively uniform throughout the lung at a given moment, P_{pl} exhibits substantial regional variation, primarily due to gravitational effects and the weight of overlying lung tissue. This results in a vertical gradient of parenchymal compression, with higher compressive forces in dependent regions and lower values in non-dependent regions.

This spatial heterogeneity is further amplified in the presence of lung injury, edema, or regional stiffening, where local mechanical conditions may deviate markedly from the mean estimate. Consequently, the compressive load on the parenchyma is not uniform, but greatest in dependent regions, where airway closure is also most likely to occur.

In this context, the approximation $P_{it} \approx (P_{aw} + P_{pl})/2$ should be interpreted as a conceptual framework rather than an exact local descriptor of pressure transmission. This limitation does not diminish the relevance of the concept itself, but rather highlights that its clinical implications are most pronounced in dependent lung regions, where pleural pressure, and thus parenchymal compression, is highest.

4 Experimental Support from Isolated Lungs

Direct mechanical support for this concept comes from isolated-lung experiments comparing PPV and NPV. Klassen et al. [8] and Eckert et al. [9] ventilated excised lungs either by applying positive pressure at the airway opening or by applying negative pressure externally around the lung.

Klassen et al. [8] showed that, for a given tidal volume, PPV required approximately twice the driving pressure needed during NPV. This already suggested greater internal flow limitation during PPV. Even more striking was their observation that a small peripheral defect at the lung surface leaked almost five times more during NPV than during PPV at comparable tidal volumes. Eckert et al. [9] reported concordant findings.

The interpretation is straightforward. During NPV, peripheral regions remain ventilated and in communication with the airway tree, allowing gas to reach and escape through the peripheral defect. During PPV, by contrast, the much smaller leakage indicates that the distal lung is poorly ventilated or functionally excluded. These experiments therefore provide direct evidence that PPV promotes peripheral airway narrowing or closure, whereas NPV preserves distal airway patency.

5 Clinical Analogue: Delayed Pneumothorax

A similar phenomenon appears to occur clinically in delayed pneumothorax during PPV. In a recent case report [10], a pneumothorax remained occult during ongoing PPV and became apparent only after the patient resumed spontaneous breathing.

This behaviour mirrors the isolated-lung findings. During PPV, elevated P_{aw} and P_{pl} increase parenchymal compression, so that a pleural defect in a poorly ventilated peripheral region may not communicate effectively with the central airways. Air leak into the pleural space then remains limited, and pneumothorax may not become clinically evident. When spontaneous breathing resumes, P_{pl} becomes more negative, peripheral airways reopen, and the distal defect again communicates with the airway tree. The pneumothorax then declares itself.

Thus, delayed pneumothorax can be understood as an in vivo counterpart of the reduced peripheral leak observed during PPV in isolated lungs [8,9].

LESSONS FROM COPD: AVOIDANCE OF COMPRESSIVE LOADING

The mechanical consequences of elevated P_{it} are well illustrated in patients with chronic obstructive pulmonary disease (COPD). These patients characteristically avoid forceful expiration, as increased P_{pl} leads to airway narrowing and premature closure of small airways. Instead, they adopt a breathing pattern with prolonged, low-flow expiration and often operate at an increased end-expiratory lung volume.

By elevating FRC, COPD patients maintain airway patency and reduce airway resistance, thereby minimizing the compressive effects of P_{it} on peripheral airways. This adaptive strategy reflects an intuitive avoidance of the very mechanism that may be imposed during PPV.

In this context, PPV—by increasing P_{pl} and P_{it} during inspiration—may counteract these protective adaptations, promoting airway closure and increasing resistance, particularly in already vulnerable lung regions [11].

6 PEEP: Stabilization and Compression

The effects of positive end-expiratory pressure (PEEP) require careful interpretation. PEEP is often described as "recruiting" the lung, but its action is mechanically dual.

On the one hand, PEEP raises P_{aw} and thereby raises P_{it}, which increases compressive loading of the parenchyma, especially in dependent regions. On the other hand, the resulting increase in lung volume enlarges airway caliber and may stabilize small airways against collapse. Because airway resistance decreases strongly with airway radius, this volume effect can be substantial.

The apparent benefit of PEEP may therefore reflect geometric expansion and airway stabilization rather than true relief of tissue compression. The net effect depends on the balance between increased absolute pressure and increased lung volume. This duality may help explain why PEEP sometimes improves oxygenation and compliance while not necessarily reversing the underlying compressive mechanism.

6.1 Flow Dependence of Airway Closure

Airway closure is influenced not only by static pressure levels but also by the temporal pattern of pressure application. Because different lung regions have different time constants, rapid inspiration preferentially fills units with short time constants, typically more central or less compressed regions.

During fast inspiration, proximal units fill early and raise pleural and parenchymal pressure before more distal regions have had time to fill. This early rise in P_{it} may further compress peripheral airways, making the distal lung progressively less accessible during the same breath. In contrast, a more gradual flow profile allows distal regions more time to fill before compressive forces increase.

This concept offers a plausible mechanical explanation for the benefits reported with flow-controlled strategies. Flow-controlled expiration (FLEX) [12] reduces rapid pressure decline during expiration and may thereby limit derecruitment. Likewise, regulated inspiratory and expiratory flow, as used in devices such as the EVONE ventilator [13], may promote more homogeneous distribution of ventilation by avoiding abrupt pressure changes.

7 Clinical Evidence: Obesity, ARDS, and AOP

Clinical observations also support a major role of elevated P_{pl} in airway closure. In supine obesity, increased abdominal pressure displaces the diaphragm cranially and raises P_{pl}. Behazin et al. [14] described complete airway closure under such conditions, with inspiratory flow appearing only after P_{aw} exceeded the AOP.

AOP is a useful physiological marker, but it should not be interpreted too simplistically. The measured AOP most likely represents the pressure at which the first previously closed regions reconnect with the central airways, not the pressure at which the entire lung has reopened. Because P_{pl} varies substantially from non-dependent to dependent lung, reopening must be expected to proceed gradually over a pressure range.

Thus, the presence of an AOP confirms airway closure, but the absence of a clearly measurable AOP does not exclude it. If PEEP is already close to or above the opening pressure of the least dependent regions, flow may appear immediately during inspiration as P_{aw} rises, even though much of the lung was initially functionally closed. This distinction is important in obesity and ARDS, [15,16] where elevated P_{pl} may cause widespread airway closure without a dramatic or easily recognized AOP.

PLEURAL PRESSURE, THORACIC VOLUME, AIRWAY CLOSURE AND THE "BABY LUNG" IN ARDS

As emphasized by Grasso [17], the reduced compliance of the respiratory system in ARDS may arise from either the lung or the chest wall. Distinguishing between these requires knowledge of P_{pl}, which can be estimated from oesophageal pressure measurements. Several studies have applied this approach to guide ventilator settings, notably those by Talmor [18], Beitler [19], and Kassis [20]. Selected data from these studies are summarized in Table 1.

Two observations emerge consistently from these data.

First, the calculated compliance of the thoracic wall remains within a near-normal range. C_{TW} can be estimated from tidal volume (TV) and the difference between end-inspiratory and end-expiratory P_{pl} ($EIPpl$ and $EEPpl$, respectively):

$$C_{TW} \approx TV/(EIPpl - EEPpl) \tag{2}$$

Across the reported datasets, this yields values on the order of 120 $ml.cmH_2O^{-1}$, suggesting that the thoracic wall itself is not markedly stiff.

Second, $EEPpl$ is markedly elevated, typically around +15 to +18 cmH_2O. If one assumes a normal reference P_{pl} of approximately −6 cmH_2O at FRC, this implies an increase in thoracic volume of roughly:

$$\Delta V \approx (EEPpl + 6) \times C_{TW} \tag{3}$$

which corresponds to an increase of several litres above FRC. Thus, the thorax appears to operate at substantially elevated volumes even at end-expiration.

These observations have important implications for airway patency. To maintain an alveolus open at such elevated P_{pl}, P_{alv} must exceed P_{pl} by a sufficient margin. If one assumes that a pressure difference on the order of a few cmH_2O (≈ 2–3 cmH_2O) is required to maintain airway patency, then P_{alv} in such regions must lie well above P_{pl}.

However, the P_{aw} available at end-expiration is limited by the applied PEEP. When the pressure required to keep peripheral units open exceeds this P_{aw}, those regions can no longer remain in communication with the airway tree and must therefore be functionally closed.

This reasoning suggests that, under the conditions reported in Table 1, a substantial fraction of the lung is likely to be excluded from ventilation at end-expiration. The concept of the "baby lung" [21] in ARDS is consistent with this interpretation: only a relatively small portion of the lung remains aerated and ventilated, while the remainder is functionally closed or fluid-filled.

An important consequence is that, during a low-flow inflation manoeuvre, the measured AOP may not be clearly discernible if PEEP is already close to or above the opening pressure of the least dependent lung regions. In that situation, the absence of a clearly defined AOP does not exclude substantial airway closure, because flow may begin immediately while a large part of the lung remains functionally closed.

Additional studies reporting elevated P_{pl} during mechanical ventilation, including observations in COVID-19 patients [22], support this overall picture of a lung compressed within a high-pressure thoracic environment. Under these conditions, airway closure, gas trapping, and redistribution of ventilation toward a limited "baby lung" appear as natural mechanical consequences [23] rather than isolated phenomena.

In addition, if expiratory flow limitation is present, incomplete emptying may further increase end-expiratory lung volume and P_{pl}, reinforcing airway closure and contributing to the characteristic combination of hyperinflation and a reduced "baby lung".

Table 1. Pleural pressure (P_{es}) measurements in mechanically ventilated ARDS patients. Data extracted from the studies of Talmor [18], Beitler [19] and Kassis [20]. Cited variables are tidal volume, *TV*, End-Expiratory and End-Inspiratory pleural pressures, *EEPpl* and *EIPpl* and plateau pressure. The thorax wall compliance (C_{TW}) and the extra volume above FRC (Extra V>FRC) were calculated form the provided data.

Author	Series	N	*TV* (ml)	*EEPpl* (mbar)	*EIPpl* (mbar)	PEEP (mbar)	Plateau (mbar)	C_{TW} (ml/mbar)	Extra V > FRC (ml)
Talmor	P_{es} guided (base)	30	484	17.2	21.2	14.0	29	121	2807
	Conventional (base)	30	491	16.9	20.7	15.0	29	129	2959
	P_{es} guided (72 h)	30	472	18.4	21.7	18.0	28	143	3490
	Conventional (72 h)	30	418	14.3	17.9	12.0	25	116	2357
Beitler	P_{es} guided	102	396	16.0	19.0	14.0	28	132	2905
	Emperical PEEP	98	362	15.0	18.0	12.5	27	121	2531
Kassis	Day 1	40	360	13.7	16.1	13.5	25	150	2955
	Day 3	38	390	13.0	15.9	13.0	24	134	2546

From a clinical perspective, it may be useful to consider whether the reduction in ventilated lung volume is predominantly driven by inflammatory consolidation or by pressure-dependent airway closure. Bedside physiological markers such as the stress index and the recruitment-to-inflation (R/I) ratio may provide indirect insights into this distinction. The stress index, derived from the shape of the airway pressure–time curve during constant-flow inspiration, may suggest intratidal recruitment when compliance increases during inflation. The R/I ratio estimates the proportion of volume gain with higher PEEP that is attributable to recruitment rather than further inflation of already open units.

For example, a high recruitability, reflected by an elevated R/I ratio, may indicate that non-aerated regions can be reopened, whereas a low recruitability may be consistent with consolidated tissue or regions that remain closed due to persistent compressive forces. However, this distinction remains imperfect, as airway closure and inflammation frequently coexist and interact.

This underscores the importance of considering the mechanical environment, particularly pleural pressure, when interpreting the “baby lung” concept at the bedside.

8 Improvement by Reduction of Pleural Pressure

Experimental and clinical observations support the importance of P_{pl} in determining lung mechanics and injury. In a porcine model, Yoshida et al. [24] demonstrated that continuous negative abdominal pressure significantly reduced the severity of VILI. By lowering P_{pl}, this intervention reduced the compressive load on the lung and improved aeration of dependent regions.

More recently, Xiong and colleagues [25] applied negative pressure around the abdomen to limit and resolve postoperative atelectasis, further supporting the physiological rationale of external decompression of the thorax.

These findings are consistent with the broader physiological principle that reduction of P_{pl} facilitates airway patency and lung expansion. Interventions that decrease P_{it}—such as negative pressure applied externally or preservation of spontaneous inspiratory effort—tend to counteract airway closure and promote recruitment.

Spontaneous breathing during assisted ventilation illustrates this mechanism, as does Neurally Adjusted Ventilatory Assist [26]. Inspiratory muscle activity lowers P_{pl} and may partially offset the rise in P_{pl} induced by the ventilator. In this way, part of the required pressure is generated by the diaphragm rather than imposed via the airway, limiting increases in compressive load within the thorax.

Prone positioning provides a clinically well-established example of the beneficial effects of reducing P_{pl}. When applied correctly—i.e., with the abdomen allowed to hang freely—abdominal pressure on the diaphragm is reduced, permitting caudal displacement of the diaphragm and lowering P_{pl}, particularly in dependent lung regions. This reduction in compressive load promotes more homogeneous ventilation and facilitates recruitment.

The physiological and clinical benefits of prone positioning in ARDS, including improved oxygenation and reduced mortality, have been demonstrated in the PROSEVA trial by Guérin et al. [27]. While these effects are commonly attributed to improved ventilation–perfusion matching and redistribution of lung densities, the associated reduction in P_{pl} may, at least in part, represent a key underlying mechanism contributing to the improved homogeneity of ventilation observed during prone positioning.

Together, these observations support the concept that reducing P_{pl} is not merely a theoretical consideration but a practical means of improving lung function and mitigating injury.

9 Absorption Atelectasis and Pulmonary Edema

Once a lung unit has become isolated by airway closure, gas absorption may convert functional exclusion into persistent atelectasis. Oxygen is gradually absorbed into the pulmonary capillary blood, reducing alveolar gas volume and lowering P_{alv}. If insufficient poorly soluble gas remains, the alveolus may collapse completely. This is the mechanism of absorption atelectasis emphasized by Hedenstierna [28] and others and explains why high inspired oxygen fractions may aggravate collapse in poorly ventilated lungs.

The subsequent fate of such a collapsing unit is governed not only by gas dynamics but also by fluid balance across the alveolo-capillary barrier. This balance is described by the Starling equation:

$$J = K[(P_1 - P_2) - \sigma(\pi_1 - \pi_2)] \tag{4}$$

where P denotes hydrostatic pressure, π oncotic pressure (largely determined by plasma proteins such as albumin), K the filtration coefficient, and σ the reflection coefficient.

Under normal conditions, hydrostatic and oncotic forces are balanced, resulting in minimal net fluid flux. However, a decrease in P_{alv} due to gas absorption alters the local hydrostatic gradient across the alveolar wall. This shift favours movement of fluid from the interstitium into the alveolar space.

As a result, the gas volume lost by absorption may be replaced by liquid, stabilizing the collapsed state. In this way, airway closure not only initiates atelectasis, but may also promote its persistence through fluid accumulation [29].

10 Implications for Ventilation Strategy

These considerations suggest that lung-protective ventilation should not focus exclusively on tidal volume reduction [30]. An equally important goal may be limitation of excessive P_{pl} and P_{it}.

PEEP should be interpreted as a compromise between airway stabilization and tissue compression. AOP should be used as an indicator of closure, but its absence not as proof of full reopening. Flow-controlled ventilation deserves attention because gradual pressure change may reduce peripheral exclusion.

Preservation of spontaneous inspiratory effort, when well synchronized with ventilator support, may also be beneficial because diaphragmatic activity can partly substitute for ventilator-generated pressure and thereby limit the rise in P_{pl}. By contrast, vigorous inspiratory effort against a closed system may generate very negative P_{alv}'s and promote edema.

Finally, NPV and related decompressive approaches merit renewed consideration. By lowering P_{pl} rather than raising P_{aw}, NPV expands the lung while reducing parenchymal compression and promoting peripheral airway patency. Historical observations, experimental data, and recent clinical applications of extra-thoracic or abdominal negative pressure all support the physiological rationale for revisiting this principle with modern monitoring techniques.

11 Conclusions

Airway closure during mechanical ventilation should not be regarded merely as an incidental or late phenomenon. It is a predictable mechanical consequence of elevated absolute pressure around the parenchyma, especially in dependent regions and in lungs with reduced compliance or increased chest wall load.

The distinction between P_{tp} and absolute P_{it} is therefore crucial. During PPV, the rise in P_{aw} is accompanied by a rise in P_{pl}, so that inflation occurs under conditions of increased parenchymal compression. This environment promotes peripheral airway closure, impaired recruitment, gas trapping, absorption atelectasis, and possibly pulmonary edema. In contrast, spontaneous breathing and NPV expand the lung while lowering the surrounding pressure.

Recognizing airway closure as a consequence of lung tissue compression may help reinterpret several familiar clinical phenomena, including AOP, PEEP responsiveness, delayed pneumothorax, hyperinflation, and the "baby lung". It also suggests that future lung-protective strategies should pay greater attention not only to volume, but to the absolute pressure environment within which that volume is delivered.

Importantly, airway closure should not be viewed solely as a pathological phenomenon. Under physiological conditions, it likely serves a protective role by limiting ventilation of regions where effective gas exchange is not beneficial and by preventing excessive local stress. The paradox arises when this inherently protective mechanism is exposed to an altered mechanical environment. During positive pressure ventilation, elevated intrathoracic pressure transforms airway closure from a regulated, adaptive process into a widespread and persistent phenomenon, contributing to gas trapping, impaired recruitment, and lung injury. In this context, what is normally protective becomes pathological.

ABBREVIATIONS

The following abbreviations are used in this manuscript:

ARDS Adult Respiratory Distress Syndrome

PEEP Positive End Expiratory Pressure

COPD Chronic Obstructive Pulmonary Disease

FRC Functional Residual Capacity

TV Tidal Volume

NPV Negative Pressure Ventilation

PPV Positive Pressure Ventilation

P_{alv} Alveolar pressure

P_{tp} Transpulmonary pressure ($= P_{alv} - P_{pl}$) opposite to $P_L = P_{aw} - P_{pl}$

P_{aw} Airway pressure

P_{pl} Pleural pressure

P_{it} Intrathoracic pressure $= (P_{aw} + P_{pl})/2$

C_{lungs} Compliance of the lungs

C_{TW} Compliance of the thorax wall

EEPpl End-Expiratory pleural pressure

EIPpl End-Inspiratory pleural pressure

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Calcium Hydroxide Induced Apexification in an Immature, Non-Vital Permanent Tooth – A Case Report

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ABSTRACT

The purpose of the present manuscript is to show case successful formation of apical barrier in an immature young permanent tooth following dental trauma using calcium hydroxide as an intra-canal medicament. Following 9 month follow-up, apical barrier formation and absence of periapical radiolucency was evident on intraoral periapical radiographic examination with clinical absence of signs and symptoms. This case report strongly confirms that calcium hydroxide still remains as age old, gold standard medicament in inducing apical barrier formation thereby facilitating a dental practitioner to perform smooth root canal treatment.

Index Terms: Apexification • Apical barrier formation • Blunder bus canal • Calcium hydroxide • Immature • non-vital tooth

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CASE REPORT

Calcium Hydroxide Induced Apexification in an Immature, Non-Vital Permanent Tooth - A Case Report

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Abstract

The purpose of the present manuscript is to show case successful formation of apical barrier in an immature young permanent tooth following dental trauma using calcium hydroxide as an intra-canal medicament. Following 9 month follow-up, apical barrier formation and absence of periapical radiolucency was evident on intraoral periapical radiographic examination with clinical absence of signs and symptoms. This case report strongly confirms that calcium hydroxide still remains as age old, gold standard medicament in inducing apical barrier formation thereby facilitating a dental practitioner to perform smooth root canal treatment.

Keywords: *Apexification, Apical barrier formation, Blunder bus canal, Calcium hydroxide, Immature, non-vital tooth*

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1 Introduction

Occurrence of dental trauma is more common in children and teenagers due to frequent fall and sport activities [1,2]. When dental trauma involves young permanent teeth, its management is a great challenge not only for a paediatric dentist but for all dental specialists [1-3]. Young permanent teeth exhibit wide pulp canal, wide open apex and thin dentin walls. Therefore, using conventional endodontic treatment comprising root canal treatment is not possible as it does not provide tight hermetic seal [4,5]. As a result, to obtain apical barrier formation, calcium hydroxide cement was introduced to overcome this issue, which successfully resulted in apical barrier formation [6]. However, calcium hydroxide exhibited various disadvantageous like loss of root dentinal fluid, long-term follow-up for barrier formation and brittleness leading to the fracture of the root on long term usage. To overcome the short comings of calcium hydroxide material Mineral Trioxide Aggregate Cement (MTA) was introduced in the endodontic field which provided immediate apical plug barrier so that immediate root canal treatment can be performed. However, MTA has also showed few disadvantages making it inappropriate in case of large apical opening cases [7]. The 'quest' went on and finally resulted in introduction of different alternative techniques [8-12]. However, the newly introduced alternatives requires increased cost, equipment and protocols. Therefore, to render immediate, cost-effective and appropriate justice to the patient, practitioner has to practice sometimes the well-established treatment protocol like calcium hydroxide apexification. The purpose of the current manuscript is to show case successful formation of calcium hydroxide introduced apical barrier formation in a 10 year old Indian male patient following dental trauma.

2 Case Report

A 10 year old male patient reported to the department of Pediatric and Preventive Dentistry complaining of pain in the upper front tooth since fifteen days. Patient was moderately built and well nourished. Patient reported a past history dental trauma due to fall one year back. Following clinical examination, Ellis' class IV fracture pertaining to permanent maxillary right central incisor was present. Tooth was discoloured and found tender to percussion test with absence of clinical gingival abscess. To rule out the condition of the root and apical region, patient was subjected to radiographic examination. On intraoral periapical radiograph (IOPA), incomplete root formation and wide open apex was noticed. There was periapical radiolucency measuring 1.5x1.5 mm size (Figure 1). Considering clinical and radiographic findings, a treatment plan consisting of calcium hydroxide apexification was planned.

In the first appointment, an access cavity was prepared with a straight line entry access into the root canal. Working length was determined within 1 mm of the radiographic apex. Following this, complete debridement of canal was done followed by thorough irrigation with normal saline. Later, canal was dried using paper points. Calcium hydroxide powder was mixed with normal saline and this mixture was placed into the canal and pushed to the short of apex using plugger. Finally, access opening was

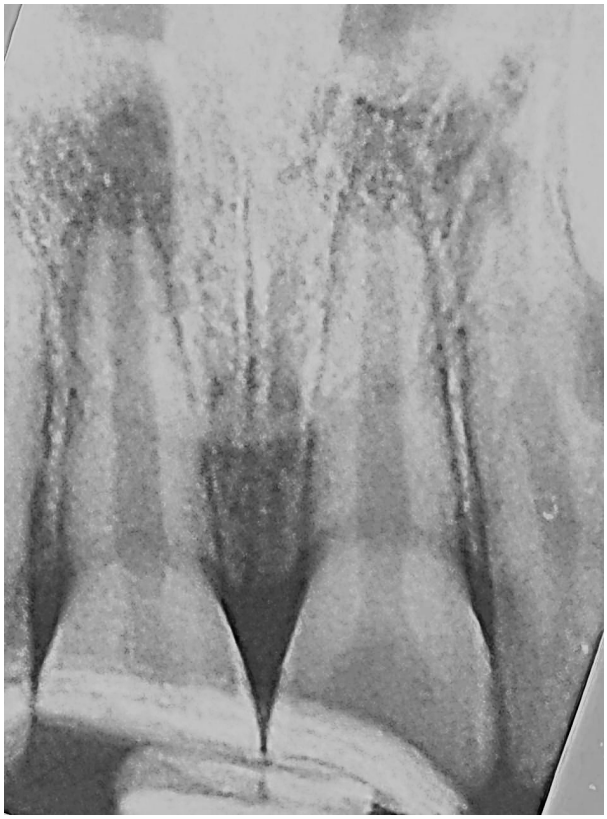

Figure 1. Permanent maxillary right central incisor with open apex and periapical radiolucency

closed using glass ionomer cement. Patient was followed up every 3 months once for a period of 9 months (Figures 2, 3 and 4). Following 9 months follow-up, radiographic examination was performed which showed complete formation of the root apex with complete periapical healing, absence of periapical radiolucency and with no clinical signs and symptoms (Figure 4). Presence of apical barrier formation was confirmed using a 30 size paper point which provided a resistant or stop and absence of haemorrhage, sensitivity and exudate. Patient was scheduled for further treatment.

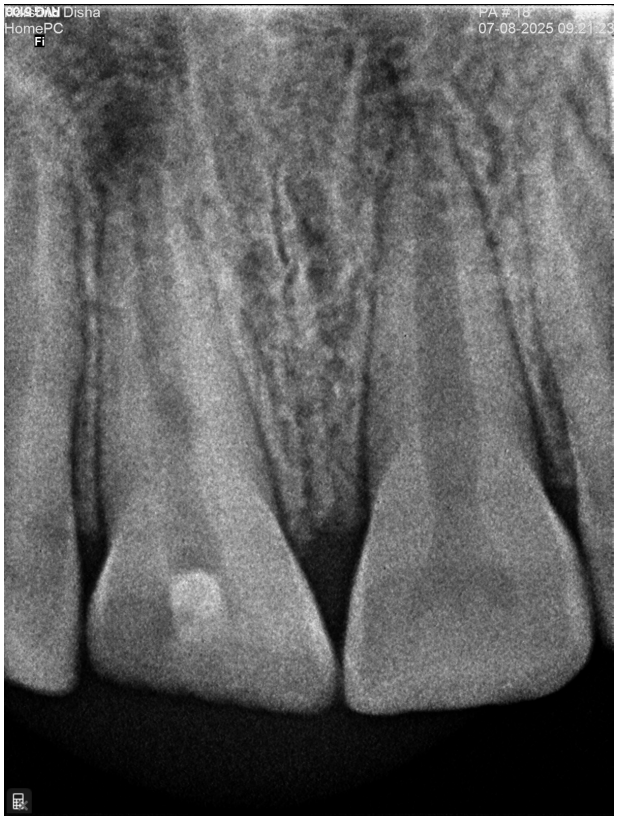

Figure 2. 3 month post-operative radiograph of 11

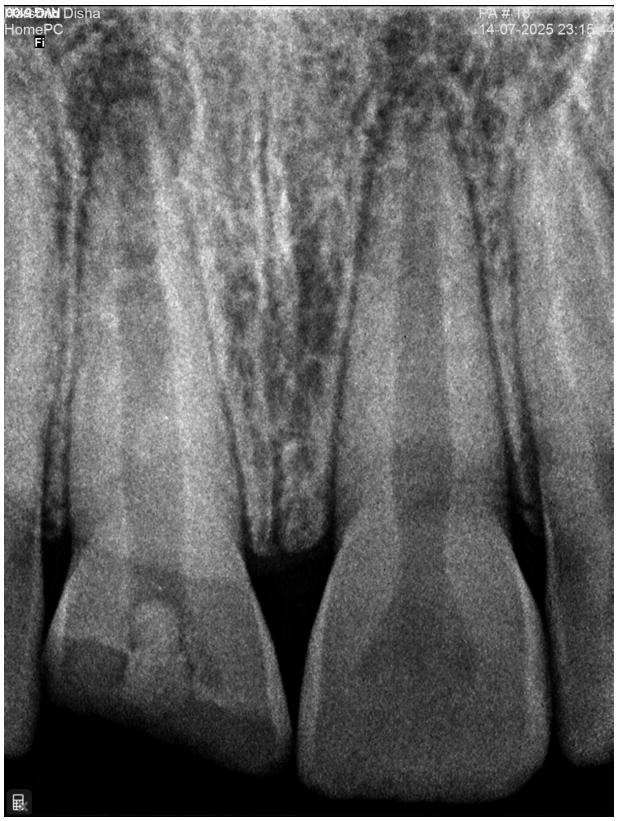

Figure 3. 6 month post-operative radiograph of 11

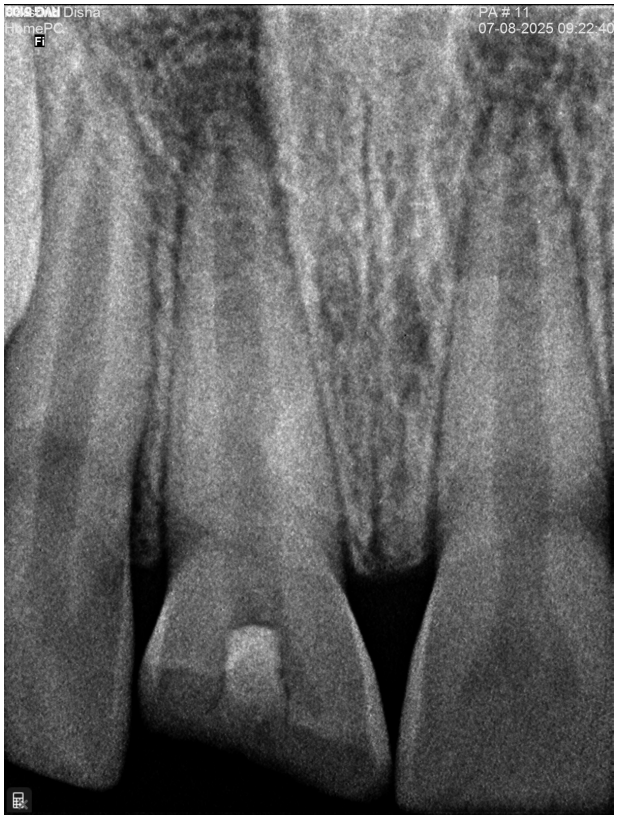

Figure 4. 9 month post-operative radiograph showing apical barrier formation and periapical healing in 11.

3 Discussion

The completion of root development and closure of the root apex takes place till 3 years following eruption of the tooth. Dental traumatic injuries affect 30% of children and often result in pulpal inflammation and necrosis with subsequent incomplete development of dentinal wall and root apices. The treatment of pulpal injury during this period enables a significant challenge for all dental practitioners. The importance of careful case diagnosis and accurate pulpal treatment are very essential and should not be overemphasized. The standard/golden rule of the endodontic practice is to debride and obturate the root canals efficiently and three dimensionally as possible in an appropriate amount of time and appointments. Long back, the clinical management of the blunder buss canal usually consisted of surgical approach constituting apicectomy procedure for placement of an apical seal into the fragile, open and flaring apex. But, apicectomy technique further reduces the root length resulting in a very unfavourable crown root ratio. Therefore, the treatment of choice for necrotic young permanent teeth is apexification which involves induction of apical closure to produce more favourable conditions for conventional root canal treatment [1-4]. The most commonly suggested medicament of choice is calcium hydroxide. In 1964, Kaiser, a great pioneer and researcher was the one who proposed that this material mixed with camphorated parachlorophenol (CMCP) would stimulate the formation of a calcified barrier across the root apex [13].

Extensive review of pediatric endodontic literature exhibited numerous materials for apexification procedure comprising of calcium hydroxide in combination with sterile water, saline, local anesthetic, zinc oxide paste with cresol and iodoform, camphorated paracholorophenol, tricalcium phosphate, chlorhexidene, cresatin and polyantibiotic paste. However, all these different materials have shown some promising results. Although recent novel techniques like use of MTA and regenerative endodontic procedures have been introduced calcium hydroxide still remains as a gold standard in management of open apex in immature permanent teeth [7-12]. Different factors which contribute to the success and wide acceptance of calcium hydroxide in the literature are its easy availability for clinician and affordability for patients and increased success rate [13].

The mechanism behind the barrier formation is associated with the alkalinity of non-setting calcium hydroxide which stimulates the formation of mineralized and fibrous tissue by the granulation tissue cells in the apical part of the root canal. It also acts as disinfectant and stimulates the physical barrier. Other postulated mechanisms of calcium hydroxide are presence of high calcium concentration which increases the activity of calcium dependent pyrophosphatase, direct effect on the apical and periapical soft-tissue, antibacterial activity and high pH, which may activate alkaline phosphatase activity. The final mineralized tissue formed consists of osteodentine, bone, osteocementum or sometimes combination of the three. The newly formed apical barrier prevents the passage of toxins and bacteria into periapical tissues from root canals. The calcific barrier formed can be either a complete or an incomplete hard tissue bridge at the root end or a few millimetres short of it. In case series reported by Nagaveni et al [6], the barrier was formed at the apex in both cases. In one case it appeared as a radiopaque line measuring 1 mm and in another case it was 2 mm thick. The calcific barrier formed is confirmed clinically by using a paper point inserting into the canal and felt for ‘resistance’ or ‘stop’ and there should be absence of intracanal

bleeding, exudate or absence of pain. The same procedure was followed in the present case too. In the case presented here calcific barrier was formed across the root apex. From previous report [6] and from the present case, it is evident that placement of calcium hydroxide inside the root canal is very important for apical barrier formation to be at the apex. If the cement is placed short of the apex, the barrier will form short of the apex. Therefore, proper working length determination is highly essential so that the cement can be easily placed exactly at the apex or slightly into periapical region. This procedure finally results in a proper barrier at the root apex not short of apex or with incomplete apex.

There are various opinions regarding the concentration and number of calcium hydroxide dressing for the apical barrier formation. A pioneer author based on his experiments suggested that the amount of calcium hydroxide in the single root canal dressing was sufficient to initiate and complete the barrier in 92% of the teeth [14]. Chosack et al [15] explained that repeated root filling is not required as CAOH is only required to initiate healing process. It has to be replaced if there are any symptoms or when dislodgment of the medicament happens. Nagaveni and co-authors reported two cases in that apical barrier formation happened following only single dressing change in one case. The frequency of CAOH dressing change is one among different variables which is under clinician's control and which has an effect on the speed of barrier formation. There are various studies showcasing that, when the frequency of change was low, rapid barrier formation was seen and there was also some studies where the frequency of dressing change was high, there was slow barrier formation [16-20]. Hence it is concluded that, if the root apex is disturbed by repeated instrumentation and dressing changes then the time required for apex formation prolongs. Therefore it was also suggested that a single dressing is sufficient to stimulate the apical barrier formation. Sheehy and Roberts suggested that use of calcium hydroxide for apical barrier formation was successful in 74-100% of cases and the average time for apical barrier formation was ranging from 5 months to 20 months [16]. The two cases reported by Nagaveni et al showed that the time required for apical barrier formation was 9 months to 2 years [6]. The present case strongly witness on successful closure of root apex in an immature non-vital permanent tooth using an age old, gold standard simple technology of CAOH assisted apexification. The apical barrier was formed after 7 months following calcium hydroxide apexification.

4 Conclusion

Based on the present case report and from existing literature, it was concluded that calcium hydroxide medicament still remains a gold standard in inducing apical barrier formation in the management of necrotic, immature young permanent teeth. Although time required is long, it is easy to perform by a practitioner, cost-effective to the patients thereby providing successful results. However, long term clinical trials are essential to compare longevity of the tooth with other endodontic procedures dealing with wide open apex.

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Effectiveness of Recombinant Enzymes in Cellulite Treatment: A Case Report

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ABSTRACT

Cellulite is a common aesthetic concern that may significantly impact on individuals' self-image and quality of life. Despite being a non-threatening condition, it may have a negative effect on the psychological well-being of affected individuals. This condition is multifactorial and involves several physiopathology pathways. The role of enzymes in the management of cellulite is a novel approach, particularly lipase and collagenase, which play key roles in adipocyte size reduction and collagen degradation, respectively. The potential of high-molecular-weight hyaluronic acid to promote tissue repair and regeneration is also highlighted. Our case report describes the effectiveness of an association of recombinant enzymes and high-molecular-weight hyaluronic acid by reducing cellulite manifestations in a patient, with a history of multiple unsuccessful treatments, showing visible improvements from the initial treatment session. The importance of understanding the complex physiopathology of cellulite and choosing a targeted approach is emphasized.

Index Terms: recombinant enzymes • cellulite • collagenase • lipase • lyase • hyaluronic acid

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CASE REPORT

Effectiveness of Recombinant Enzymes in Cellulite Treatment: A Case Report

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Abstract

Cellulite is a common aesthetic concern that may significantly impact on individuals' self-image and quality of life. Despite being a non-threatening condition, it may have a negative effect on the psychological well-being of affected individuals. This condition is multifactorial and involves several physiopathology pathways. The role of enzymes in the management of cellulite is a novel approach, particularly lipase and collagenase, which play key roles in adipocyte size reduction and collagen degradation, respectively. The potential of high-molecular-weight hyaluronic acid to promote tissue repair and regeneration is also highlighted. Our case report describes the effectiveness of an association of recombinant enzymes and high-molecular-weight hyaluronic acid by reducing cellulite manifestations in a patient, with a history of multiple unsuccessful treatments, showing visible improvements from the initial treatment session. The importance of understanding the complex physiopathology of cellulite and choosing a targeted approach is emphasized.

Keywords: *recombinant enzymes, cellulite, collagenase, lipase, lyase, hyaluronic acid*

Correspondence: Jorge López Berroa

1 Introduction

Cellulite represents one of the most prevalent and undesirable aesthetic concerns among women[1, 2]. It is a multifactorial condition that affects 85% of post-pubertal females and is characterized by a dimpled skin appearance. Several predisposing factors have been associated with cellulite, including genetic predisposition, gender, ethnicity, eating habits, sedentary lifestyle, smoking, and pregnancy[2, 3]. In addition, multiple hypotheses have been proposed to explain the physiopathology of cellulite, including structural and architectural alterations, anomalies of the topographic anatomy of fatty tissue, differences in the distribution of white and brown adipose tissue, vascular alterations, and hormone-dependent reactive processes, especially those linked to estrogens[2, 4].

From a psychological perspective, the impact of cellulite on individuals' self-image and quality of life is significant, even though it does not pose a direct physical threat. Cellulite may considerably influence quality of life, as demonstrated by validated scores in 84.6% of affected participants in a study[5]. In addition, another study revealed that 70% of patients who had received treatment for cellulite perceived a substantial positive impact on their lives[6].

Understanding the etiology, physiopathology, and severity of cellulite is highly important for the development of targeted treatments. In aesthetic medicine, cellulite management involves pharmacological agents, device-based therapies, and, in selected cases, surgical correction[2, 7]. Recent advances in protein engineering and molecular biology have led to the synthesis of recombinant enzymes. In general terms, these enzymes act on the skin promoting tissue remodeling and improving skin texture, elasticity, and overall appearance[8]. Pbserum HA 1.5 Medium consists of the combination of three recombinant enzymes (collagenase, lipase and lyase) together with high-molecular-weight hyaluronic acid (HMWHA). Although each enzyme exerts a distinct biological effect, their combined action produces synergistic outcomes in tissue regeneration and remodeling. This case report is aimed to show the beneficial effects of the therapeutic application of these recombinant enzymes in the treatment of cellulite.

2 Case Report

A 59-year-old female patient was evaluated in the aesthetic medicine clinic. Her history was remarkable for a healthy lifestyle, including daily physical training. In the past five years, she had several evaluations for cellulite, with multiple treatments (radiofrequency, carboxytherapy, manual massage, and lipomassage). The physical examination revealed grade 4 cellulite according to the Nuremberg-Muller scale, mainly affecting intergluteal and trochanteric areas (Fig. 1a, 1b). After obtaining informed consent and considering the patient's expectations and goals, a tailored therapy with combined recombinant enzymes and HMWHA (pbserum HA 1.5 Medium, Proteos Biotech S.L.) was suggested.

The application was performed in 3 sessions, scheduled at 15-day intervals. During the first session, a final volume of 20 ml (1.5 ml of reconstituted product, 0.5 ml of 2% lidocaine without epinephrine, and 18 ml of dilution solution) was applied in the buttock, infragluteal, and trochanteric areas, using a 30-gauge needle. The area was gridded, and a dose of 0.1 ml was applied from deep to superficial in retroinjection symmetrically, with 1 cc points every 2 cm. A similar strategy was used on the areas with greater fat tissue hypertrophy.

In the first follow-up visit, a significant improvement in cellulite appearance was already reported and a new treatment session was performed. Thirty days after the first visit, skin appearance and laxity

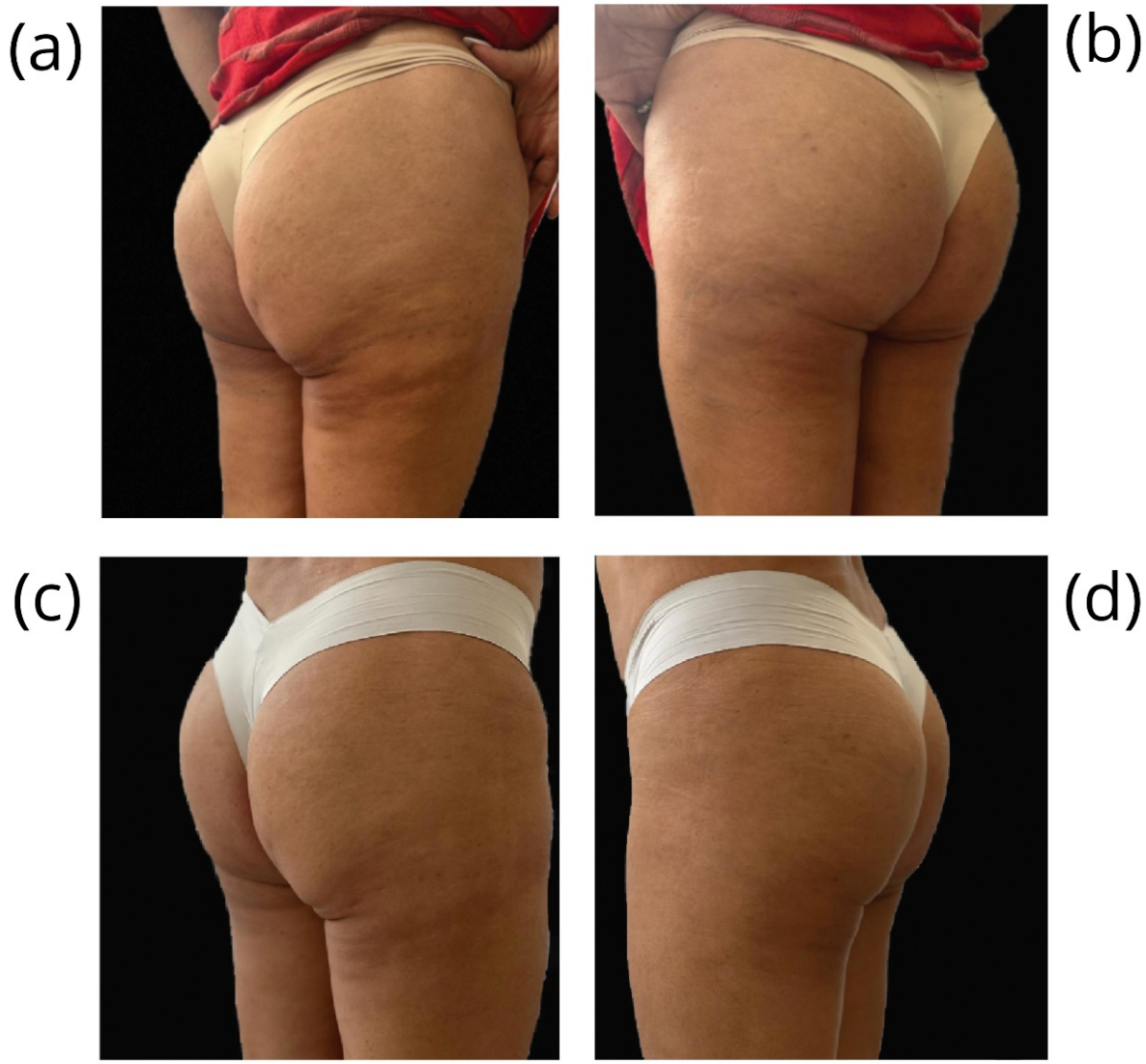

Figure 1. Changes in the appearance of the patient's skin: (a) and (b) Basal conditions, grade 4 cellulite (Nurenberg-Muller scale); (c) and (d) After 45 days from the first session of treatment with pbserum HA 1.5 Medium.

were further improved. In this final session, a similar protocol was considered. After 45 days from the first session (Fig. 1c, 1d), the improvement of cellulite was notable, and the patient's weight remained unchanged from the beginning of the treatment.

3 Discussion

Early studies using thigh and buttock biopsies showed that cellulite histopathology is characterized by fibrotic and fibrosclerotic septa, changes in tissue thickness, and protrusion of subcutaneous fat into the dermis. These alterations are attributed to the progressive pressure of fat tissue against the fibrous septa, which transmits tension to the dermis and produces the characteristic uneven skin appearance[9]. Since conventional therapies have limited effectiveness on these structures, there is a clear need for new strategies capable of remodeling the septa and restoring normal tissue architecture. By contrast, combined recombinant enzymatic therapy provides a comprehensive approach to cellulite management, particularly by targeting its pathogenic mechanism. The enzymes included in pbserum HA 1.5 Medium, which are commonly present in connective tissues such as the skin, tendons, blood vessels, and bones, improve the fibrous septa that contribute to the dimples and depressions associated with cellulite. Lipase facilitates the hydrolysis of triglycerides into free fatty acids and glycerol, resulting in adipocyte size reduction and contributing to the improvement of fat cell protrusion into the dermis and the visible skin irregularities[10]. Collagenase cleaves the specific Pro-X-Gly-Pro bonds prevalent in collagen. By degrading native collagen fibrils, this enzyme plays a significant role in remodeling structural abnormalities and restoring the integrity of the collagen network[11]. Subcutaneous injections of collagenase in minipigs were also seen to induce a decrease in the thickness of adipose tissue[12]. And lyase, an enzyme responsible for the enzymatic degradation of GAGs, increases the permeability of the skin and connective tissue, facilitating the penetration and spread of collagenases through dense extracellular structures[13]. The combination of these three enzymes

with HMWHA offers a promising therapeutic potential for addressing cellulite[9, 11, 13].

It has been shown that hyaluronic acid, a hydrophilic GAG, accumulates during adipocyte maturation and is associated with increased expression of adipogenic markers[14]. HMWHA enhances hydration and structural integrity of the extracellular matrix, promoting intercellular signaling, cellular proliferation, migration, and adhesion during tissue repair processes[15].

The clinical improvement observed in our patient adds evidence about the effectiveness of recombinant enzymes in enhancing the appearance of cellulite. This targeted application directly addressed the specific characteristics of cellulite, resulting in a significant improvement that was evident from the first session. Our results highlight the potential of enzymatic therapy as a valuable intervention for cellulite management. Further large-scale, randomized and rigorously conducted studies are warranted to obtain more robust and reliable data.

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Evaluating Midwives' Knowledge and Attitudes Regarding Pre-Eclampsia Management at Presbyterian Hospital

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ABSTRACT

Background: Pre-eclampsia is a major contributor to maternal and perinatal morbidity and mortality globally and in Ghana. Midwives play a critical role in the early detection and management; however, their knowledge, attitudes, and the challenges they encounter influence the quality of care. Methodology/Principal Findings: A descriptive cross-sectional study was conducted among 50 midwives using a structured self-administered questionnaire. Data were analyzed using SPSS version 26. Descriptive statistics summarized demographic characteristics, knowledge, attitudes, barriers, and recommendations. Chi-square tests and logistic regression examined associations between demographic variables and knowledge/attitude levels. The majority of respondents were aged 20–39 years (70.0%), with 54.0% having 1–3 years of experience, and 86.0% had received prior training in pre-eclampsia management. Knowledge was generally high, with 88.0% recognizing hallmark symptoms and 84.0% identifying magnesium sulfate as the first-line anticonvulsant. Attitudes were positive; 68.0% strongly agreed that pre-eclampsia training should be mandatory. Key barriers included limited patient awareness (86.0%), understaffing (70.0%), and inadequate diagnostic tools (58.0%). Years of experience were significantly associated with knowledge level (chi-square = 19.470, p=0.003), while logistic regression showed work unit as a significant predictor of knowledge level (p = 0.037).

Conclusion: Midwives exhibited good knowledge and positive attitudes toward pre-eclampsia

Index Terms: Pre-eclampsia (PE) • Midwives • Knowledge • Attitudes • Barriers • Ghana

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Abstract

Background: Pre-eclampsia is a major contributor to maternal and perinatal morbidity and mortality globally and in Ghana. Midwives play a critical role in the early detection and management; however, their knowledge, attitudes, and the challenges they encounter influence the quality of care. Methodology/Principal Findings: A descriptive cross-sectional study was conducted among 50 midwives using a structured self-administered questionnaire. Data were analyzed using SPSS version 26. Descriptive statistics summarized demographic characteristics, knowledge, attitudes, barriers, and recommendations. Chi-square tests and logistic regression examined associations between demographic variables and knowledge/attitude levels. The majority of respondents were aged 20–39 years (70.0%), with 54.0% having 1–3 years of experience, and 86.0% had received prior training in pre-eclampsia management. Knowledge was generally high, with 88.0% recognizing hallmark symptoms and 84.0% identifying magnesium sulfate as the first-line anticonvulsant. Attitudes were positive; 68.0% strongly agreed that pre-eclampsia training should be mandatory. Key barriers included limited patient awareness (86.0%), understaffing (70.0%), and inadequate diagnostic tools (58.0%). Years of experience were significantly associated with knowledge level (chi-square = 19.470, p=0.003), while logistic regression showed work unit as a significant predictor of knowledge level (p = 0.037).

Conclusion: Midwives exhibited good knowledge and positive attitudes toward pre-eclampsia management, though systemic barriers constrain effective care. Strengthening in-service training, improving diagnostic and therapeutic resources, and enhancing patient education are recommended to optimize outcomes.

Keywords: *Pre-eclampsia (PE), Midwives, Knowledge, Attitudes, Barriers, Ghana*

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1 Introduction

Pre-eclampsia is a leading cause of adverse maternal and perinatal outcomes worldwide, contributing significantly to global maternal and neonatal morbidity and mortality. The condition affects approximately 2%–8% of pregnancies and is responsible for 14% of maternal deaths and 12% of perinatal mortality globally [1] [2] [3] [4] [5]. Pre-eclampsia (PE) is characterized by new-onset hypertension after 20 weeks of gestation, typically accompanied by proteinuria, maternal organ dysfunction, or uteroplacental insufficiency [6]. Globally, the pathogenesis of PE is strongly linked to abnormal trophoblastic invasion of the uterine spiral arteries during placental development, resulting in placental ischemia, oxidative stress, and systemic endothelial dysfunction [7] [8] [9]. These disruptions contribute to the disease's complex multisystemic nature. PE remains more prevalent in low- and middle-income countries (LMICs), with rates seven times higher than in developed countries [10]. In Africa, prevalence rates range from 1.8% to 16.7% [11] [12], with Ghana reporting prevalence between 6.55% and 7.3% [13] [14]. The higher prevalence in LMICs is influenced by socio-economic disparities, limited access to healthcare, and a range of risk factors, including early pregnancies, multiparity, advanced maternal age, anemia, and infections [15]. In Ghana, PE is a major contributor to maternal and neonatal mortality, with approximately 25% of maternal deaths attributed to hypertensive disorders in tertiary hospitals [16] [17]. Although clinical guidelines have been adopted, systemic challenges such as delayed diagnoses, inconsistent adherence to protocols, and insufficient training of healthcare workers continue to hinder effective management of PE [18] [19]. Midwives have played and continue to play a critical role in the early detection and management of PE, especially in LMICs, where they often serve as the first point of contact for pregnant women. In Ghana, midwives operate at all levels of the healthcare system, offering a range of services including antenatal care, blood pressure monitoring, administration of antihypertensive medications, and referral of high-risk cases [20] [21]. However, evidence suggests many midwives demonstrate inadequate knowledge and skills in managing pre-eclampsia [22] [23] [24]. A study revealed that only 50% of midwives in Ghana's secondary and primary health facilities demonstrated competency in managing pregnancy complications [25]. Ghana has made significant strides in increasing the midwifery workforce as part of its commitment to achieving universal health coverage (UHC). However, this increase in numbers has not necessarily resulted in improved quality of care, particularly in rural and underserved areas where PE-related complications remain prevalent [26] [27]. Although continuing professional development (CPD) programs are available for midwives, these initiatives remain

inconsistently implemented, and gaps in pre-service training persist [26] [28] [29]. PE outcomes could be significantly improved with targeted training interventions that align with global guidelines. A well-trained cadre of midwives equipped with the knowledge, skills, and confidence to manage PE is essential for reducing maternal and neonatal mortality rates in Ghana. This study aimed to assess midwives' knowledge and attitudes at Presbyterian Hospital, Agogo, toward PE management to identify critical gaps and inform evidence-based recommendations for improving midwifery care.

2 Materials and Methods

2.1 Ethics Statement

The Research Committee, Presbyterian Hospital, Agogo, approved the study (APH/ADM/RES135/25)

2.2 Study Design and Location

This study adopted a descriptive cross-sectional design to assess interventions aimed at improving midwives' knowledge and attitudes toward PE management. This design was appropriate for obtaining a snapshot of midwives' current knowledge, attitudes, and challenges in pre-eclampsia care, enabling identification of gaps and areas for improvement. This study was conducted at the Presbyterian Hospital, Agogo, located in the Ashanti Region of Ghana. Established on March 21, 1931, the hospital has grown to become a major healthcare institution, recognized as the second largest hospital in the Ashanti Region and a referral centre for various healthcare facilities, including Konongo-Odumase Government Hospital and Juaso Government Hospital. Although officially designated as a district hospital, its size, scope of operations, and range of specialized services position it as a facility of regional hospital status. The hospital offers specialized care in surgery, ophthalmology, paediatrics, internal medicine, and obstetrics and gynaecology, making it a critical healthcare provider in the region. It also attracts patients from across Ghana and internationally, establishing itself as a leading mission hospital in the country. Given its stature as a referral and specialized care centre, Presbyterian Hospital, Asante Akyem Agogo, provided an ideal setting for this study, as its midwifery workforce manages a significant number of cases involving pregnancy complications, including pre-eclampsia.

2.3 Inclusion and Exclusion Criteria

Registered midwives actively providing antenatal, intrapartum, or postpartum care at Presbyterian Hospital, Agogo were included in the study. Midwives with a minimum of six months of clinical experience at the hospital were included in the study. Midwives willing to provide informed consent to participate were included in the study. Midwives unavailable during the data collection period were excluded from the study. Midwives in administrative roles with no direct patient care responsibilities were excluded from the study. A total of 50 midwives were included in the research.

2.4 Sample Size

A purposive sampling technique was employed to select midwives who are directly involved in antenatal, intrapartum, or postpartum care at the hospital. The sample size was determined using the Cochran formula:

$$n = \frac{Z^2 \cdot p \cdot (1 - p)}{e^2}$$

where: n = required sample size, Z = Z-score for a 95% confidence interval (1.96) p = estimated proportion of midwives with adequate knowledge of pre-eclampsia (assumed at 50% for maximum variability) and e = margin of error (5%). A 10% adjustment was made to account for non-responses, yielding a final sample size of 50 midwives.

2.5 Data Collection

A structured questionnaire was used to assess midwives' knowledge, attitudes, and practices related to pre-eclampsia. The questionnaire included sections on: Knowledge of pre-eclampsia risk factors, symptoms, and management, Attitudes toward the condition and its management, barriers and challenges in managing pre-eclampsia, and recommendations to help in the management of pre-eclampsia.

2.6 Procedure

Data was collected through face-to-face interviews and self-administered questionnaires. To enhance accuracy and completeness, a brief orientation was provided to participants before they completed the questionnaire.

3 Data Analysis

Data analysis was conducted using Statistical Package for Social Sciences (SPSS) Version 26.0. Frequencies, and percentages was used to summarize demographic characteristics, levels of knowledge, and attitudes. Chi-square tests was used to examine associations between selected demographic variables (training in pre-eclampsia management, level of education, years of experience) and knowledge or attitude. Logistic regression was further used to identify predictors of adequate knowledge and positive attitudes. A p-value of 0.05 was considered statistically significant.

4 Results

The results were organized into socio-demographic characteristics, knowledge levels, attitudes, perceived barriers, and recommendations. Inferential statistics, including chi-square tests and logistic regression, were also presented to assess associations and predictors. The majority of respondents (70.0%) were aged between 20 and 29 years, followed by 22.0% in the 30–39 years group. Only a small proportion were aged 40 years and above. In terms of years of professional experience, the largest proportion (54.0%) had 1–3 years of experience, while 28.0% had less than one year. Only 18.0% had more than four years of experience. Educational background revealed that nearly half (46.0%) of respondents held a Diploma qualification, while 40.0% had a Bachelor's degree, and only 4.0% had postgraduate training. Encouragingly, a majority (86.0%) reported having received training in pre-eclampsia management. Table 1 below presents the socio-demographic profile of 50 respondents who participated in the study.

4.1 Knowledge of Pre-eclampsia

Respondents were assessed on their knowledge of pre-eclampsia using structured questions covering definition, risk factors, hallmark symptoms, complications, treatment, and monitoring. The results are summarized in Tables 2–8 and illustrated in Figures 1–2.

All respondents (100%) correctly identified pre-eclampsia as a condition characterized by high blood pressure after 20 weeks of pregnancy, often with proteinuria or maternal organ dysfunction. Table 2 below shows participants' responses to the definition of pre-eclampsia.

Recognition of risk factors was varied: Chronic hypertension (90%), History of pre-eclampsia in a previous pregnancy (82%), Advanced maternal age> 35years (68%), and Multiple pregnancies (62%) were frequently selected. Nulliparity (first pregnancy) was the least identified (28%). Table 3 below shows participant response to the recognition of the risk factors of Pre-eclampsia

Table 1. Socio-Demographic Characteristics of Respondents

Variable	Category	Frequency (n)	Percentage (%)
Age Group	20-29	35	70.0
	30-39	11	22.0
	40-49	3	6.0
	50+	1	2.0
Years of Experience	<1 year	14	28.0
	1-3 years	27	54.0
	4-6 years	6	12.0
	>6 years	3	6.0
Educational Level	Certificate	5	10.0
	Diploma	23	46.0
	Bachelor's Degree	20	40.0
	Master's Degree or higher	2	4.0
Trained in Pre-eclampsia	Yes	43	86.0
	No	7	14.0
Work setting	ANC unit	19	38.0
	Labor & delivery unit	18	36.0
	PNC unit	3	6.0
	Rotates across all unit	10	20.0
Encounter with PE Cases	Rarely	5	10.0
	Occasionally	26	52.0
	Frequently	19	38.0
	Always	0	0.0
Total		**50**	**100**

Table 2. Definition of pre-eclampsia (Q7)

Question	Selected (n)=50	Selected (%)	Not Selected (n)=50	Not Selected (%)
Q7	50	100.0	0	0.0

Table 3. Risk Factors of Pre-eclampsia (Q8a-Q8e)

Question	Selected (n)=50	Selected (%)	Not Selected (n)=50	Not Selected (%)
Q8a	14	28.0	36	72.0
Q8b	31	62.0	19	38.0
Q8c	45	90.0	5	10.0
Q8d	34	68.0	16	32.0
Q8e	41	82.0	9	18.0

Table 4. Hallmark Symptoms (Q9a-Q9e)

Question	Selected (n)=50	Selected (%)	Not Selected (n)=50	Not Selected (%)
Q9a	43	86.0	7	14.0
Q9b	37	74.0	13	26.0
Q9c	44	88.0	6	12.0
Q9d	45	90.0	5	10.0
Q9e	15	30.0	35	70.0

Most respondents correctly identified high blood pressure >140/90mmHg (90%), proteinuria (88%), persistent frontal headache despite intake of analgesia (86%) and vision changes (74%) as hallmark symptoms. However, only 30% recognized excessive weight gain unrelated to diet. Table 4 below shows participant response to the hallmark symptoms of Pre-eclampsia.

Nearly all respondents (98%) recognized eclampsia (seizures), and 74% identified preterm birth as complications. However, fewer identified placental abruption (46%), maternal stroke (46%), and fetal growth restriction (42%). Table 6 below shows participants' responses to the complications of untreated Pre-eclampsia.

A large majority (84%) identified magnesium sulfate as the first-line drug for preventing seizures in severe pre-eclampsia. However, 16% did not know. Table **??** below shows participant response to the first line treatment of Pre-eclampsia.

Most respondents (88%) correctly stated that pre-eclampsia typically develops after 20 weeks of gestation. However, 12% did not know. Table 7 below shows participant response to the gestational age Pre-eclampsia occurs.

A majority (86%) reported that blood pressure should be monitored at least every 4–6 hours in severe pre-eclampsia cases. However, 14%

Table 5. Complications of Untreated Pre-eclampsia (Q10a–Q10e)

Question	Selected (n)=50	Selected (%)	Not Selected (n)=50	Not Selected (%)
Q10a	49	98.0	1	2.0
Q10b	21	42.0	29	58.0
Q10c	37	74.0	13	26.0
Q10d	23	46.0	27	54.0
Q10e	23	46.0	27	54.0

Table 6. Complications of Untreated Pre-eclampsia (Q10a–Q10e)

Question	Selected (n)=50	Selected (%)	Not Selected (n)=50	Not Selected (%)
Q11	42	84.0	8	16.0

Table 7. First-line Treatment (Q11)

Question	Selected (n)=50	Selected (%)	Not Selected (n)=50	Not Selected (%)
Q12	44	88.0	6	12.0

Table 8. Monitoring of Blood Pressure (Q13)

Question	Selected (n)=50	Selected (%)	Not Selected (n)=50	Not Selected (%)
Q13	43	86.0	7	14.0

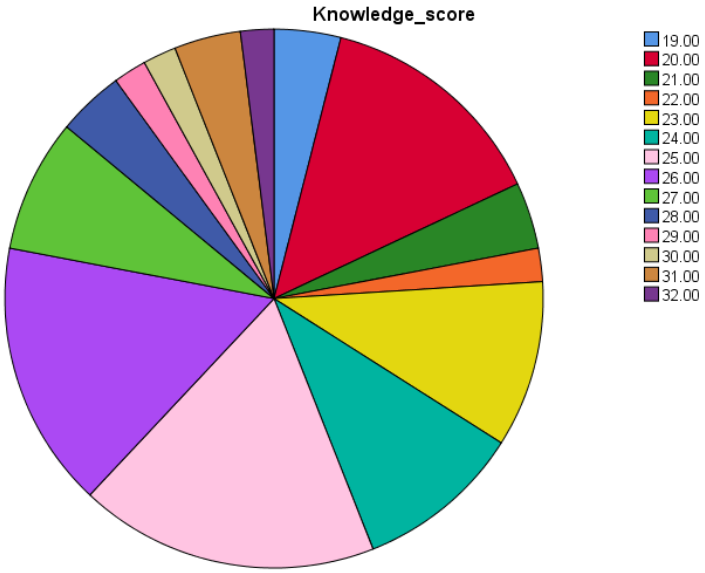

Figure 1. Pie chart showing distribution of Knowledge Scores

did not know. Table 8 below shows participant response to how blood pressure should be monitored in Pre-eclampsia.

4.1.1 Knowledge Scores. Knowledge scores ranged from 19 to 32 out of 32, with most respondents scoring ?24, classifying them as having adequate knowledge. Figure 1 below is a pie chart showing distribution of knowledge scores.

4.2 Attitudes Towards Managing Pre-eclampsia

More than half of respondents (52%) reported being very confident, while 36% were moderately confident, and a minority (12%) expressed low or no confidence. An overwhelming majority (94%) either agreed or strongly agreed that training in pre-eclampsia management should be mandatory. The majority of respondents felt prepared, with 54% strongly agreeing and 32% agreeing that they were ready to handle pre-eclampsia. Only 14% were neutral or negative. A majority (86%) agreed or strongly agreed that adequate training and resources are available, though 14% remained neutral or disagreed. Almost all respondents (94%) supported regular training, with 56% agreeing and 38% strongly agreeing. Table 9 shows participants' responses to their attitudes towards the management of Pre-eclampsia.

4.2.1 Attitude Scores. The was a high distribution of attitude scores. Figure 2 is a histogram showing the distribution of attitude score among respondents.

Table 9. Attitudes Toward Managing Pre-eclampsia (Q14-19)

Variable	Category	Frequency (n)	Percentage (%)
Confidence in Managing PE	Very confident	26	52.0
	Moderately confident	18	36.0
	Slightly confident	4	8.0
	Not confident	2	4.0
Mandatory PE MGT Training	Strongly disagree	3	6.0
	Disagree	0	0.0
	Neutral	0	0.0
	Agree	13	26.0
	Strongly agree	34	68.0
Preparedness	Strongly disagree	1	2.0
	Disagree	0	0.0
	Neutral	6	12.0
	Agree	16	32.0
	Strongly agree	27	54.0
Training & Resources	Strongly disagree	0	0.0
	Disagree	1	2.0
	Neutral	6	12.0
	Agree	27	54.0
	Strongly agree	16	32.0
Regular training Programs	Strongly disagree	2	4.0
	Disagree	0	0.0
	Neutral	1	2.0
	Agree	28	56.0
	Strongly agree	19	38.0
Institutional Support	Strongly disagree	0	0.0
	Disagree	0	0.0
	Neutral	3	6.0
	Agree	23	48.0
	Strongly agree	24	46.0
Total		**50**	**100**

Table 10. Barriers to Effective Management of Pre-eclampsia (Q20)

Barriers	Yes	n %	No	n %
Lack of training on pre-eclampsia management	29	58.0	21	42.0
Inadequate diagnostic tools (e.g., BP monitors, urine dipsticks)	29	58.0	21	42.0
Shortages of magnesium sulfate and other medications	28	56.0	22	44.0
Delayed access to laboratory investigations	37	74.0	13	26.0
Lack of locally adapted clinical guidelines	16	32.0	34	68.0
Delayed referral pathways for severe cases	35	70.0	15	30.0
Overwork or understaffing	35	70.0	15	30.0
Limited patient awareness of pre-eclampsia symptoms	43	86.0	7	14.0

4.3 Barriers to Effective Management of Pre-eclampsia

Respondents were assessed on the barriers and challenges they face, which hinder their ability to manage pre-eclampsia effectively. The results are summarized in Tables 10–13.

The majority of respondents reported limited patient awareness (86%), followed by delayed laboratory investigations (74%), overwork or understaffing (70%), and delayed referral pathways (70%). More than half also cited lack of training (58%), inadequate diagnostic tools (58%), shortages of magnesium sulfate (56%) and few reported lacks of locally adapted guidelines (32%). Table 10 below shows participants response to the barriers on the effective management of Pre-eclampsia.

Interestingly, all respondents (100%) confirmed the presence of clear facility protocols for managing pre-eclampsia. Table 11 below shows participants' responses to the presence of protocols for managing Pre-eclampsia.

Nearly half of respondents (46%) reported occasional shortages, while 20% frequently and 4% always encountered shortages of essential supplies. Only 30% said resource shortages were rare. Table 12 below shows participant response to resource shortage in pre-eclampsia management.

The most common challenges reported were limited patient awareness (26%) and insufficient diagnostic tools (24%), followed by insufficient beds (12%), refusal of magnesium sulfate due to fear/pain (12%), and staff overload (12%). A smaller proportion highlighted clinical monitoring difficulties (6%), delayed referrals/lab results (4%), and lack of competence/training (4%). Table 13 shows specific challenges participant face in the management of Pre-eclampsia.

4.4 Recommendations from Midwives

Respondents were asked to make recommendations. The results are summarized in Tables 14–16.

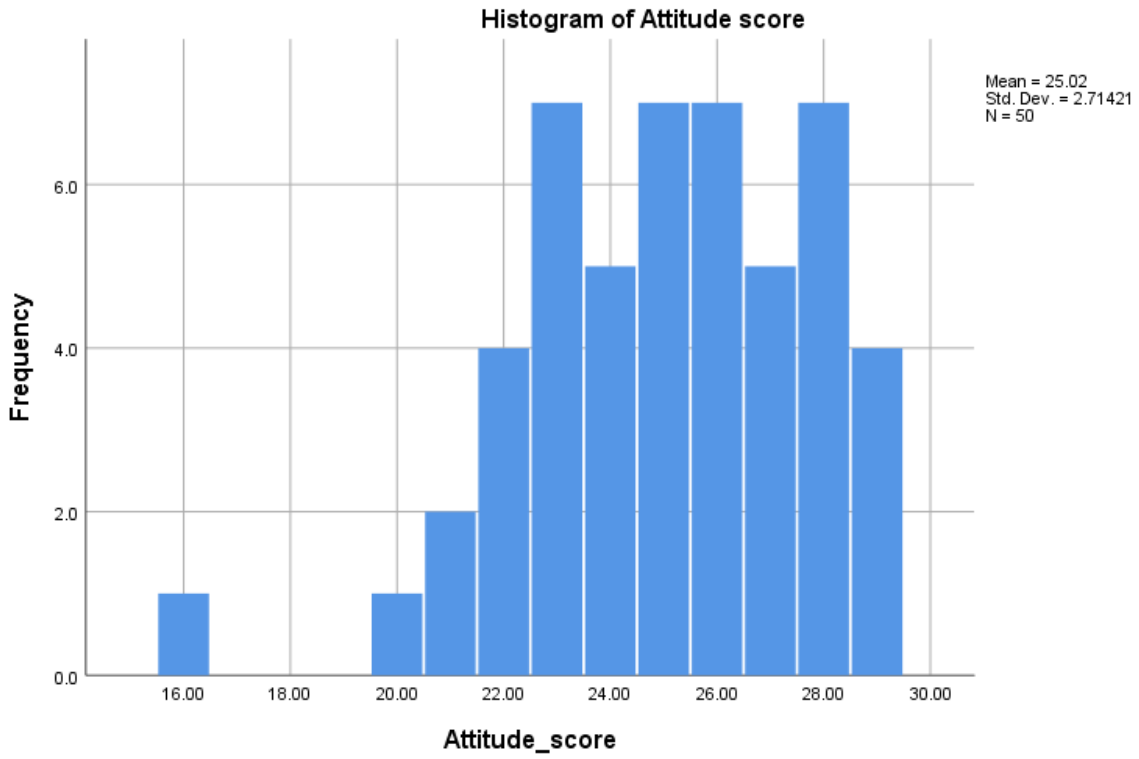

Figure 2. Histogram showing the distribution of Attitude score among Respondents

Table 11. Protocols for Managing Pre-eclampsia (Q21)

Question	Selected (n)=50	Selected (%)	Not Selected (n)=50	Not Selected (%)
Q21	50	100.0	0	0.0

Table 12. Resource shortage in Pre-eclampsia Management (Q22)

Variable	Category	Frequency (n)	Percentage (%)
Resource shortage	Rarely	15	30.0
	Occasionally	23	46.0
	Frequently	10	20.0
	Always	2	4.0

Table 13. Specific Challenges Faced in Management (Q23)

Barriers	Frequency (n)	Percentage (%)
Limited patient awareness about pre-eclampsia	13	26.0
Insufficient diagnostic tools (BP apparatus, lab)	12	24.0
Insufficient beds	6	12.0
Refusal of $MgSO_4$ by clients (Pain, fear)	6	12.0
Staff work overload/Understaffing	6	12.0
Delayed referrals/lab results	2	4.0
Lack of training/Competence	2	4.0
Clinical challenges (Urine output, colour, BP control)	3	6.0

Table 14. Interventions to improve Pre-eclampsia Management (Q24)

Question	Selected (n)=50	Selected (%)	Not Selected (n)=50	Not Selected (%)
Regular in-service training for midwives	48	96.0	2	4.0
Improved access to diagnostic tools and medications	47	94.0	3	6.0
Development of locally adapted clinical guidelines	41	82.0	9	18.0
Recruitment of additional midwives to reduce workload	39	78.0	11	22.0
Better patient education about pre-eclampsia symptoms	47	94.0	3	6.0

Table 15. Additional training programs on Pre-eclampsia Management (Q24)

Question	Selected (n)=50	Selected (%)	Not Selected (n)=50	Not Selected (%)
Yes	50	100.0	0	0.0
No	0	0.0	0	0.0

Table 16. Priority Recommendations to Effective Management of Pre-eclampsia (Q24)

Recommendations	Frequency (n)	Percentage (%)
Better patient education/awareness creation	27	54.0
Regular in-service training for midwives	17	34.0
Recruitment of more midwives/reduce workload	4	8.0
Adequate diagnostic tools and medical supplies	4	8.0
Development of locally adapted clinical guidelines	2	4.0
Encourage regular ANC attendance/early screening	3	6.0
Emergency preparedness/response	1	2.0

The majority of respondents recommended regular in-service training for midwives (96%), improved access to diagnostic tools and medications (94%), and better patient education on pre-eclampsia symptoms (94%). Additionally, 82% highlighted the development of locally adapted clinical guidelines, while 78% suggested the recruitment of additional midwives to reduce workload. Table 14 below shows participant response to interventions to improve pre-eclampsia management.

All respondents (100%) endorsed the need for additional training programs on pre-eclampsia management. Table 15 shows participant response on whether additional training programs are needed or not.

When asked to point out interventions that would make the biggest difference in pre-eclampsia management, more than half of respondents emphasized better patient education and awareness creation (54%), followed by regular in-service training (34%), while a smaller proportion highlighted recruitment of more midwives (8%), improved diagnostic tools and supplies (8%), locally adapted guidelines (4%), regular ANC attendance and early screening (6%), and emergency preparedness (2%). Table 16 shows participants' priority recommendations to effective management of pre-eclampsia.

4.5 Inferential Statistics

To examine the associations between selected socio-demographic variables and outcome variables (knowledge level and attitude level), both Chi-square tests of independence and binary logistic regression analyses were conducted.

4.5.1 Chi-Square Test Results. Chi-square tests were used to examine the associations between training in pre-eclampsia management, educational level, and years of experience with knowledge and attitude levels of respondents.

Of all variables tested, only years of professional experience was significantly associated with knowledge level. None of the socio-demographic variables showed significant associations with attitude levels. These results informed subsequent logistic regression analysis. Table 17 below shows summary of chi-square results.

4.6 Logistic Regression Analysis

4.6.1 Logistic Regression Analysis of Predictors of Knowledge. Work Unit was the only significant predictor of knowledge level ($p=0.037$). Midwives in ANC unit (Exp(B)=516.6, $p=0.004$) and Labor & Delivery unit (Exp(B)=73.400, $p=0.011$) had substantially higher odds of adequate knowledge compared to the reference group. Years of Experience was marginally non-significant ($p=0.077$). Educational level, training history, encounter rate, and age group were not significant predictors ($p> 0.05$). Table 18 shows findings of logistic regression predicting knowledge level.

4.6.2 Logistic Regression Analysis of Predictors of Attitude Level. None of the predictor variables were statistically significant (all $p> 0.05$). Training, work unit, years of experience, encounter rate, and age group, did not significantly predict attitude level. Table 19 shows findings of logistic regression predicting attitude level.

Table 17. Summary of Chi-square Results

Variable Tested	Outcome Variable	X^2 (Chi-square)	df	p-value	Significant
Trained in PE	Attitude Level	0.399	1	0.560	No
Education	Attitude Level	4.427	3	0.219	No
Experience	Attitude Level	5.357	1	0.147	No
Trained in PE	Knowledge Level	0.319	2	0.853	No
Education	Knowledge Level	8.101	6	0.231	No
Experience	Knowledge Level	19.470	6	0.003	Yes

Table 18. Logistic Regression Predicting Knowledge Level

Variable	B	S.E.	Wald	df	Sig.	Exp(B)
Experience	-1.622	0.918	3.122	1	0.077	0.197
Education (Overall)			2.458	3	0.483	
Education (1)	-4.945	49225.968	0.000	1	1.000	0.007
Education (2)	-3.245	49225.968	0.000	1	1.000	0.039
Education (3)	-5.182	49225.968	0.000	1	1.000	0.006
Trained PE (1)	0.874	1.718	0.259	1	0.611	2.396
Work Unit (Overall)			8.468	3	0.037	
Work Unit (1)	6.247	2.167	8.311	1	0.004	516.571
Work Unit (2)	4.296	1.698	6.403	1	0.011	73.400
Work Unit (3)	23.918	20632.024	0.000	1	0.999	24407852688.961
Encounter Rate	0.690	0.786	0.770	1	0.380	1.993
Age Group (Overall)			3.505	3	0.320	
Age Group (1)	-20.732	40192.957	0.000	1	1.000	0.000
Age Group (2)	-17.088	40192.957	0.000	1	1.000	0.000
Age Group (3)	-43.324	56841.321	0.000	1	0.999	0.000
Constant	22.061	63550.471	0.000	1	1.000	3811653902.426

Table 19. Logistic Regression Predicting Attitude Level

Variable	B	S.E.	Wald	df	Sig.	Exp(B)
Experience	34.037	7054.970	0.000	1	0.996	605524524306084.100
Education (Overall)			0.000	3	1.000	
Education (1)	32.958	51409.461	0.000	1	0.999	205826965598875.220
Education (2)	68.074	51208.424	0.000	1	0.999	3.667E+29
Education (3)	49.413	52349.640	0.000	1	0.999	2.882E+21
Trained PE (1)	-1.685	15646.873	0.000	1	1.000	0.185
Work Unit (Overall)			0.000	3	1.000	
Work Unit (1)	14.456	18912.710	0.000	1	0.999	1896486.409
Work Unit (2)	48.404	32884.130	0.000	1	0.999	1.051E+21
Work Unit (3)	-17.963	25461.309	0.000	1	0.999	0.000
Encounter Rate	0.000	1.500	0.000	1	1.000	1.000
Age Group (Overall)			0.000	3	1.000	
Age Group (1)	47.564	42597.743	0.000	1	0.999	4.539E+20
Age Group (2)	46.458	44909.833	0.000	1	0.999	1.501E+20
Age Group (3)	-18.573	58475.367	0.000	1	1.000	0.000
Constant	-143.092	81576.295	0.000	1	0.999	0.000

5 Discussion

The findings demonstrate that midwives at Presbyterian Hospital, Agogo generally possess good theoretical knowledge of pre-eclampsia. Universal recognition of the definition of pre-eclampsia, high awareness of its onset after 20 weeks of gestation and the need to monitor blood pressure at least every 4–6 hours in severe pre-eclampsia cases suggests strong foundational understanding of the condition. This level of knowledge exceeds findings reported from earlier studies in Ghana and other LMICs, where only about half of midwives demonstrated adequate knowledge of hypertensive disorders in pregnancy [25] [30].

High recognition of major risk factors such as chronic hypertension, previous history of pre-eclampsia, advanced maternal age and multiple gestations align with WHO and ISSHP guidelines and indicates effective transmission of core obstetric knowledge. However, poor identification of nulliparity as a risk factor highlights persistent gaps in comprehensive risk assessment. This finding is consistent with studies from South Africa that reported fragmented understanding of risk factors of pre-eclampsia [31]. Failure to recognize early risk factors may delay intensified surveillance during antenatal care, increasing the likelihood of adverse outcomes.

Knowledge of the hallmark symptoms such as hypertension, proteinuria, persistent headache, and visual disturbances was high, reflecting improved awareness of clinical warning signs. Nonetheless, limited recognition of non-specific symptoms such as unexplained excessive weight gain suggests that subtle early manifestations of pre-eclampsia may be overlooked. This is clinically significant, as early

detection remains central to preventing progression to severe disease [32] [33] [34].

Regarding complications, respondents demonstrated stronger awareness of maternal complications (eclampsia, preterm birth) than fetal complications such as fetal growth restriction and placental abruption. Failure to identify neonatal risks associated with pre-eclampsia can lead to severe adverse outcomes [32] [33]. This imbalance emphasizes the need to ensure a more balanced understanding of this risk factors to promote holistic maternal-fetal care.

Encouragingly, most respondents correctly identified magnesium sulfate as the first-line anticonvulsant, consistent with WHO recommendations. However, the minority who failed to recognize this remains concerning, as incorrect management of severe pre-eclampsia can result in preventable maternal mortality.

Overall, midwives demonstrated positive attitudes towards the management of pre-eclampsia. High levels of confidence and perceived preparedness indicate that midwives are psychologically willing to manage the condition. Similar positive attitudes have been reported in Bujumbura and Tanzania, although confidence levels vary across settings [35] [36].

An overwhelming majority supported mandatory and regular training, reflecting strong self-awareness of the need for continuous professional development. This aligns with evidence from Ghana showing that midwives prefer structured workshops and in-service training to maintain clinical competence [37] [38].

Although respondents largely reported institutional support and availability of resources, perceived adequacy may not reflect actual clinical realities. Systemic challenges such as inconsistent drug supply, malfunctioning equipment, and delayed investigations have been widely documented in Ghanaian hospitals [38] [39]. Therefore, confidence and positive attitudes may not always translate into effective practice if structural barriers persist.

Despite good knowledge and positive attitudes, respondents identified several significant systemic and patient-related barriers and challenges to effective pre-eclampsia management. Limited patient awareness emerged as the most frequently reported challenge. This finding support existing literature that highlights poor health literacy, sociocultural beliefs, and delayed care-seeking behaviors as major contributors to adverse maternal outcomes in LMICs [40] [41] [42].

Health system barriers, including delayed laboratory investigations, understaffing, inadequate diagnostic tools, and insufficient beds, were also prominent. These challenges have been repeatedly reported in Ghana and other sub-Saharan African countries and undermine the timely diagnosis and management of pre-eclampsia [39] [43]. Even when protocols exist, inadequate resources limit their effective implementation.

Work overload and understaffing further compound these challenges. High patient-to-midwife ratio increases stress, impairs clinical decision-making, and contributes to burnout, which may compromise quality of care [44] [45]. Additionally, patient refusal of magnesium sulfate due to fear or misconceptions highlights the need for improved patient counselling and community education.

Inferential analysis revealed that years of experience and work unit were significant predictors of knowledge level. This suggests that practical exposure, particularly in high-risk unit such as antenatal and labor wards, enhances clinical understanding of pre-eclampsia. These findings are consistent with earlier studies demonstrating that clinical experience improves competence in obstetric emergencies [19].

The lack of strong predictors for attitude level may indicate that attitudes are influenced more by professional values and institutional culture than by individual demographic factors.

6 Conclusion

Midwives at Presbyterian Hospital, Agogo demonstrated good knowledge and positive attitudes towards the management of pre-eclampsia, particularly in relation to diagnosis, monitoring and use of magnesium sulfate. However, gaps remain in recognizing some risk factors and fetal complications, while systemic barriers such as limited patient awareness, understaffing, delayed investigations, and inadequate resources continue to hinder effective care. Clinical experience and work unit significantly influenced knowledge levels, highlighting the importance of practical exposure. Overall, strengthening health systems through regular training, improved resources, and patient education is essential to optimize pre-eclampsia management and reduce preventable maternal and neonatal morbidity in Ghana.

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The Effect of Dietary Fiber on Glycemic Control in Patients with Type 2 Diabetes Mellitus Receiving Oral Hypoglycemic Therapy

CORRESPONDENCE

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ABSTRACT

Introduction: Nutritional recommendations for patients with T2DM from various global communities agree on the need to increase dietary fiber (DF) intake; however, there are currently no specific and unified recommendations regarding the recommended amount and type of DF. Studying the effect of DF on glycemic control in patients with T2DM may play an important role in refining intake recommendations and motivating patients to comply these recommendations.

Objective of the Study: Evaluation of the effect of Nestlé OptiFibre DF on glycemic control parameters in patients with T2DM treated with combination hypoglycemic therapy with metformin plus dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) or with metformin plus sodium-glucose cotransporter type 2 inhibitors (SGLT2 inhibitors).

Materials and Methods: The study included 80 patients with T2DM, with duration not more than 5 years...

Full abstract continues on the metadata continuation sheet.

Index Terms: type 2 diabetes mellitus • gut microbiota • dietary fiber • oral hypoglycemic therapy

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Dr. T. Yu. Demidova*

FULL ABSTRACT

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Materials and Methods:

The study included 80 patients with T2DM, with duration not more than 5 years, with HbA1c of not more than 7.5%, and BMI of 27–35 kg/m2, without severe comorbidity. All patients were treated with a combination of metformin and a DPP-4 inhibitor or metformin and an SGLT2 inhibitor. Forty patients comprised the Main Group, where patients received Nestlé OptiFibre DF, a partially hydrolyzed guar gum (PHGG), for 3 months according to the instructions for use. The other patients, who comprised the Control Group, underwent the same examinations as the patients in the Main Group as part of routine clinical practice over a period of 3 months. Changes over time in HbA1c, fasting plasma glucose, blood glucose self-monitoring data, and ambulatory blood glucose profile based on flash glucose monitoring (FGM, FreeStyle Libre, Abbott) were evaluated. Laboratory parameters were evaluated at baseline (2–3 days from the start of the study) and at the completion of the study (84 ± 3 days from the start of the study). A FGM sensor was also applied at Days 2–3 from the start of the study; the readings were obtained and evaluated after 14 days. Repeated FGM application was performed at Day 72 ± 3, and the readings were obtained at Day 84 ± 3.

Results:

In the group of patients who received DF, there was a statistically significant decrease in the HbA1c level from 6.35 [5.9–7.07]% to 5.95 [5.7–6.3]%, p = 0.01, while in the Control Group almost no changes were found: at baseline, the HbA1c level was 5.85 [5.5–6.7]%, and at study completion it was 6.15 [5.5–6.78]%, p = 0.99. Fasting plasma glucose in the Main Group decreased from 7.0 [6.33–7.78] mmol/L to 6.65 [5.72–7.75] mmol/L, p = 0.18, while in the Control Group, on the contrary, an increase this parameter increased from 6.30 [5.7–7.0] mmol/L to 6.9 [5.6–7.78] mmol/L, p = 0.05. The evaluation of the ambulatory glucose profile (AGP) data showed that the Time in Range (TIR) was significantly higher by the end of the study in the Main Group vs the Control Group by 2.5%: 94.5 [92.0–97.0]% vs 92.0 [77.25–96.0]% (p = 0.01). Time Below Range (TBR) in the Main Group decreased by 0.5% while no changes were observed over time in the Control Group, and the increase in Time Above Range (TAR) in the Main Group was 0.5% lower than in the Control Group. In addition, a decrease in the mean duration of hypoglycemia was found in patients who received DF, from 144.39 ± 76.49 (95% CI 115.87; 172.91) to 118.32 ± 54.49 (95% CI 96.81; 139.84), p = 0.15, as well as a decrease in the frequency of hypoglycemic events from 6.0 [3.0–16.0] to 5.0 [3.0–9.75], p = 0.47.

Conclusions:

The study obtained data on the positive effect of daily intake of PHGG for 3 months on the HbA1c, fasting plasma glucose and AGP parameters, which is important not only from the point of view of managing T2DM, but also from the standpoint of the prevention of micro- and macrovascular complications and correction of risk factors. Further research is needed on the effects of DF, taking into account the duration of use, doses, and various DF types and forms.

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RESEARCH ARTICLE

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Dr. T. Yu. Demidova* **and A. S. Teplova**

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Results: In the group of patients who received DF, there was a statistically significant decrease in the HbA1c level from 6.35 [5.9–7.07]% to 5.95 [5.7–6.3]%, p = 0.01, while in the Control Group almost no changes were found: at baseline, the HbA1c level was 5.85 [5.5–6.7]%, and at study completion it was 6.15 [5.5–6.78]%, p = 0.99. Fasting plasma glucose in the Main Group decreased from 7.0 [6.33–7.78] mmol/L to 6.65 [5.72–7.75] mmol/L, p = 0.18, while in the Control Group, on the contrary, an increase this parameter increased from 6.30 [5.7–7.0] mmol/L to 6.9 [5.6–7.78] mmol/L, p = 0.05. The evaluation of the ambulatory glucose profile (AGP) data showed that the Time in Range (TIR) was significantly higher by the end of the study in the Main Group vs the Control Group by 2.5%: 94.5 [92.0–97.0]% vs 92.0 [77.25–96.0]% (p = 0.01). Time Below Range (TBR) in the Main Group decreased by 0.5% while no changes were observed over time in the Control Group, and the increase in Time Above Range (TAR) in the Main Group was 0.5% lower than in the Control Group. In addition, a decrease in the mean duration of hypoglycemia was found in patients who received DF, from 144.39 ± 76.49 (95% CI 115.87; 172.91) to 118.32 ± 54.49 (95% CI 96.81; 139.84), p = 0.15, as well as a decrease in the frequency of hypoglycemic events from 6.0 [3.0–16.0] to 5.0 [3.0–9.75], p = 0.47.

Conclusions: The study obtained data on the positive effect of daily intake of PHGG for 3 months on the HbA1c, fasting plasma glucose and AGP parameters, which is important not only from the point of view of managing T2DM, but also from the standpoint of the prevention of micro- and macrovascular complications and correction of risk factors. Further research is needed on the effects of DF, taking into account the duration of use, doses, and various DF types and forms.

Keywords: *type 2 diabetes mellitus, gut microbiota, dietary fiber, oral hypoglycemic therapy*

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1 Introduction

Despite the progressively increasing possibilities of drug therapy for T2DM, the modern diabetology gives nutrition an increasingly important role in metabolic control. The goal of T2DM therapy, including nutritional recommendations for patients with T2DM, is to reach target glycemic control values, achieve and maintain optimal body weight, manage cardiovascular risks, and select drug therapy from the point of view of cardiorenal protection [1].

Macronutrient intake standards are the basis of nutritional recommendations for patients with T2DM. Protein intake is recommended in the amount of 10–20% of the daily dietary energy value for patients under 65 years of age with a GFR of more than 60mL/min/1.73m^2 For patients over

65 years of age, a higher protein content in the diet 15–20%) is recommended. With regard to fat consumption, the focus of the recommendations is to limit unsaturated fatty acids to less than 10% of the daily dietary value, and trans fats to less than 1% . It is also recommended to substitute all consumed fats with mono- and polyunsaturated fatty acids. Finally, consumption of carbohydrates for patients with T2DM requires taking into account the glycemic index (GI) and glycemic load (GL) of foods, preference for low GI and GL foods, and for patients treated with insulin therapy, bread units counting is necessary. An important role is given to limiting the consumption of added sugars to 10% of the daily dietary energy value [2].

On the contrary, it is recommended to diversify the diet with dietary fiber (DF), which has a central place in modern nutritional recommendations, but the amounts recommended for daily intake vary significantly in global recommendations (Fig. 1). For example, specialists from the European Association for the Study of Diabetes (EASD) recommend daily intake of not less than 35g/day (4gper1, 000kJ) of DF [3]. At the same time, the recommendations of the American Diabetes Association (ADA) are to consume 14 g of DF per 1,000 kcal/day [4]. The Eurasian Dietary Guidelines for Cardiovascular Diseases recommend a daily intake of 20–25g/day of DF, or 10 g per 1, 000kcal , for patients with T2DM [5]. The Russian algorithms for specialized care for DM patients mention DF in the section "Lifestyle modification in DM and IHD," where patients are recommended to consume 35 –45 g of fiber daily [6]. It is also important to mention the gender differences in DF intake recommendations: for women, the recommended standard is slightly lower than for men (25g/ day vs 38g/day) [7].

Association	Recommended intake of dietary fiber
ADA (American Dietetic Association)	14 g dietary fiber per 1,000 kcal or 25 g for women, 38 g for men
EFSA (European Food Safety Organisation)	25 g/day
AHA (American Heart Association)	25–30 g/day
CDA (Canadian Diabetes Association)	25–50 g/day

Figure 1. Differences in the Recommended Amounts of DF in global clinical guidelines

Thus, treatment algorithms for T2DM, obesity, cardiovascular disease, and many other conditions highlight the justified need to identify recommendations for the mandatory integration of DF into patients' diets, since the regular consumption of DF has its effect on the achievement of the above goals.

The role and place of DF in nutritional recommendations for both patients with T2DM and healthy individuals become obvious, given the variety of positive effects of DF on the human body. The influence of DF on the gastrointestinal tract (GIT) is covered in detail in modern publications. The most well-known effects of DF on digestion are the regulation of intestinal peristalsis, acceleration of intestinal transit, an increase in the amount of feces and in the frequency of bowel movements. These effects are actively used to facilitate defecation in chronic obstructive constipation. Patients with irritable bowel syndrome are a special category for whom facilitating bowel movements is of fundamental importance. The reduction of bloating, discomfort and pain represent another advantage of DF consumption. Facilitating defecation, reducing discomfort, pain and bleeding are also of special importance in the treatment of hemorrhoids [8].

A special place in the structure of the positive effects of DF on digestion is occupied by data on the gut microbiota (GM) modulation. DF, being a nutrient substrate for the gut microbiota (GM), leads to

an increase in the number and biodiversity of microorganisms, to an increase in the activity of "beneficial" microorganisms that produce metabolites important for the human body, as well as to a decrease in the activity of opportunistic and pathogenic microorganisms by modulating the physicochemical properties of the intestinal contents [9]. In addition to the GM composition modulation, DF influences the GM synthetic function by controlling the production of GM metabolites, with short-chain fatty acids (SCFAs), which mediate the interaction between the GM and the human body, being the main ones. It is due to the effects of SCFAs on the respective receptors of various organs and tissues that the "gut-brain-periphery" axis function is ensured, which provides the relationship between the intestine, GM, brain and peripheral tissues and organs through the secretion of biologically active substances and metabolites and regulates a wide range of various metabolic processes [10].

Acetic, propionic and butyric acids, which have both local and systemic effects, are represented in the largest amounts in the body. For example, butyric acid, which has been the subject of the greatest array of research, is the main source of energy for colonocytes, as well as a substrate for the synthesis of their membranes, thus maintaining the integrity of the intestinal wall and implementing its protective potential. With regard to propionic acid, data are provided on the antiatherogenic and antibacterial effects due to the regulation of immune homeostasis in the intestine (blocking the adhesion of pathogens to the epithelium). In addition, propionic acid is a substrate for gluconeogenesis [11, 12].

Acetic and propionic acids entering the colonocyte at the level of the large intestine are involved in the regulation of its bloodstream, improving the blood supply in the mucous membrane, and thereby exhibit an anti-ischemic effect [13].

At the systemic level, these SCFAs are involved in the regulation of carbohydrate and lipid metabolism, have a protective effect on pancreatic β -cells, influence the immune system and even exhibit anticarcinogenic properties [14].

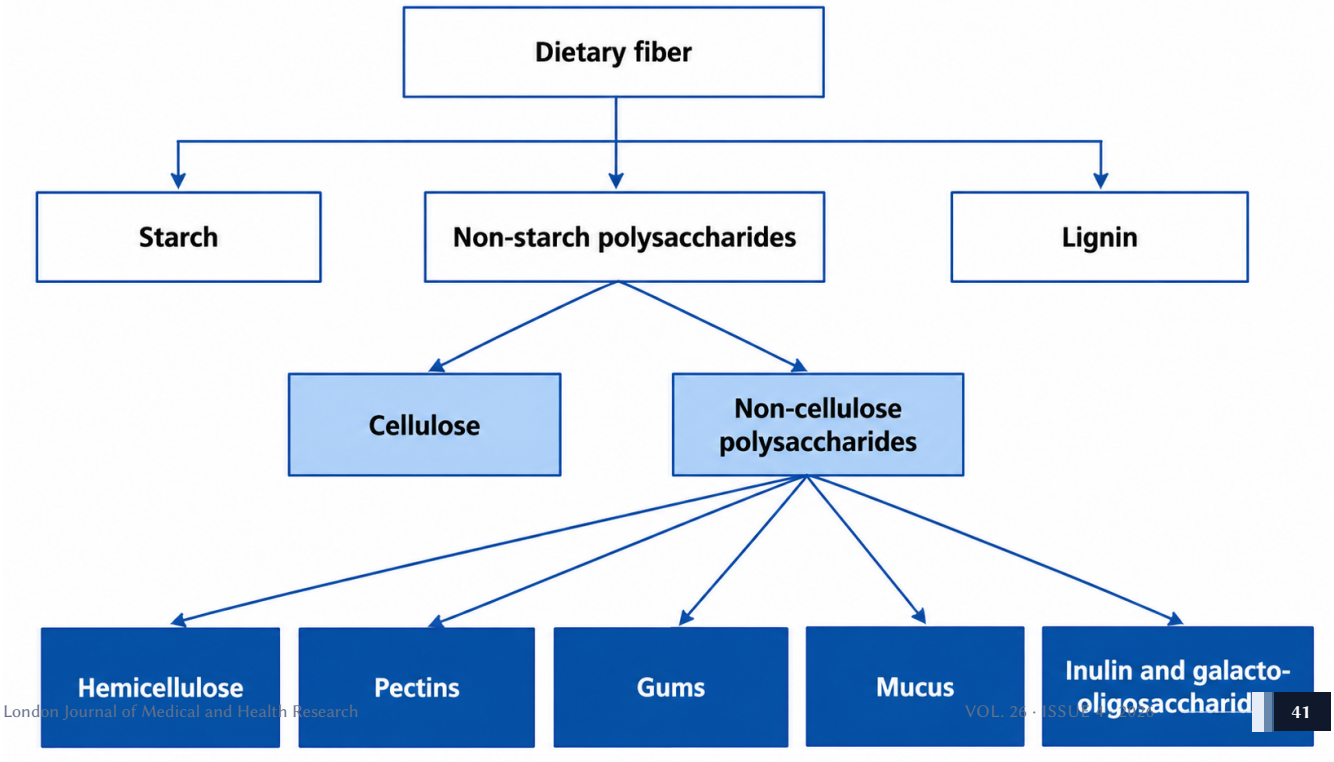
In addition to the DF digestive effects referred to as "classical" in a number of publications, there is currently a large amount of data on the metabolic effects of DF. When listing the effects of DF on carbohydrate metabolism, the decrease in glucose absorption due to the acceleration of food passage through the intestines should be mentioned first [15]. In addition, the effect of regular intake of DF on the secretion of incretin hormones by intestinal enteroendocrine cells has been demonstrated. The effects of DF on the reduction of insulin resistance and systemic inflammation [16], which are among the main pathogenetic links in T2DM, are also known.

The effect on lipid metabolism is explained by the involvement of acetic and propionic acids in the modulation of lipid synthesis processes [17], including through the regulation of the expression of human genes responsible for the regulation of lipid metabolism. DF involvement in the regulation of bile acid synthesis is an equally important component of lipid metabolism and cardioprotective properties modulation [18].

Finally, body weight regulation is an important systemic effect of DF. This effect is achieved by modulating eating behavior, due to the accelerated onset of satiety when consuming DF, as well as by prolonging the time while food contents remain in the stomach, which contributes to a longer feeling of satiety and, as a result, reduces the need for additional food intake [19].

However, an analysis of publications on the evaluation of DF consumption suggests that the recommendation for adequate DF intake is not adequately met [20]. The main reasons are the high cost of some vegetables and fruits, which are the main sources of DF, undesirable gastrointestinal manifestations in the form of flatulence and increased frequency of stools, associated in some patients with the peculiarities of DF tolerability, as well as the lack of motivation in patients to daily consume the recommended amounts of DF. In addition, the lack of consensus in global recommendations on the required amount and type of DF for daily intake is an obstacle to the unification of DF intake recommendations. It is worth mentioning that most clinical recommendations provide standards for DF intake from food [37]. However, if it is impossible to reach the recommended amount, additional DF intake in the form of food supplements (FS) is possible.

DF classification for their chemical structure implies division into starch, non-starch polysaccharides, and lignin. The largest number of options are represented by non-starch polysaccharides, which include cellulose and non-cellulose polysaccharides. The latter are subdivided into hemicellulose, pectin substances, mucus, inulin- and guar-like storage polysaccharides, and gum (Fig. 2) [21].



Gums from the stems or seeds of tropical or subtropical trees, plants, and shrubs are the most widely represented ones on the DF market. OptiFibre DF used in this study is an extract of Cyamopsis tetragonolobus seeds and is a partially hydrolyzed guar gum for its chemical structure. The partially hydrolyzed nature of DF helps improve the taste characteristics of the gum and reduce its viscosity. Thus, the studied type of DF is the most convenient and comfortable one for use by patients, and also exhibits the greatest range of positive properties among other DF options [22].

2 Materials and Methods

A prospective-and-retrospective, observational, minimally interventional study was conducted, which included 80 patients with T2DM. Patients were divided into two groups of 40 subjects each: the Main and Control Groups. Patients in the Main Group were enrolled prospectively, while the Control Group included patients who, as part of routine clinical practice, underwent examination in a scope similar to that for the patients in the Main Group; their data were retrospective. In accordance with the inclusion criteria, the study included patients aged 45–60 years with a duration of T2DM of not more than 5 years, satisfactory glycemic control (HbA1c not more than 7.5%) and BMI 27−35kg/m^2 , treated with combination therapy with metformin and DPP-4 inhibitors or metformin and SGLT2 inhibitors. Prior to inclusion in the study, patients were treated with the specified therapy for at least 3 months. Therapy with metformin plus SGLT2 inhibitors or plus DPP-4 inhibitors was chosen based on the optimal indications for this combination in patients with a short history of T2DM in terms of reducing both glycemic control and correction of risk factors for complications of T2DM, as well as correction of risk factors. In this case, metformin represents the “gold standard” of pathogenetic therapy for T2DM, while innovative drugs, along with a safe hypoglycemic effect, exhibit a number of additional pleiotropic properties. In addition, the tablet form of all prescribed medications, which provided the ease of use for patients, was an important aspect in favor of this combination.

Patients included in the prospective part of the study were prescribed Nestlé OptiFibre dietary fiber, which is a partially hydrolyzed guar gum (PHGG) product. In accordance with the instructions for use, in order to minimize possible adverse events during DF intake, the treatment started with a minimum dose of 5g/day , followed by titration in the increments of 5g/day every 3 days until a dose of 15g/day was reached. The DF was dissolved in liquid food or drinks. Patients in the Control Group received no DF; they were only given recommendations in accordance with the general principles of proper nutrition for patients with T2DM.

The study design provided for 7 visits, during which patients were given consultation, anthropometric data were evaluated, and blood and stool were sampled (Fig. 3).

At Visit 1, corresponding to baseline, the patient was introduced to the Investigator, a detailed medical history was taken, and anthropometric data (height, body weight, BMI, and waist circumference) were evaluated. During this visit, the patient also received detailed information about the study stages, recommendations on diet and physical activity, glucose self-monitoring, and instructions on how to prepare for blood and stool sampling. Voluntary informed consent was signed. The patient was prescribed Nestlé OptiFibre DF in accordance with the instructions for use.

The date o Visit 2 corresponded to Day 23 from the start of the study. During this Visit, venous blood was sampled, a FGM system was applied, a stool biosample was collected, and the patient’s self-monitoring diary for the previous 24 hours was evaluated. At this and all subsequent visits,

DF tolerability was evaluated and the patient was questioned about the occurrence of adverse events.

At the end of FGM system operation, the patient was invited for Visit 3 for FGM data reading and interpretation, which corresponded to Day 16 ± 2 from the start of the study. In addition, the patient’s anthropometric data and DF tolerability were evaluated.

At Visit 4 at Day 44 ± 3 from the start of the study, the patient’s anthropometric parameters and DF tolerability were evaluated, and self-monitoring data for the previous day were analyzed.

Visit 5 (Day 72 ± 3 from the start of the study) included anthropometry, evaluation of DF tolerability, and application of a FGM system.

At Visit 6 (Day 84 ± 3 from the start of the study), anthropometric data were evaluated, the FGM sensor was removed, and the obtained data were interpreted. Venous blood was sampled and a stool biosample was collected. DF tolerability was evaluated, and self-monitoring data for the previous day were analyzed.

Visit 7 (Day 90 ± 3 from the start of the study) was the final one. At this visit, a final conversation was held with the patient, and final recommendations were given for further treatment and lifestyle changes.

Table 1. Comparison of the formed groups by the anthropometric characteristics, age and carbohydrate metabolism parameters

Parameters	OptiFibre Group	Control Group	p-value
Age, years	55 [52–57]	54.5 [52–57]	—
BMI, kg/m^2	31.66 [29.42–33.77]	31.01 [29.17–32.77]	0.441
Waist circumference at Study Day 2 ± 1, cm	101.25 ± 9.06 (95% CI 98.32–104.18)	97.85 ± 8.59 (95% CI 95.07–100.63)	0.093
HbA1c, %	6.35 [5.9–7.07]	5.85 [5.5–6.7]	0.060
Fasting glucose, mmol/L	7.0 [6.3–7.7]	6.3 [5.7–7.0]	0.002

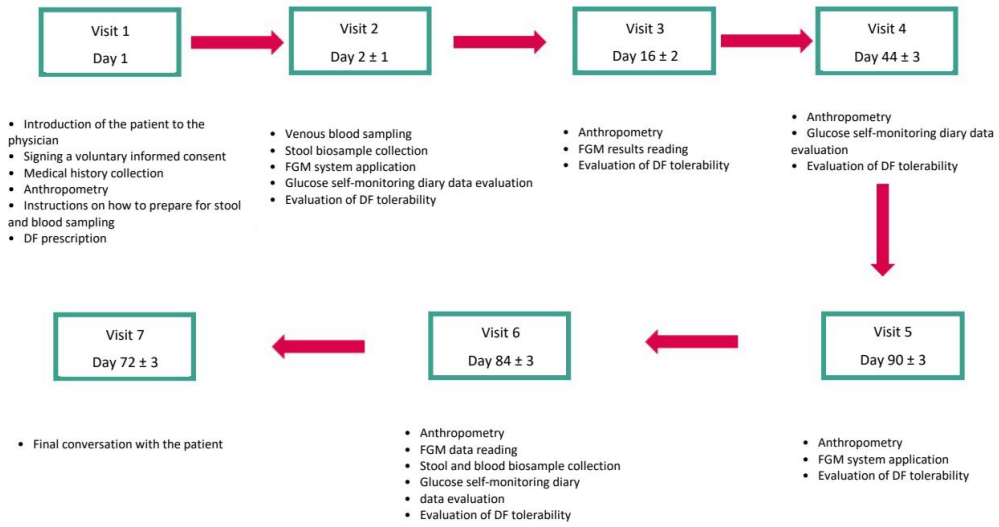


Figure 3. Study Design

To evaluate carbohydrate metabolism, the following parameters were studied: HbA1c (glycated hemoglobin), fasting plasma glucose, structured glucose self-monitoring using a glucose meter (measurements on an empty stomach, 2 hours after breakfast, lunch, dinner, and at night), flash glucose monitoring (FGM) (FreeStyle Libre system) parameters including an evaluation of the mean glucose level, glucose monitoring index (GMI), Time In Range (TIR), Time Above Range (TAR), Time Below Range (TBR), mean duration of hypoglycemic events, frequency of hypoglycemic events, and coefficient of variability.

The primary endpoint of the study was a statistically significant reduction in HbA1c and fasting plasma glucose compared with the Control Group at Day 84 ± 3 from the start of observation and treatment.

The secondary endpoint included statistically significant improvement in the mean glucose level, glucose monitoring index (GMI), Time In Range (TIR), Time Above Range (TAR), Time Below Range (TBR), mean duration of hypoglycemic events and determination of the frequency of hypoglycemic events based on flash glucose monitoring data (FreeStyle Libre system) vs baseline in the Study Group and the Control Group.

3 Results

The Main Group included 19 female and 21 male subjects, and the Control Group consisted of 21 female and 19 male subjects. In the OptiFibre Group, 50% of patients were treated with DPP-4 inhibitors $^+$ metformin, and 50% were treated with SGLT2 inhibitors $^+$ metformin. In the Control Group, the proportion of patients treated with DPP4 inhibitors $^+$ metformin was 45% and the proportion of patients treated with SGLT2 inhibitors $^+$ metformin was 55% . Table 1 summarizes a comparison of the formed groups by the anthropometric characteristics, age, and carbohydrate metabolism parameters.

The formed groups were evaluated for comorbidities. The most common diseases were arterial hypertension and obesity. Arterial hypertension was observed in 20 patients from the Control Group, which constituted 50% of all patients in the group. In the OptiFibre group, the number of patients with hypertension was 25, which was equivalent to 62.5% . IHD was reported in 4 patients in the Control Group (10%) and in 8 patients in the OptiFibre Group (20%) . Obesity was observed in 28 patients in the Control Group (70%) and in 25 patients in the OptiFibre Group (62.5%) . Eye disorders were found only in one patient in the Control Group (2.5%) . Chronic kidney disease (CKD) and peripheral arterial disease were not reported in any patient. The distribution of comorbidities is shown in Fig. 4.

Table 2. Laboratory parameters of carbohydrate metabolism in the Control Group

Parameters	Baseline (Day 2 ± 1)	Completion (Day 84 ± 3)	p-value
HbA1c, %	5.85 [5.5–6.7]	6.15 [5.5–6.78]	0.99
Fasting plasma glucose, mmol/L	6.30 [5.7–7.0]	6.9 [5.6–7.78]	0.05

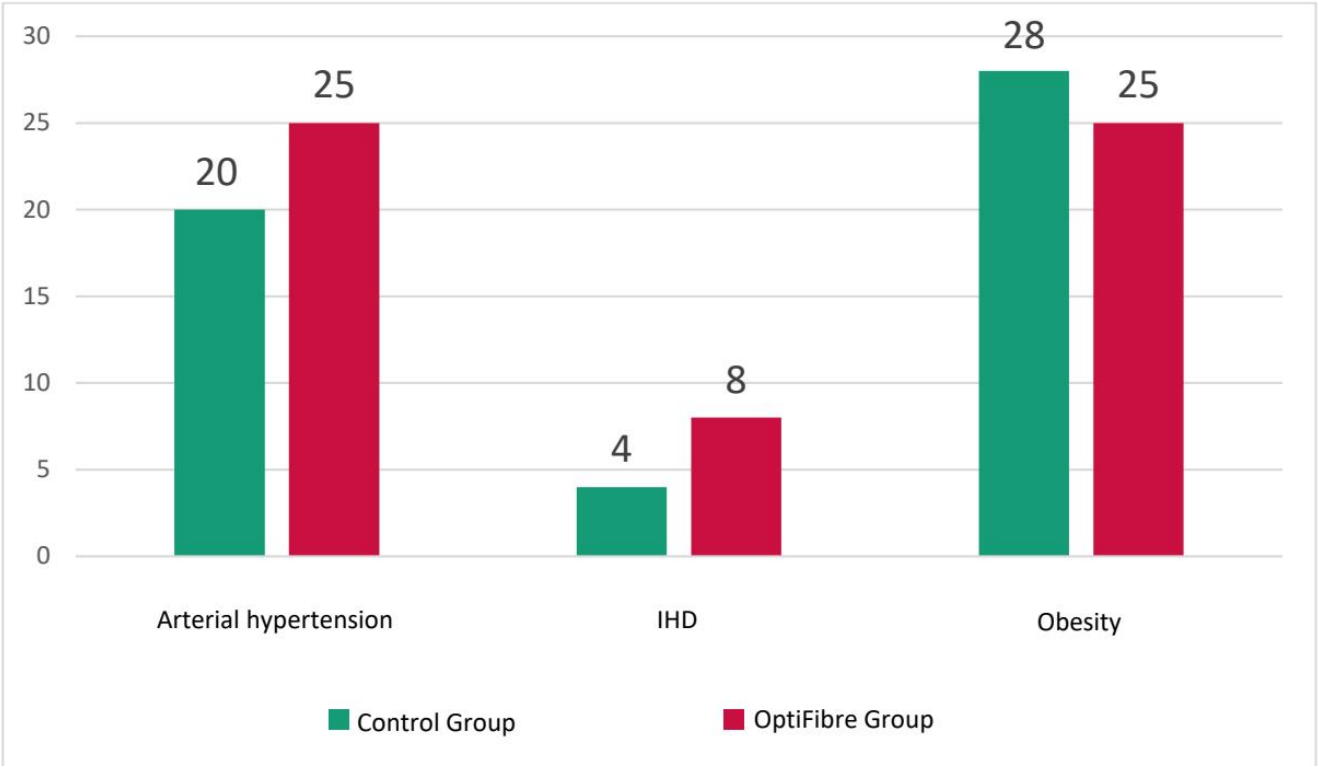


Figure 4. Distribution of comorbidities in patients in the formed groups

Thus, the formed groups were completely comparable for the main anthropometric characteristics, age, gender, carbohydrate metabolism parameters and treatment, as well as for the comorbidities, which made it possible to evaluate the effect of DF on the carbohydrate metabolism of patients and compare the data with the parameters in the Control Group, excluding the potential interference of extraneous factors.

During the study, at each visit, an evaluation of adverse events during treatment with Nestlé OptiFibre was performed: a detailed survey was conducted on the patients' well-being and GIT function (presence of flatulence, diarrhea, bloating and other gastrointestinal complaints). None of the patients reported any adverse events during the study.

4 Evaluation of changes over time in laboratory parameters of carbohydrate metabolism

Evaluation of the changes over time in HbA1c levels indicates that the primary endpoint was reached, which, in accordance with the study protocol, was a statistically significant reduction in the HbA1c level from 6.35% [5.9–7.07%] to 5.95% [5.7–6.3%], $p = 0.01$, while almost no changes were found in the Control Group: at baseline, the HbA1c level was 5.85% [5.5–6.7%] and at study completion it was 6.15% [5.5–6.78%], $p = 0.99$ (Tables 2 and 3).

A statistically significant 0.3% decrease in HbA1c in the OptiFibre Group and no changes over time in the Control Group undoubtedly represent a consequence of the positive effect of long-term DF consumption on carbohydrate metabolism. Positive changes over time were also found for the fasting blood plasma glucose: this parameter in the Main Group decreased from 7.0 [6.33–7.78] mmol/L to 6.65 [5.72–7.75] mmol/L, $p = 0.18$, while in the Control Group, on the contrary, this parameter increased from 6.30 [5.7–7.0] mmol/L to 6.9 [5.6–7.78] mmol/L, $p = 0.05$.

In the OptiFibre Group, there was a tendency towards a significant decrease in fasting blood glucose by 0.35 mmol/L, while in the Control Group, on the contrary, negative changes over time were observed: fasting blood glucose at Study Day 84 ± 3 exceeded the baseline value by 0.6 mmol/L.

Table 3. Laboratory parameters of carbohydrate metabolism in the OptiFibre Group

Parameters	Baseline (Day 2 ± 1)	Completion (Day 84 ± 3)	p-value
HbA1c, %	6.35 [5.9–7.07]	5.95 [5.7–6.3]	0.01
Fasting plasma glucose, mmol/L	7.0 [6.33–7.78]	6.65 [5.72–7.75]	0.18

5 Evaluation of ambulatory glucose profile based on flash glucose monitoring data

The ambulatory glucose profile (AGP) was analyzed to assess in detail the DF effect on the changes over time in glucose level and its variability during the day in the short and long term, which would not have been possible using only laboratory parameters. By assessing the AGP, it was possible to obtain data on glucose levels over time in a continuous mode, including the time spent within, above, and below the target range, on the presence and severity of hypoglycemia, glucose level variability and the glucose profile stability. The investigation of the above data is particularly relevant in the study group of patients due to the fact that these features of glucose level play an important role in the pathogenesis of micro- and macrovascular complications, including with satisfactory glycemic control based on laboratory evaluation methods; however, these parameters are not given due attention in routine laboratory examination in patients with T2DM.

AGP was evaluated using the generally accepted algorithm, taking into account the main five steps in the FGM data interpretation: data quality analysis, Time In Range (TIR) evaluation, hypoglycemia evaluation, glucose variability evaluation, and glucose profile stability evaluation. The sensor activity time at baseline was 38.5 [81.75–94.00]% in the Main Group and 87 [77.00 94.00]% in the Control Group, and at the end of the study it was 86 ;[77.25—93.25]% in the Main Group and 91 [81.75 — 96.00]% in the Control Group. The obtained data are consistent with a satisfactory amount of information on the AGP (more than 70%) and demonstrate a high level of patient compliance with glucose measurement when using the FGM system.

6 AGP characteristics in the Main Group patients

The Time In Range (TIR) at baseline was within the normal range, confirming satisfactory compensation of carbohydrate metabolism and patient eligibility in terms of the inclusion criteria for the study. A 1.5% reduction in TIR from 96.0% [92.25–98.00%] to 94.5% [92.0–97.0%] was not statistically significant but could be associated with the progression of T2DM during the study period. It is worth noting that these parameters are at the upper limit of the target range and demonstrate a high level of glycemic control and the proximity of the AGP parameters to the physiologically normal values.

To interpret the data in detail and understand the reasons for the changes over time in the Time In Range, it is also necessary to study the Time Above Range and Time Below Range. The Time Above Range in the Main Group was 0.0% [0.0–2.75%] at baseline and 2.0% [0.0–4.0%] ($p = 0.03$) at study completion. Evaluation of the Time Below Range showed a decrease from 2.0% [0.0–6.75%] to 1.0% [0.0–3.75%] ($p = 0.94$), which indicates an increase in the safety profile of hypoglycemic therapy in patients who received DF. It is also worth noting that the mentioned changes occur within the normal ranges and can only be interpreted as a variant of the physiological changes over time and natural progression of T2DM.

These findings are supported by the evaluation of hypoglycemia in the Main Group: a decrease in the mean duration of hypoglycemia in patients who received DF from 93.5 [30.0–170.75] to 80.0 [0.0–143.0], $p = 0.15$, as well as a decrease in the frequency of hypoglycemic events from 4.0 [0.25–7.75] to 3.0 [0.0–7.0], $p = 0.36$, along with a significant decrease in the frequency of nocturnal hypoglycemic events are also arguments in favor of bringing the AGP closer to physiological values characteristic of the healthy population.

Glucose variability in this study was evaluated by the coefficient of variability, with mean value increasing from 20.34 ± 3.48 95% CI 19.1621.52) to 22.83 ± 4.99 95% CI 19.7722.55) ($p = 0.37$) . When interpreting this parameter, it is necessary to take into account that normal values for this parameter are considered to be values of not more than 36, which indicates that the resulting data almost reached the middle of the target range and are as close as possible to the physiologically normal values.

Due to the fact that current scientific research increasingly attaches importance to the role of TIR changes over time in the development of macro- and microvascular complications of T2DM, this parameter was evaluated over time in the group of patients who received DF. In 35% of patients, an increase in TIR was observed at Study Day 84 ± 3 compared with Study Day 16 ± 3 , while 15% reached an increase in TIR of more than 10% from baseline.

AGP parameters comparison in the Main and Control Groups

Tables 4 and 5 summarize the main AGP data of patients in the Control and Main Groups.

TIR evaluation found statistically significant differences in the Control Group and the group of patients who received OptiFibre at Day 84 ± 3 Visit, while in the OptiFibre Group this parameter was 1.5% higher, while a comparison of TIR at Day 84 ± 3 Visit in the Control vs the Main Group indicated a statistically significant difference ($\mathbf{p} = 0.01$) , supposing a significantly greater effect of DF on increasing the Time In Range of patients with T2DM (Fig. 5).

Table 4. AGP parameters in the Control Group

Parameters	Baseline (Day 16 ± 3)	Completion (Day 84 ± 3)	p-value
Sensor activity time, %	87 [77.0–94.0]	91 [81.75–96.0]	0.13
TIR, %	96.0 [92.25–98.0]	93.0 [81.0–96.75]	0.04
TAR, %	0.0 [0.0–1.0]	1.0 [0.0–3.75]	0.08
TBR, %	2.0 [0.0–5.5]	1.0 [0.0–4.0]	0.14
Mean hypoglycemia duration, min	114.5 [45.0–182.0]	83.5 [30.0–142.5]	0.21
Frequency of hypoglycemia	4.5 [1.0–9.0]	2.0 [1.0–6.0]	0.14
Coefficient of variation, %	21.26 ± 4.42	22.83 ± 4.99	0.16
GMI, %	5.7 [5.5–6.15]	5.95 [5.53–6.3]	0.13
Mean glucose, mmol/L	5.6 [5.1–6.5]	6.15 [5.2–7.0]	0.11

Table 5. AGP parameters in the Main Group

Parameters	Baseline (Day 16 ± 3)	Completion (Day 84 ± 3)	p-value
Sensor activity time, %	88.5 [81.75–94.0]	86 [77.25–93.25]	0.16
TIR, %	96.0 [92.25–98.0]	94.5 [92.0–97.0]	0.42
TAR, %	0.0 [0.0–2.75]	2.0 [0.0–4.0]	0.03
TBR, %	2.0 [0.0–6.75]	1.0 [0.0–3.75]	0.94
Mean hypoglycemia duration, min	93.5 [30.0–170.75]	80.0 [0.0–143.0]	0.15
Frequency of hypoglycemia	4.0 [0.25–7.75]	3.0 [0.0–7.0]	0.36
Coefficient of variation, %	20.34 ± 3.48	22.83 ± 4.99	0.37
GMI, %	5.7 [5.5–6.0]	5.75 [5.5–6.07]	0.90
Mean glucose, mmol/L	5.6 [5.03–6.57]	6.0 [5.4–7.15]	0.05

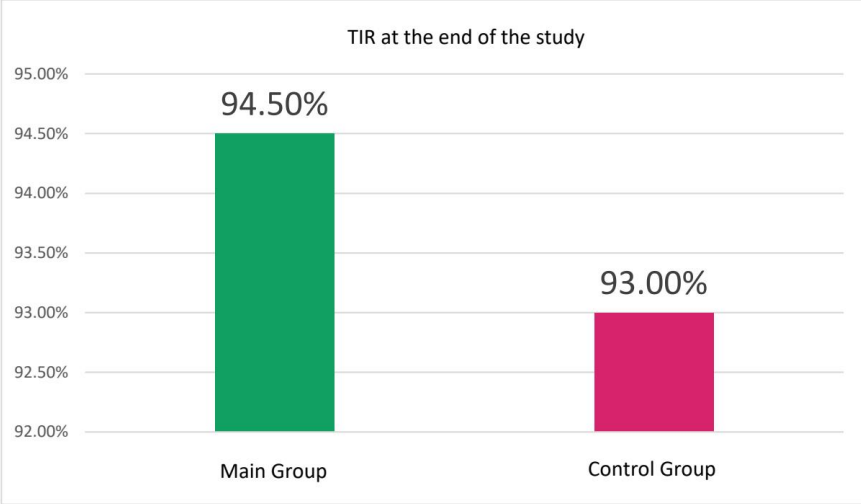


Figure 5. Comparison of TIR in the Main and Control Groups at Study Day 84 ± 3

TAR evaluation also found an increase in this parameter in both groups, however in the Control Group the increase in TAR was 1.0% greater than in the Main Group, indicating an increase in the glucose profile stability in patients who received DF.

Finally, TBR remained unchanged in the Control Group, while a 1.0% reduction was reached in the OptiFibre Group, which supports an improved safety profile of therapy in both cases due to a reduction in the duration of hypoglycemic events.

Comparison of the TIR, TAR and TBR data in the Main and Control Groups is shown in Figures 6 and 7.

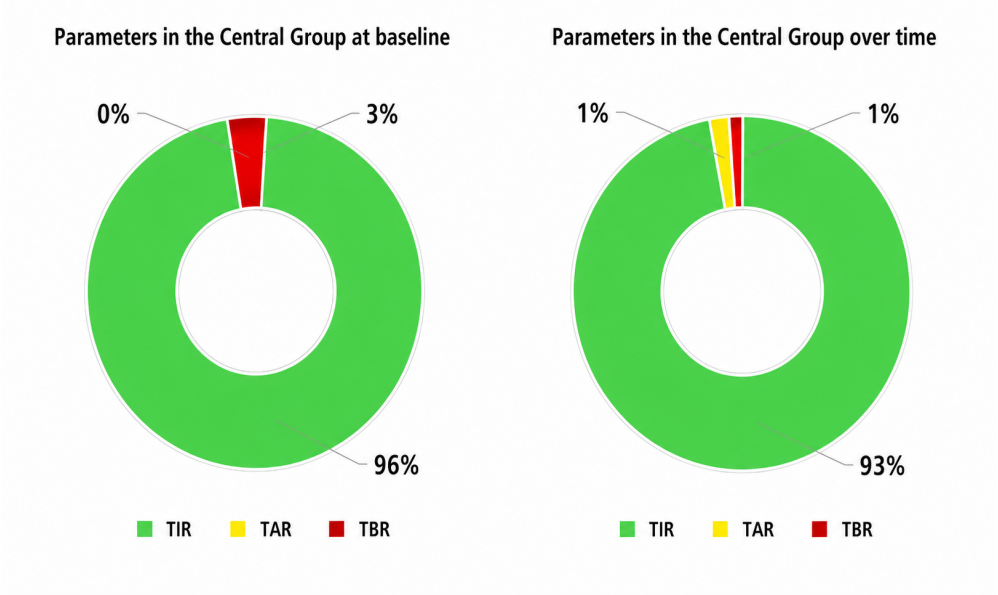


Figure 6. TIR, TAR, and TBR in the Control Group

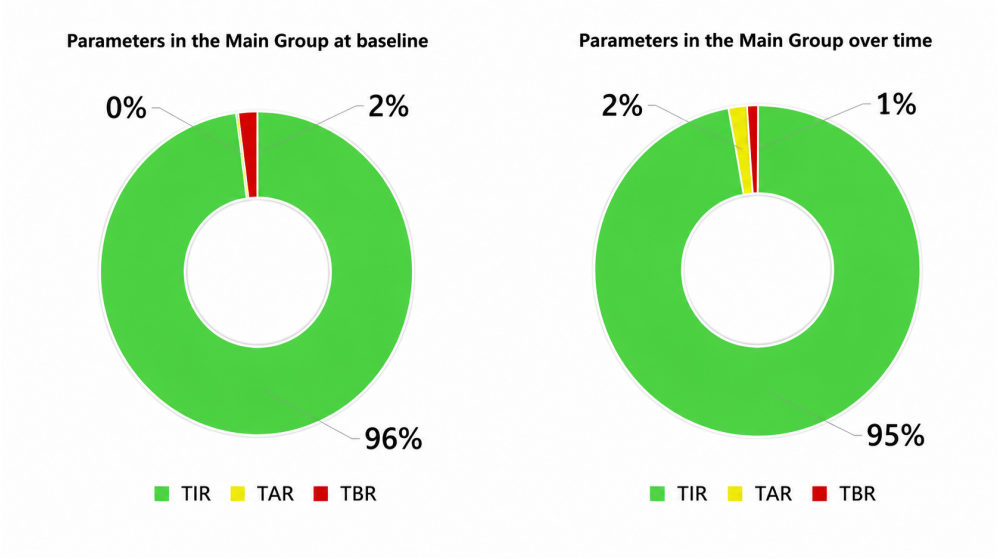


Figure 7. TIR, TAR, and TBR in the Main Group

Therefore, the evaluation of the time in, above, and below target range, provided for a conclusion of the relative stability and positive changes over time in the parameters in the OptiFibre Group vs the negative changes over time in the Control Group.

From the point of view of the DF effect on the AGP, the evaluation of the changes over time in the AGP parameters depending on the DF dose at baseline deserves special attention. Patients in the Main Group received 5g of DF daily at Study Days 1 to 3, 10 g/day at Days 4 to 6, and 15 : g/day thereafter, therefore the TIR, TAR, and TBR parameters were evaluated for the specified time intervals separately. The median TIR of patients in the Main Group was 87.60 [83.28 96.99]% at Study Days 1 to 3, 96.15 [89.8398.18]% at Days 4 to 6, and 97.24 [93.63 −99.02]% at Days 7 to 14. The median TAR was 0.00 [0.00−1.68]°∘, 0.38 [0.00−3.50]°∘ and 0.14 [0.00 1.99]% , and the median TBR was 3.43[0.99 − 15.65]°%, 0.70[0.00 − 3.73]% and 0.83 [0.074.90]%, respectively, at the specified time intervals. Thus, during the period of DF intake by patients in the Main Group, there is an obvious tendency towards an increase in the median Time In Range and approaching of this parameter to 100% , as well as a more than threefold decrease in the median Time Below Range and an approaching of this value to 0% (Fig. 10).

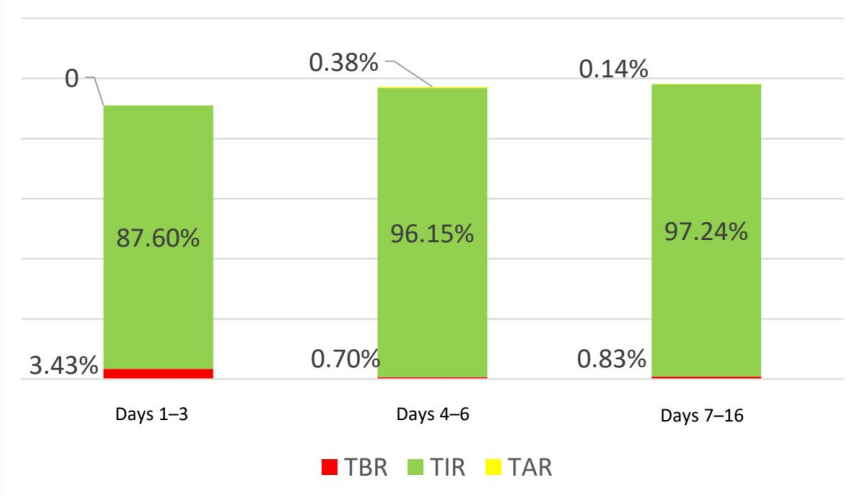


Figure 8. Changes in AGP parameters over time depending on the DF dose at baseline

For patients of the Main and Control Groups, the parameters of glucose level in, above and below target range, were compared. In both patient groups, reduction in the frequency and in the mean duration of hypoglycemic events was observed.

No statistically significant differences were found among the compared parameters; however, an increase in the coefficient of variability was observed in both groups, which may also be associated with the changes in TIR and TBR over time. Moreover, in the OptiFibre Group, the increase in this parameter was not as significant as in the Control Group, allowing to conclude that the glucose level stability was more marked in the group of patients who received DF.

The evaluation of AGP parameters showed a decrease in Time In Range, while in the Control Group it was more marked and statistically significant. In terms of Time Below Range, a reduction was also observed in both groups, but it was more marked and statistically significant in the OptiFibre Group. Finally, Time Above Range increased in the Control Group but remained unchanged in the OptiFibre Group.

The found changes indicate a positive effect of OptiFibre intake on the AGP. A statistically significant reduction in Time Below Range is a criterion for increased safety of therapy with respect to hypoglycemia, which allows considering DF as an additional component of hypoglycemic therapy, including in patients with a high risk of hypoglycemia.

A clinical example of changes over time in the AGP in a patient receiving DF

Figure 9 shows an example of the AGP data of patient V., evaluated in accordance with the "5- step" algorithm. Data quality was satisfactory (84%) . At baseline, the AGP was characterized by TIR, TAR and TBR alignment within the normal limits (89% , 5% and 6% , respectively), but at the same time, attention was drawn to the relatively high frequency and duration of hypoglycemia, mainly in the early morning hours, as well as occasionally during the day. Ten glycemic events of varying severity were observed, with a total duration of 144 minutes, including two severe hypoglycemic events, down to 2.2mmol/L . The coefficient of variability in this case was 26% which corresponded to almost the middle of the target range. The median and interdecile intervals are mostly within the target range, but the plot is neither narrow nor flat, indicating relatively high variability during the day.

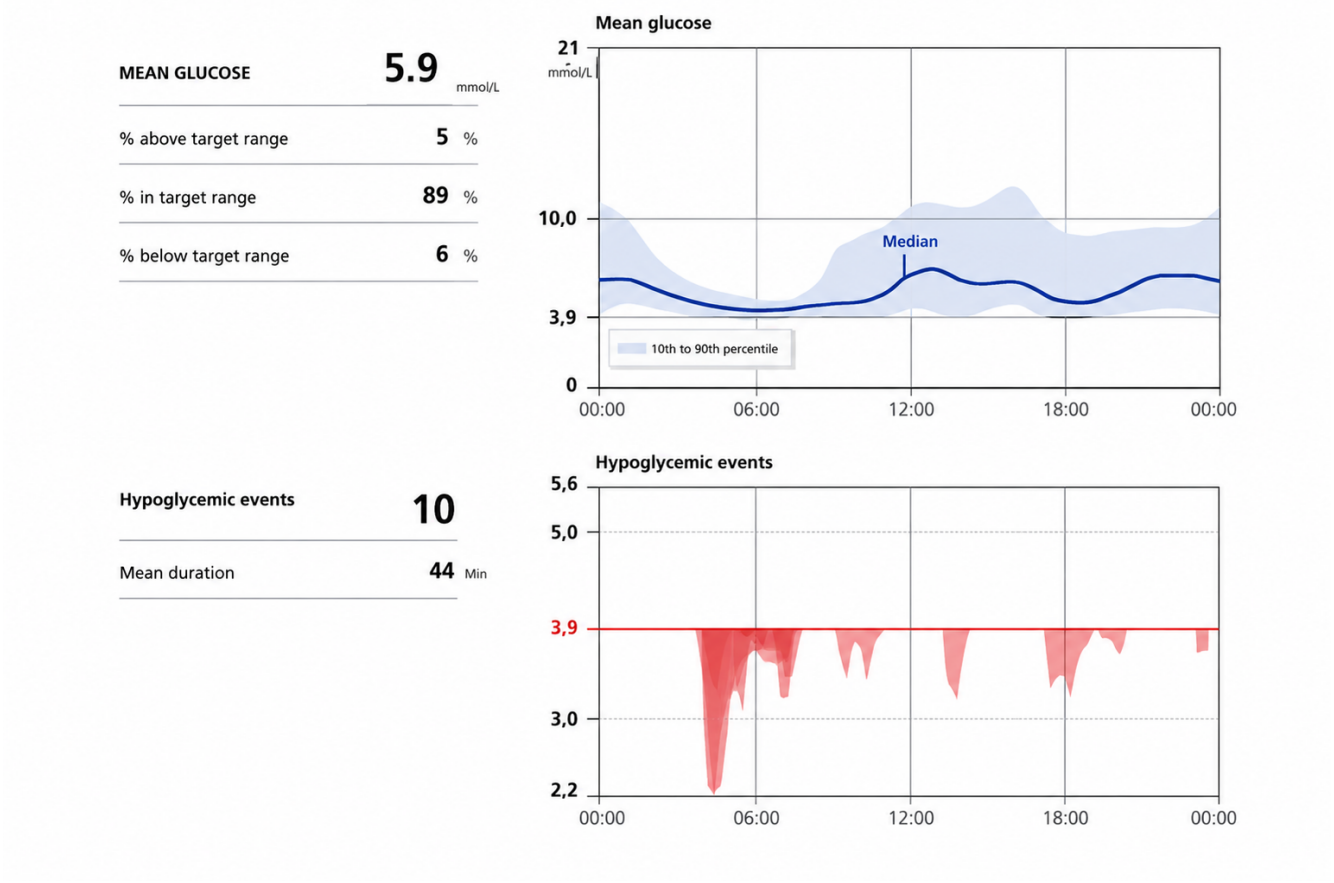


Figure 9. AGP of Patient V. at Study Day 16 ± 2 Visit

By the end of the study (Fig. 10), the quality of the AGP data was still satisfactory (the sensor activity percentage was 90). As compared with the previous AGP, TIR increased by 8% and amounted to 97% , TAR decreased by 2% , and TBR was found to decrease to 0% , which indicates almost complete absence of hypoglycemia.

This observation is further illustrated by a marked reduction in the number and duration of hypoglycemic events: only a single mild hypoglycemic event was reported in the early morning hours, lasting 59 minutes. The patient reached a more than twofold reduction in the duration of hypoglycemia. No significant changes over time were observed for the coefficient of variability: it was 27% , which is fully consistent with the physiologically normal value. Compared with the AGP at baseline, in this case a large area of the plot corresponds to the limits of the target range, and the plot is also narrower, especially during the daytime.

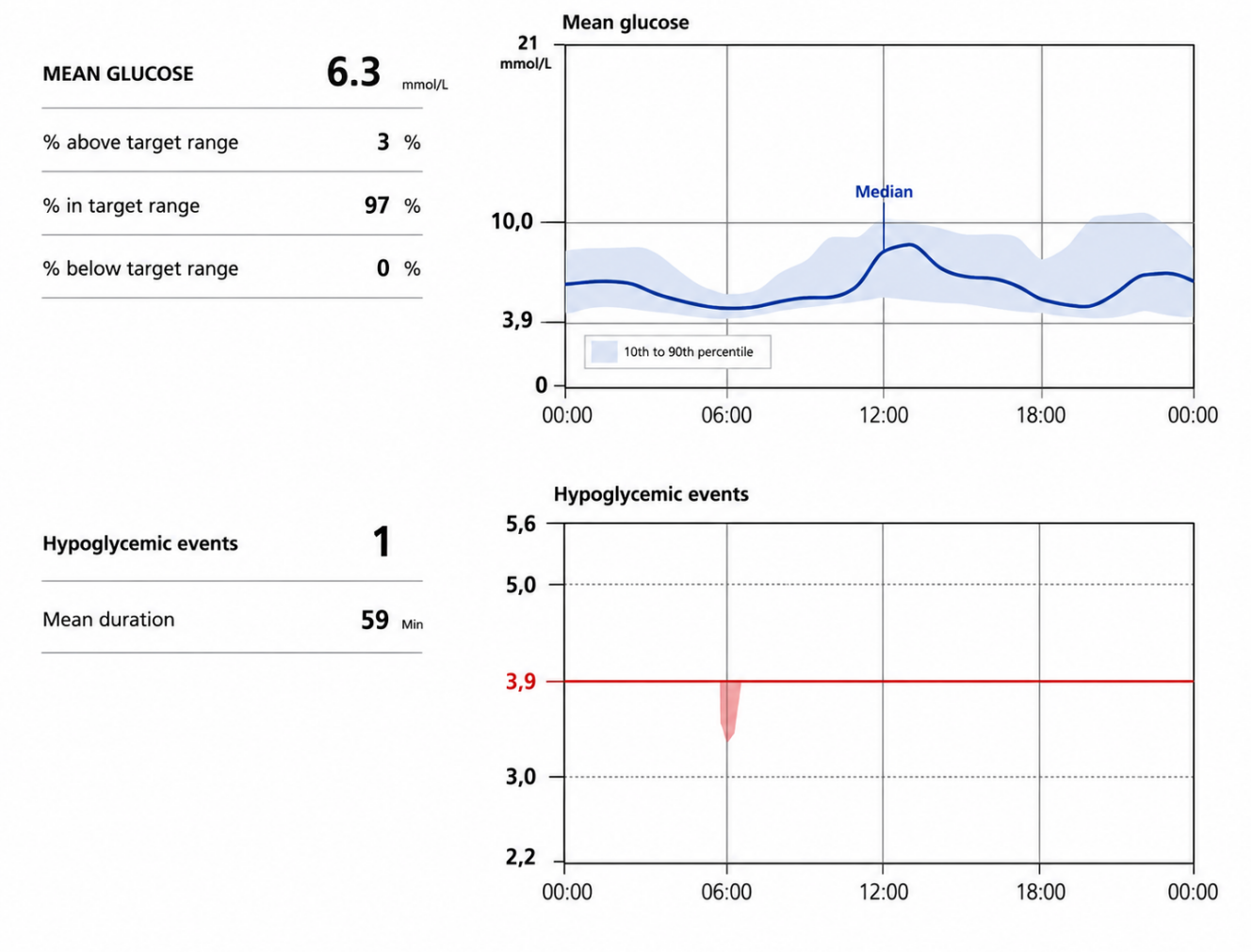


Figure 10. AGP of patient V. at Study Day 84 ± 3 Visit

7 Discussion

The study findings clearly indicate a justified positive effect of daily consumption of PHGG on carbohydrate metabolism parameters. This assumption is confirmed by a statistically significant ($p = 0.01$) decrease in HbA1c in the Main Group by 0.49% at Study Day 84 ± 3 compared with Study Day 16 ± 3 against a complete absence of changes over time in the Control Group, as well as by a decrease in fasting plasma glucose at Study Day 84 ± 3 compared with Study Day 2 ± 3 by 0.35 mmol/L ($p = 0.18$) against negative changes over time in the Control Group. It is likely that the increase in blood glucose levels in the Control Group is associated with the natural progression of T2DM, while in the OptiFibre Group not only was there no evidence of progression, but, on the contrary, evidence of a statistically significant improvement in glycemic control was found.

The AGP data showed statistically significant intergroup differences for TIR and TAR: patients in the Main Group had a statistically significantly higher TIR value and a lower TBR value. Of particular interest is the evaluation of the number of patients who experienced an increase in TIR: an increase in TIR was observed in 35% of patients, while in 15% it exceeded 10% of the baseline TIR. The findings may be associated with the fact that the partially hydrolyzed nature of the PHGGs enhanced their absorption and, as a consequence, caused a certain increase in blood glucose. The latest data are particularly relevant given the increasing attention paid to TIR in modern scientific research. Data are provided on a 64% increase in the risk of retinopathy, a 40% increase in the risk of microalbuminuria and on the risk of a 6.4% increase in the abnormal thickness of the carotid artery intima-media complex as TIR decreases by every 10% [2325]. Only 12.5% of patients had a decrease in TIR of more than 10% , indicating that the number of patients who reached positive changes over time was significantly higher compared with the number of patients with a decrease in TIR.

On the other hand, the number and total duration of hypoglycemic events decreased in both groups of patients, with the reduction being more significant in the OptiFibre Group. The obtained data can also be considered as an advantage of daily consumption of DF, which allowed patients in the Main Group to make the glucose level profile safer and to bring the parameters closer to those of healthy people relative to the Control Group.

The effect of DF on the glucose profile can be explained by a number of mechanisms, some of which have not yet been fully studied. The most obvious mechanisms include changes in gastrointestinal tract (GIT) motility when consuming DF, which results in an increase in the rate of transit of food contents and, as a consequence, a decrease in the absorption of macronutrients, including carbohydrates.

Table 6. Findings of studies investigating the effect of DF on metabolic (adapted from [29])

Authors	Sample characteristics	Duration	DF type and amount	Key findings
Su et al [30], 2021 (China)	16 patients with T2DM, aged 41–76 years	90 days	Combination of probiotics, prebiotics and whole grains (44 g/day) + standard diet	Reduction of HbA1c from 6.9 ± 1.1% to 5.9 ± 1.0% ($p < 0.01$)
Pedersen et al [31], 2016	32 male subjects with T2DM aged 42–65 years	12 weeks	Oligosaccharide mix 5.5 g/day or maltodextrin 5.5 g/day (control)	No statistically significant changes in fasting glucose or HbA1c
Farhangi et al., 2016 [32]	46 female patients with T2DM	8 weeks	Chicory (10 g/day), placebo (control)	Statistically significant reduction in fasting plasma glucose and HbA1c
Gargari et al. [33]	60 female patients with T2DM aged 30–60 years, BMI ≥ 30 kg/m^2	8 weeks	Resistant starch (10 g/day), placebo (control)	Statistically significant decrease in HbA1c (−0.3%) ($p < 0.05$)

The modulation of GM with a change in its metabolic activity, a decrease in the formation of metabolites with a negative effect and an increase in the production of SCFAs, which have a beneficial effect on a number of metabolic processes, including carbohydrate metabolism, can be considered another key mechanism. In addition, due to GM correction, systemic inflammation may be reduced in general, which may be manifested in a decrease in insulin resistance and, as a consequence, in an improvement in glycemic control [26].

Another important aspect of the interpretation of the obtained data comprises the partially hydrolyzed form of Nestlé OptiFibre DF: gums are known to be highly viscous, but due to the partially hydrolyzed form, their viscosity is significantly reduced, which makes using this form of DF more comfortable for patients [27]. Presumably, DF hydrolysis has a certain effect on increasing the amount of carbohydrates absorbed in the intestine, which would explain the effect of daily DF intake on Time Below Range reduction and bringing the AGP parameters of patients who received DF closer to the parameters characteristic of people who have no carbohydrate metabolism disorders.

To date, there are no similar Russian or foreign studies examining the long-term effect of PHGG on the glucose profile of patients with T2DM. The study closest in design to this one is that by Dall'Alba et al., which examined the effect of PHGG on key metabolic parameters in patients with T2DM over 6 weeks. A total of 44 patients were included in the study. Patients in the Main Group received 10 g of PHGG daily in addition to a standard diet, while patients in the Control Group followed a standard diet. At study completion, the Main Group showed a decrease in HbA1c from 6.88 ± 0.99% at baseline to 6.44 ± 0.94% at Study Week 4 and 6.57 ± 0.84% at Study Week 6 [28]. The main data of studies examining the effect of DF on metabolic parameters are summarized in Table 6.

Of no less interest are studies whose design involves the evaluation of the effect of DF on glucose levels using LMWH or FGM. For example, a study by Arias-Cordova et al. examined data from 10 patients with T2DM aged 2865 years with a BMI ≥ 25kg/m^2. Patients received natural banana starch, high-amylose corn starch, or easily digestible corn starch in addition to their main diet for 4 days. During the administration of DF, the FGM characteristics and variability indices were studied in patients. Patients receiving natural banana starch had the most significant increase in Time Above Range (TAR): from 11.63 [4.42, 99.57]% at Day 2 to 9.37[2.60, 94.10]% at Day 3 and 48.09 [3.12, 100.4]% at Day 4. The same parameter in the group of patients who received high-amylose corn starch increased from 100.4]% at Day 4, while in the group receiving easily digestible corn starch, on the contrary, it decreased from 14.24 [0.0, 59.20]% at Day 2 to 7.98 [0.00, 61.02]% at Day 4; however, no statistically significant changes in glycemic variability (GV) were reported in the study [34]. Studies investigating the effect of DF on the ambulatory glucose profile of T2DM patients are poorly represented in modern foreign and domestic publications. A large number of studies primarily investigated the effects of various types of nutrition and DF intake on glycemic control in patients with T1DM, which may be explained by the fact that in routine clinical practice, the use of LMWH is more common among patients with T1DM. However, given the differences in the pathogenesis of T1DM and T2DM, a comparison of the data from this study with the data from studies conducted in a population of T1DM patients is not advisable.

8 Conclusion

Therefore, this study showed a positive effect of DF on glycemic control in patients with T2DM, as demonstrated by a statistically significant reduction in HbA1c, a significant reduction in fasting plasma glucose, and a significant improvement in AGP parameters. The study data provide the basis for increasing the efficacy of T2DM therapy for both glycemic control and minimizing the risk factors for T2DM complications. The listed changes have been repeatedly substantiated from the point of view of the mechanism of action of DF and are consistent with the available data in the international publications. This study is unique in that strict inclusion criteria made it possible to create a sample of patients in whom the effect of DF on glycemic control was studied against a "clean" background, which allowed to exclude the influence of extraneous factors, and also in that the modern Russian and international literature currently presents single studies investigating the effect of DF on glycemic control in patients with T2DM using a comparable sample size and similar duration of patient follow-up. However, to achieve the goal of introducing DF into clinical guidelines for the management of patients with T2DM, further research is required to examine the effects of different types, regimens, and durations of administration, as well as the daily DF dose.

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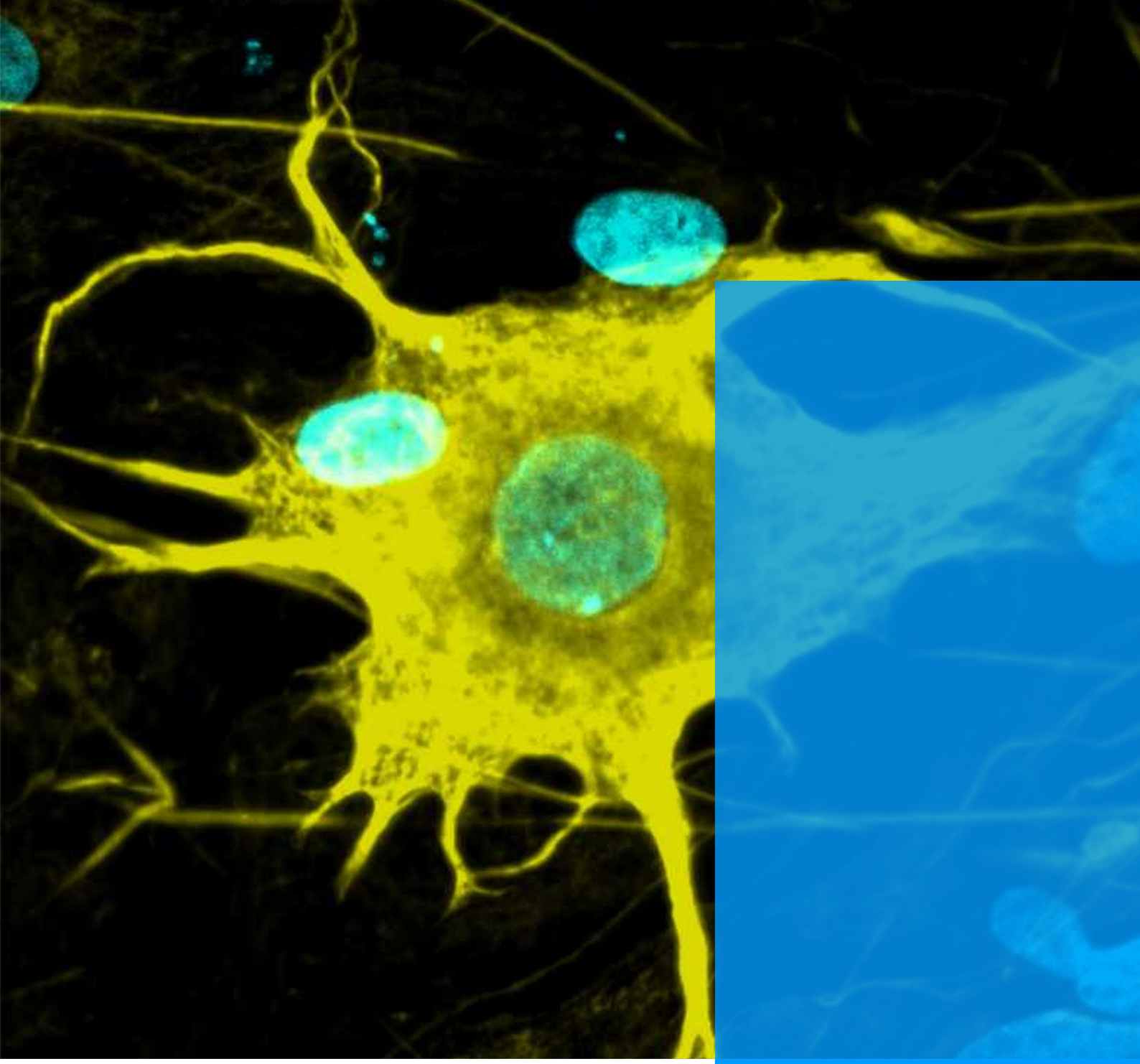

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