UDC: 616.329-002-02:616.33-008.17+616.379-008.64

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THE DUAL ASSOCIATION BETWEEN GASTROESOPHAGEAL REFLUX DISEASE AND TYPE 2 DIABETES MELLITUS

https://doi.org/10.52556/2587-3873.2025.2(104).34

Summary

Gastroesophageal reflux disease (GERD) and type 2 diabetes mellitus (T2DM) are among the most prevalent chronic conditions globally. This study aims to synthesise recent findings on the pathophysiological association between GERD and T2DM, with an emphasis on the potential for integrated therapeutic approaches. A narrative literature review was conducted using sources from PubMed, Scopus, and EMBASE. Data were extracted on epidemiology, pathophysiology, gut microbiota, inflammatory markers, diagnostic challenges, and therapeutic implications. Recent evidence highlights a bidirectional interaction between GERD and T2DM, contributing to mutual disease exacerbation and suboptimal patient outcomes. T2DM predisposes to GERD via autonomic neuropathy, delayed gastric emptying, and altered oesophageal motility. Conversely, GERD impairs glycaemic control through disrupted sleep, poor medication adherence, and increased counter-regulatory hormone levels. Obesity, dysbiosis, and proinflammatory adipokines, such as leptin, tumour necrosis factor-α (TNF-α), further link both diseases. Despite consensus guidelines, screening for GERD in diabetics and vice versa remains underutilised. Emphasis should be placed on early screening using validated tools, targeted weight management, and dual-purpose therapies. Innovative pharmacologic agents such as GLP-1 receptor agonists and microbiota-directed therapies hold promise for management in both diseases. The GERD-T2DM connection reflects a shared metabolic-inflammatory pathophysiology requiring an important shift toward integrated care models. Collaboration between gastroenterologists, endocrinologists, and family physicians is essential.

Keywords: *gastroesophageal reflux disease, Type 2 diabetes mellitus*

Rezumat

Asocierea bidirecțională dintre boala de reflux gastroesofagian și diabetul zaharat de tip 2

Boala de reflux gastroesofagian (BRGE) și diabetul zaharat de tip 2 (DZT2) se numără printre cele mai răspândite afecțiuni cronice la nivel global. Acest studiu își propune să sintetizeze descoperirile recente privind asocierea dintre BRGE și DZT2, cu accent pe potențialul abordărilor terapeutice integrate. A fost efectuată o analiză narativă utilizând literatura de specialitate națională și internațională publicată, cu aplicarea motorului de căutare din PubMed, Scopus și EMBASE. Studiile recente evidențiază o interacțiune bidirecțională între BRGE și DZT2, ceea ce contribuie la exacerbarea reciprocă a acestor patologii și rezultate suboptimale la tratament. DZT2 predispune la BRGE prin neuropatie autonomă, golire gastrică întârziată și motilitate esofagiană alterată. În schimb, BRGE afectează glicemia prin aderența slabă la tratament, motivată fiind de simptomele chinuitoare nocturne. Obezitatea, dimicrobismul intestinal și adipokinele proinflamatorii leagă în continuare ambele patologii. În ciuda recomandărilor ample stipulate de ghiduri, screeningul pentru BRGE la diabetici și viceversa nu este standardizat și efectuat sporadic. Atenția specialiștilor ar trebui îndreptată spre diagnosticul precoce folosind instrumente validate și intervenții terapeutice comune precum gestionarea țintită a greutății și terapii cu dublă utilizare. Agenții farmacologici inovatori, cum ar fi agoniștii receptorilor GLP-1 și terapiile direcționate către microbiotă, sunt promițători pentru gestionarea ambelor boli. Legătura bidirecțională dintre BRGE și DZT2 reflectă mecanisme fiziopatologice comune, care necesită o schimbare importantă către modele de îngrijire integrată. Colaborarea dintre gastroenterologi, endocrinologi și medicii de familie este esențială.

Cuvinte-cheie: *boala de reflux gastroesofagian, diabet zaharat de tip 2*

Резюме

Двунаправленная ассоциация между гастроэзофагеальной рефлюксной болезнью и сахарным диабетом 2 типа

Гастроэзофагеальная рефлюксная болезнь (ГЭРБ) и сахарный диабет 2 типа (СД2) являются одними из наиболее распространенных хронических заболеваний в мире. Целью данного исследования является синтез последних результатов патофизиологической связи между ГЭРБ и СД2 с акцентом на потенциале комплексных терапевтических подходов. Описательный обзор был проведен с использованием литературы полученной из PubMed, Scopus и EMBASE. Последние данные подчеркивают двунаправленное взаимодействие между ГЭРБ и СД2, что способствует взаимному обострению заболевания и неблагоприятным результатам лечения. СД2 предрасполагает к ГЭРБ через автономную нейропатию, замедленное опорожнение желудка и измененную моторику пищевода. С другой стороны, ГЭРБ ухудшает гликемию через нарушенный сон, плохое соблюдение приема лекарств и повышенные уровни контррегуляторных гормонов. Ожирение, дисбактериоз и провоспалительные адипокины, такие как лептин, фактор некроза опухоли-α еще больше связывают оба заболевания. Несмотря на консенсусные рекомендации, скрининг ГЭРБ у диабетиков и наоборот остается недостаточно используемым. Следует уделять больше внимания раннему скринингу, целенаправленному контролю веса и терапии двойного назначения. Инновационные фармакологические агенты, такие как агонисты рецепторов ГПП-1 и направленная на микробиоту терапия, обещают быть эффективными для лечения обоих заболеваний. Связь ГЭРБ-СД2 отражает общую патофизиологию требующую важного сдвига в сторону интегрированных моделей лечения. Сотрудничество между гастроэнтерологами, эндокринологами и семейными врачами имеет важное значение.

Ключевые слова*: гастроэзофагеальная рефлюксная болезнь, сахарный диабет 2 типа*

Introduction

With each impacting more than 10% of the adult population, gastroesophageal reflux disease (GERD) and type 2 diabetes mellitus (T2DM) are among the most frequent chronic conditions worldwide [43,42]. Consistent epidemiological evidence has shown that patients with diabetes have GERD more often and a more severe type. A 2015 study by Wang et al. showed symptomatic GERD incidence of 40–50% in individuals with T2DM as opposed to 18–20% in the general population [43]. Endoscopic studies have also shown higher rates of erosive esophagitis and Barrett's oesophagus in T2DM patients. Furthermore, GERD symptom intensity and treatment resistance are positively correlated with the severity and duration of diabetes as well as with inadequate glycaemic control (HbA1c > 8%) [42].

Although the individual pathophysiological mechanisms of each disease are well established, increasing evidence suggests their frequent co-occurrence and exhibits a complex, bidirectional interaction that is often under-recognised in both clinical and academic environments. The implications of this connection affect treatment effectiveness, quality of life, and healthcare costs as well as symptom burden and disease progression [25].

A growing body of evidence highlights the prevalence and clinical impact of gastrointestinal (GI) complications in individuals with T2DM. Notably, studies indicate that a substantial proportion of individuals with T2DM, ranging from 40% to 50%, experience symptoms consistent with GERD. This high prevalence underscores the importance of considering and actively screening for GI symptoms in the management of T2DM [11].

The underlying mechanisms contributing to these GI complications in T2DM are multifaceted and may involve factors such as autonomic neuropathy affecting the nerves that control GI motility, alterations in gut hormones, and the impact of hyperglycaemia on smooth muscle function within the digestive tract [25].

In individuals with T2DM, diabetic autonomic neuropathy is a key factor in the development of GERD. This neuropathy leads to impaired vagal function, resulting in altered gastric motility and delayed gastric emptying. Consequently, intra-abdominal pressure (IAP) increases, promoting reflux. Furthermore, hyperglycaemia worsens GERD symptoms by reducing lower oesophageal sphincter (LES) tone [25, 11]. Concomitantly, GERD may reciprocally impact glycaemic control in diabetic individuals. Heartburn and regurgitation, two reflux-related symptoms, might interfere with oral consumption and drug adherence, therefore exacerbating glycaemic variability [29].

Obesity is found to be a common denominator in the pathophysiological pathways of GERD as well as T2DM, according to many studies conducted. A major cause of GERD development, central obesity raises IAP and encourages momentary LES relaxations [10]. Simultaneously, visceral adiposity releases inflammatory adipokines, such as leptin and resistin, thus aggravating insulin resistance and pancreatic β-cell stress [2].

The part of the gut microbiota is yet another field of study developing. Changes in microbial diversity and composition have been associated with both metabolic syndrome and functional GI diseases. Dysbiosis could further aggravate the clinical course of patients with coexisting GERD and T2DM by influencing mucosal integrity, immune responses, and gut-brain axis signalling [2].

These findings help to validate the theory that, via several processes, GERD and T2DM are pathophysiologically linked with each other rather than just comorbid conditions. Developing integrated diagnostic, preventative, and therapeutic approaches depends on their bidirectional interrelationship. Given the growing worldwide burden of both diseases and their effect on patient's quality of life, a multidisciplinary approach including gastroenterology, endocrinology, nutrition, and behavioural medicine is required. This article highlights the significance of integrated management for patients with both GERD and T2DM to improve patient outcomes.

Aim of the study

This study aims to explore and synthesise current evidence regarding the interrelationship between GERD and T2DM, with an emphasis on shared risk factors, underlying mechanisms, and clinical implications.

Materials and methods

A comprehensive literature review of publications from 2000 to 2025 was conducted using a thorough search through PubMed, Scopus, and EMBASE. We used Medical Subject Headings (MeSH) and free-text keywords, particularly "GERD AND diabetes", "gastroparesis AND diabetes", and "LES dysfunction AND hyperglycemia" combined. From every suitable article, we gathered information on prevalence rates, underlying pathophysiological mechanisms, patient quality-of-life indices, and reported therapeutic interventions.

Finally, original publications, narrative articles, and meta-analysis studies, which presented relevance and innovation on this subject, were selected.

When necessary, other sources of information were consulted to explain and clarify certain concepts. After a thorough analysis of the articles, 50 bibliographic references were included in the literature review.

Results

Epidemiologically, several big cohort studies and meta-analyses have shown that the prevalence of GERD among patients with T2DM varies from 25% to 50%, substantially larger than the 10% to 20% prevalence seen in the general population [42]. Wang et al. in 2015, discovered that 43% out of 3,000 diabetic patients in a population-based investigation demonstrated classic GERD symptoms including heartburn and regurgitation, while 18% had endoscopically confirmed erosive esophagitis [43]. This disparity was even more pronounced among patients with poorly controlled diabetes, longer course of disease duration, and those with coexisting diabetic complications such as neuropathy, nephropathy, and obesity [4, 43].

One of the most critical mechanisms underlying GERD in T2DM patients is autonomic neuropathy. Chronic hyperglycemia damages the vagus nerve (CN-X), disrupting its regulation and influencing gastrointestinal motility. This results in delayed gastric emptying- gastroparesis, characterised by the slowed transit of food from the stomach to the small intestine.[48,26] Impaired GI motility also leads to an increase in IAP, and a higher frequency of transient lower oesophageal sphincter relaxations (TLESRs), all of which promote the retrograde movement of gastric acid into the oesophagus[27,31]. High-resolution manometry studies have shown significantly lower baseline LES pressure and prolonged oesophageal acid exposure in diabetic patients, particularly in those with confirmed autonomic dysfunction [49].

Hyperglycemia adversely affects oesophageal motility, aggravating underlying diseases via a complicated set of processes. Notably, abrupt blood glucose level changes have been shown to directly impair the activity of smooth muscle inside the oesophagus and help to lower LES tone. At least in part, perturbations in nitric oxide production and alterations in intracellular calcium signalling pathways mediate this impairment [9]. A randomised crossover experiment run by Zhang, Q. in 2004 showed a notable negative connection between LES pressure and postprandial glucose spikes, therefore increasing reflux event vulnerability [43]. Furthermore, chronic hyperglycemia causes systemic inflammation, with increased cytokine levels including tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), all of which are known to impair tissue repair and disrupt insulin signalling [33, 15].

Also, reciprocally impacting glycaemic control and diabetes management is GERD. Chronic reflux symptoms like heartburn, oesophageal pain, and regurgitation can cause erratic eating habits and food avoidance, therefore leading to unstable blood glucose levels [23]. Nocturnal GERD attacks contribute to sleep fragmentation and increased cortisol and catecholamine levels, both of which promote hepatic gluconeogenesis and aggravate insulin resistance [45, 47]. Poor sleep has been consistently related to elevated HbA1c levels and diminished adherence to antidiabetic plans [35]. In a recent study, T2DM patients with untreated GERD had a 0.5% higher HbA1c over six months than individuals receiving efficient GERD treatment [24]. Furthermore, chronic oesophageal inflammation also leads to increased systemic cytokines like TNF-α and IL-6, which are known to exacerbate insulin resistance and glucose metabolism [27, 33].

Obesity serves as a central mediating factor in the GERD-T2DM axis. Central adiposity raises intra-abdominal pressure, promoting reflux by mechanically compromising the LES [21,6]. Additionally, adipose tissue functions as an active endocrine organ, releasing adipokines such as leptin, resistin, and adiponectin. Leptin has been shown to promote nitric oxide-mediated smooth muscle relaxation in the LES by modulating its synthesis in oesophageal tissues, reducing its tone and predisposing to GERD symptoms [32,13]. Low levels of adiponectin, which have anti-inflammatory and insulin-sensitising effects, are commonly observed in both obese and diabetic individuals and are correlated with increased GERD symptom severity and mucosal inflammation [13, 32].

Recent studies also implicate gut microbiota as a shared pathological substrate in GERD and T2DM. Dysbiosis is defined as an imbalance in microbial populations and is known to alter bile acid metabolism, impair mucosal integrity, and affect gastrointestinal motility [50,3]. Patients with T2DM often display reduced microbial diversity and an increased Firmicutes-to-Bacteroidetes ratio, which has been associated with insulin resistance and mucosal inflammation [22, 34]. Secondary bile acids produced by dysbiotic bacteria can activate TGR5 receptors on smooth muscle cells, further lowering LES tone and contributing to reflux [20]. Dysbiosis-derived bile acids can modulate LES tone and worsen reflux episodes, while decreased levels of advantageous SCFAs, such as butyrate, could impair mucosal healing and increase oesophageal sensitivity to acid exposure [36].

Screening practices remain suboptimal despite the clear epidemiological and pathophysiological overlap. A survey-based study found that very few endocrinologists routinely assessed GERD symptoms in their diabetic patients, and only some employed validated symptom questionnaires such as the GERD Questionnaire (GERDQ). The result is underdiagnosis and undertreatment of GERD in diabetic populations, particularly among those with atypical or extra-oesophageal symptoms such as chronic cough, hoarseness, or asthma. Conversely, gastroenterologists rarely screen GERD patients for T2DM, even though acid suppression therapy may mask classic diabetic symptoms like polyuria and polydipsia [25, 46].

The diagnostic overlap between GERD and T2DM is further complicated by atypical presentations, particularly in elderly patients, pregnant women with gestational diabetes, and individuals with type 1 diabetes mellitus (T1DM). These subpopulations present unique challenges in clinical identification and therapeutic intervention, often resulting in delayed diagnosis and suboptimal outcomes. Additionally, cultural, socioeconomic, and behavioural determinants play a pivotal role in disease manifestation and healthcare access, necessitating context-sensitive strategies for diagnosis and management [14, 40, 44].

Discussion

By combining the existing material, GERD and T2DM do have a greater degree of coexistence and interdependence. Many epidemiological, clinical, and mechanistic investigations have investigated this bidirectional link, and all results repeatedly show a mutual worsening of symptoms, illness burden, and treatment complexity. Here, the results presented combine findings from several populations and clinical cohorts which investigated the prevalence, risk factors, mechanisms, and clinical consequences of this interrelationship.

One of the key themes in understanding the GERD–T2DM relationship is the emerging recognition of metabolic and immunological convergence between the two conditions. Both diseases are characterised by chronic low-grade inflammation, which contributes to disease pathogenesis and progression. Several studies have demonstrated that the inflammatory markers elevated in T2DM, such as interleukin-1β, tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), are also associated with increased GERD symptom severity [25, 33, 15].

Moreover, oxidative stress has been increasingly implicated in the pathophysiology of both GERD and T2DM. Hyperglycemia promotes mitochondrial dysfunction and reactive oxygen species (ROS) production, which impairs neuronal and vascular function [44]. Similarly, oxidative stress in the oesophageal epithelium has been shown to contribute to mucosal damage and impaired healing responses in GERD [7, 12].

Another evolving concept is the potential role of neuroendocrine signalling pathways in bridging GERD and T2DM. The gut-brain axis, encompassing the vagus nerve, enteric nervous system, and neurohormonal pathways, is disrupted in diabetes through autonomic neuropathy [1]. This disruption not only alters gastric motility and LES tone but also affects central processing of satiety and discomfort, potentially modifying symptom perception in GERD. Additionally, hormones such as ghrelin, glucagon-like peptide-1 (GLP-1), and cholecystokinin-integral to glucose metabolism and gastrointestinal function, may serve dual roles in regulating both glycaemic status and reflux activity [19]. Therapeutic agents targeting these hormones, including GLP-1 receptor agonists, are now being evaluated for their potential to address both metabolic and gastrointestinal symptoms in T2DM patients [37].

The clinical impact of GERD on quality of life and diabetes outcomes is significant but often underestimated. Reflux-related sleep disturbances, for example, are common in GERD and have downstream consequences for glycaemic control, as poor sleep is associated with increased cortisol, reduced insulin sensitivity, and appetite dysregulation [45,41]. Several studies have suggested that treatment of GERD, whether through pharmacologic or lifestyle means can improve sleep quality and, by extension, metabolic outcomes. Nevertheless, there is a paucity of prospective interventional studies evaluating whether aggressive reflux control leads to sustained improvements in glycaemic indices in T2DM patients [25, 29].

Polypharmacy is another issue that complicates the management of coexisting GERD and T2DM. Patients with both conditions often require multiple medications, including insulin, metformin, SGLT2 inhibitors, and proton pump inhibitors (PPIs). Drug-drug interactions altered absorption due to changes in gastric pH, and overlapping adverse effect profiles can complicate therapeutic planning. For instance, chronic PPI use has been associated with hypomagnesemia, altered gut microbiota, and even increased risk of enteric infections, all of which could worsen diabetic outcomes [18]. Conversely, metformin may exacerbate gastrointestinal symptoms, including bloating and abdominal discomfort, which can be misattributed to GERD or even exacerbate true reflux episodes [16, 30].

Another underexplored but potentially important area is the role of genetic predisposition in the

GERD-T2DM axis. Genome-wide association studies (GWAS) have identified several loci associated with both conditions, including polymorphisms near the FTO and TCF7L2 genes, which are known to influence both metabolic regulation and gastrointestinal motility [8, 39].

Despite the wealth of emerging evidence, current clinical practices continue to treat GERD and T2DM as siloed entities. This fragmented approach ignores the intricate web of interactions that sustain and exacerbate these diseases. The present findings argue for a paradigm shift toward integrated care models, wherein endocrinologists, gastroenterologists, nutritionists, and behavioural therapists collaborate to develop comprehensive treatment strategies. Consensus guidelines recommending routine screening for GERD symptoms in individuals with long-standing diabetes, implementation remains low [25, 40]. Similarly, patients presenting with refractory GERD symptoms or atypical manifestations such as chronic cough or hoarseness are rarely evaluated for glycaemic abnormalities unless obvious risk factors are present.

Sociodemographic factors further modulate the GERD-T2DM relationship. Socioeconomic status, race, and education level influence access to healthcare, dietary habits, medication adherence, and risk perception. Lower-income groups tend to have higher rates of both GERD and T2DM yet are less likely to receive guideline-concordant care [38, 40].

Additionally, dietary patterns have been identified as shared contributors to both GERD and T2DM pathogenesis. Diets rich in processed carbohydrates, saturated fats, and low in fibre promote insulin resistance while also increasing the risk of reflux through delayed gastric emptying and increased gastric acid production [25]. On the other hand, Mediterranean-style diets have been associated with reduced GERD symptoms and better glycaemic control.

Emerging research has also suggested that circadian rhythm disturbances may play a role in the GERD-T2DM axis. Disruption of the sleep-wake cycle has been linked to both metabolic dysregulation and increased GERD symptoms [35, 47].

Moreover, data on non-Western populations remain sparse. Considering that both GERD and T2DM are increasing rapidly in Asia, Africa, and Latin America, region-specific studies are crucial to understanding cultural, genetic, and environmental influences on disease interplay [28].

From a therapeutic perspective, future research should prioritise trials evaluating combined pharmacological strategies that target both conditions, such as GLP-1 receptor agonists or microbiota-directed therapies like faecal transplantation [19]. Future therapeutic research for GERD should focus on clinical trials assessing combined pharmacological approaches that simultaneously address both the gastrointestinal and extraesophageal manifestations of the disease. This is particularly relevant given the growing understanding of overlapping pathophysiological mechanisms and the frequent comorbidity with conditions like obesity and metabolic syndrome.

Promising avenues include the investigation of GLP-1 receptor agonists, which have shown efficacy in weight management and may also exert beneficial effects on oesophageal motility and inflammation. Another critical area for exploration is microbiota-directed therapies, such as faecal microbiota transplantation (FMT), prebiotics, and probiotics. Evidence suggests a link between gut dysbiosis and GERD symptoms, and manipulating the gut microbiome could offer a novel therapeutic strategy.

Rigorous, well-designed trials are needed to evaluate the safety and efficacy of these combined and microbiota-focused interventions in diverse GERD patient populations, considering factors such as disease severity, presence of comorbidities, and long-term outcomes. Further research into the underlying mechanisms of action will also be crucial for optimising these therapeutic approaches.

Advancements in digital medicine offer additional avenues for innovation. Telemedicine platforms can facilitate early diagnosis and continuous management of GERD and T2DM, especially in underserved regions. Wearable glucose monitors, reflux detection patches, and AI-assisted dietary logging systems can empower patients to manage their conditions more effectively while providing clinicians with real-time data for decision-making.

Conclusion

The evidence reviewed in this study strongly supports a bidirectional and multifactorial relationship between GERD and T2DM, highlighting the urgent need for integrated, cross-disciplinary clinical and research approaches.

From an epidemiological standpoint, diabetic individuals exhibit a significantly elevated risk of GERD symptoms and complications, such as erosive esophagitis and Barrett's oesophagus. Conversely, GERD, particularly when persistent and nocturnal, can disrupt metabolic control by impairing sleep quality and exacerbating stress hormone levels, thereby increasing insulin resistance.

Both conditions, among the most prevalent chronic disorders globally, share a constellation of pathophysiological mechanisms, including autonomic

dysfunction, hormonal dysregulation, chronic inflammation, oxidative stress, and gut microbiota dysbiosis, that fuel a vicious cycle of mutual exacerbation.

For the diagnosis, implementation of routine GERD symptom screening in diabetic patients and vice versa, particularly through validated instruments like the GERDQ and routine HbA1c screening in reflux patients, is imperative.

In terms of therapeutics, several dual-targeted strategies show promise. Weight loss through lifestyle intervention, bariatric surgery, and dietary modification significantly benefits both conditions. Pharmacologic agents such as GLP-1 receptor agonists, which modulate gastric emptying and improve insulin sensitivity, hold potential for simultaneous treatment. Moreover, modulation of gut microbiota via tailored probiotic formulations and microbiota transplants could revolutionise the management of metabolic-GI comorbidities. However, to fully validate these approaches, robust, longitudinal studies are needed.

GERD and T2DM are no longer separable comorbidities but must be recognised as interwoven conditions requiring comprehensive, patient-centred care. Recognising their mutual influence is critical to preventing disease progression, reducing complications, and improving overall quality of life. By aligning research priorities and clinical guidelines toward an integrative model, the healthcare system can more effectively address the needs of a growing global population burdened by these chronic conditions.

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