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Diabetes mellitus and associated complications in the digestive tract

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ABSTRACT

Diabetes mellitus presents an increasing prevalence and severe multisystemic complications, with notable personal, professional and social implications. Diabetes is generally known by hyperglycemia and subsequent metabolic disorders. In addition to hyperglycemia, it appears that other factors (related to anthropometric-pathophysiology and genome-based subphenotyping) are involved not only in the clinical course but also in the occurrence of diabetes complications. This review presents several diabetes-induced complications on the digestive tract (periodontal disease, xerostomia, oral infections, dental caries, taste disturbances, gastroesophageal reflux disease, gastroparesis, gastric ulcer and cancer, diabetic enteropathy, inflammatory bowel diseases, colorectal cancer, etc.), many of them with major implications and unfavorable long-term prognosis. Consequently, prompt recognition and treatment of diabetes and its complications, as well as strict follow-up education, still remain essential for the effective management of this complex metabolic disease.

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Introduction

Diabetes mellitus is a metabolic disease characterized by the chronic exposure of tissues to elevated blood glucose levels, affecting more than 425 million people worldwide [1]. This prevalence is expected to rise due to population growth, urbanization, and the adoption of a Western lifestyle rich in processed foods and excessive meat consumption [2]. Clinical and laboratory studies show the essential role of oxidative stress reactions in the pathogenesis of type 1 and 2 diabetes, both in terms of specific clinical manifestations and in the development of complications. Not only elevated blood glucose and oxidative stress, but also other factors such as blood pressure, heart rate, plasma lipids, serum uric acid, body weight etc. seem to contribute to the development of diabetes complications.

The most well-documented complications of diabetes are related to vascular involvement, including micro- and macroangiopathy, which increase the risk of cardiovascular disease, chronic kidney disease, retinopathy, and neuropathies. However, complications from the digestive tract are less known by doctors from other specialties [3]. This review aims to identify the main gastrointestinal complications of diabetes mellitus from the literature, explore the mechanisms supporting these complications, examine how specific treatments may influence them, and

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assess whether there is a bidirectional relationship between preexisting diseases and diabetes regarding onset, treatment, and any specific considerations that should be factored into the management of such patients.

Discussions

Oral cavity involvement

Elevated blood glucose levels can affect the oral cavity by impairing neutrophil function, collagen synthesis, and collagenase activity, as well as through microangiopathy and neuropathy. As a result, 90% of diabetic patients develop one or more oral pathologies [4]. Common conditions include dental caries, gingivitis, oral candidiasis, taste disorders, xerostomia, and delayed wound healing within the oral cavity [5].

Periodontal disease

Periodontal disease is characterized by chronic inflammation due to the formation of biofilm on the tooth surface, caused by gram-negative bacteria such as Porphyromonas gingivalis and Tannerella forsythia [6], which lead to the destruction of periodontal bone. The presence of bacterial lipopolysaccharides and genetic material triggers increased production of pro-inflammatory cytokines that activate the nuclear factor κB (NF-κB) pathway, leading to neutrophil activation and the release of reactive oxygen species (ROS) [7].

This cascade stimulates osteoclast activity, resulting in tissue destruction. Diabetic patients, due to their elevated blood glucose levels, experience higher bacterial growth [8] and increased levels of pro-inflammatory proteins such as TNF-α, IL-1β, and prostaglandin E, which further promote osteoclast formation and ongoing bone destruction [9].

Another mechanism contributing to increased bone destruction involves the interaction between advanced glycation end-products (AGEs) and their receptor (RAGE) via the RANKL pathway [10], which promotes neutrophil activation and ROS release, ultimately leading to osteoblast apoptosis [11].

The relationship between diabetes and periodontal disease is bidirectional. Chronic inflammation in the oral cavity due to bacterial infection can increase insulin resistance [12] and may result in bacteremia with the release of pro-inflammatory mediators, further exacerbating insulin resistance and stimulating excessive insulin production by pancreatic β-cells, eventually leading to their depletion. However, appropriate treatment of periodontal disease can improve glycemic control [4].

Treating periodontal disease in diabetic patients plays a crucial role in reducing glycated hemoglobin (HbA1c) levels, fasting blood glucose, and peak glucose levels. Systemic administration of minocycline, the use of topical antimicrobial agents, or, in extreme cases, root and tooth extraction can lead to glycemic reductions of 8.95 to 10 mg/dL compared to patients without such treatment [13]. Furthermore, good oral hygiene through proper brushing can improve glycemic control compared to patients who neglect or perform inadequate oral care, suggesting that rigorous oral hygiene could be an effective adjunctive measure for glycemic control (between blood sugar control and the inflammatory and infectious status, there is a mutual relationship) [14].

Xerostomia in diabetic patients

Xerostomia, or dry mouth, is characterized by a sensation of oral dryness and can occur in various chronic inflammatory diseases, including diabetes mellitus [15]. In diabetic patients, structural changes in the salivary glands, systemic inflammatory alterations, and autonomic neuropathy can result in inadequate saliva quantity and poor quality [16]. The consequences include more frequent dental caries, fungal infections, and worsening periodontal disease, along with dysphagia, dysgeusia, and difficulties with speech and chewing, which collectively reduce patients' quality of life [17]. Treatment for xerostomia focuses on stimulating saliva production through the use of malic or citric acid, which have strong sialogogue effects. Incorporating these agents into chewing gums can further activate salivary glands via mechanical action [18].

In diabetic patients, it is essential to use sugar-free chewing gum to avoid glycemic spikes. Another option is the use of several cholinergic agents like pilocarpine and cevimeline, though these drugs carry risks of cardiovascular side effects or asthma exacerbations [17]. Artificial saliva products enriched with negatively charged polymers, known for their good biodegradability and biocompatibility, can also be effective. These products are available in the form of solutions or liposomes and have shown promising results in alleviating symptoms [19].

Increased susceptibility to oral infections in diabetic patients

Patients with elevated blood glucose levels are more prone to bacterial and fungal infections in the oral cavity due to increased bacterial growth and immune suppression [20]. Dental caries are more common in these patients, partly due to the proliferation of Streptococcus mutans, a bacterium that converts carbohydrates into acids [21]. Additionally, reduced saliva secretion and altered saliva composition, combined with a high-calorie diet and poor oral hygiene, further exacerbate the problem [22].

Caries progression is particularly accelerated in patients with type 1 diabetes, as both elevated glucose levels and a significant reduction in the quality and quantity of saliva impair the immune defense of the oral cavity. Improved glycemic control associated with better oral hygiene measures contributes significantly to improving this condition. [23,24].

Management of dental caries in diabetic patients

When treating dental caries in diabetic patients, a minimally invasive approach is preferred. Efforts should focus on preserving as much of the dental pulp as possible, while avoiding extensive cavity excavation and fillings. The use of bactericidal solutions, proper oral hygiene, and substitute solutions can extend the lifespan of affected teeth. Nyvad et al. demonstrated that maintaining proper dental hygiene could delay the need for invasive interventions by approximately 18 months [25].

Taste disorders in diabetic patients

Taste disorders can occur in diabetic patients due to nerve damage that impairs the transmission of impulses to the brain, as well as altered interactions between substances and taste receptors caused by elevated blood glucose levels [26]. These dysfunctions can affect sensitivity and the ability to distinguish between different tastes, even in the absence of autonomic or sensory neuropathy, especially in patients with type 1 diabetes, where an autoimmune component plays a significant role [27].

Esophageal involvement

Esophageal dysfunction in diabetic patients arises through several mechanisms, including hyperglycemia, changes in esophageal biomechanics, and alterations in the shape of the esophagus. These factors facilitate the development of gastroesophageal reflux disease (GERD) and impair esophageal motility [28]. High glucose levels can reduce the velocity and amplitude of peristaltic waves by up to 10 mmHg compared to normal baseline values, which leads to relaxation of the lower esophageal sphincter (LES) [29]. This effect is further exacerbated by decreased parasympathetic activity through vagus nerve dysfunction, promoting the occurrence of reflux disease [30].

Increased blood glucose levels also affect extracellular signaling within the esophagus. Accumulation of extracellular matrix proteins, as a consequence of AGE (advanced glycation end-product) buildup, reduces esophageal distensibility and impairs the transport of food from the pharynx to the stomach [31]. AGEs further disrupt esophageal motility by binding to cell surface receptors, stimulating the production of collagen- and fibronectin-rich extracellular matrix, leading to esophageal wall remodeling. This results in weaker peristaltic waves, reduced esophageal clearance, and faster contractions in older adults [32].

Esophageal motility disorders and reflux disease

Esophageal motility disorders in diabetic patients manifest as weak contractions (less than 450 mmHg/second) or inefficient contractions with a total force below 100 mmHg, affecting more than 50% of swallows. These disorders can worsen when other systemic diseases such as rheumatic diseases or eosinophilic esophagitis are present [33]. The velocity of peristaltic wave propagation also decreases, with rates falling to as low as 3.5 cm/second compared to healthy individuals. This decline is due to damage to the myenteric and sensory plexuses, which can diminish symptom perception in these patients [34].

Gastroesophageal reflux disease (GERD) in diabetes

GERD is more prevalent among diabetic patients compared to the general population. Elevated glucose levels increase oxidative cascades and free radical production, leading to nerve dysfunction, demyelination, and alterations in peristalsis. These factors also impair the relaxation and contraction of the lower esophageal sphincter (LES) [35]. As a result, diabetic patients experience esophageal motility disorders and dysfunction at the esophagogastric junction, which prolongs acid exposure on the esophageal mucosa. This predisposes patients to more severe esophagitis and Barrett's esophagus [36]. Hyperglycemia plays a significant role in intestinal metaplasia of the esophageal mucosa, as it occurs alongside hyperinsulinemia. The latter stimulates the production of insulin-like growth factor 1 (IGF-1), increasing the risk of metaplasia and esophageal cancer development [37].

One of the primary therapeutic approaches for motility disorders and gastroesophageal reflux is the administration of proton pump inhibitors (PPIs). The relationship between diabetes and PPI use is bidirectional: on the one hand, PPIs can alter the composition of the colonic microbiota, exacerbating metabolic imbalances [38]. On the other hand, in patients with high blood glucose levels, PPI use may increase the risk of aspiration pneumonia, chronic kidney disease, and osteoporosis by reducing calcium absorption in the intestines [39]. Therefore, for diabetic patients, it is recommended to prioritize treatments that stimulate esophageal motility rather than focusing solely on reducing acid secretion, along with maintaining good metabolic control. The most commonly used prokinetic agents include dopamine receptor antagonists and serotonin receptor agonists, which stimulate peristalsis and improve esophageal mucosal clearance [40].

Metoclopramide and domperidone are dopamine receptor antagonists that can be used to manage esophageal motility disorders induced by diabetes. However, metoclopramide is associated with extrapyramidal syndrome since it can cross the blood-brain barrier. Therefore, Relamorelin is preferred, as it has shown the potential to reduce reflux symptoms after 8 weeks of treatment, if present [41]. Another approach to counteract esophageal changes in diabetic patients is through the improvement of vagal dysfunction. Buspirone can enhance the amplitude of esophageal contractions and increase the pressure of the lower esophageal sphincter by stimulating 5-HT1A receptors in the hippocampus [42]. Additionally, it can reduce the overall cardiovascular risk by lowering

serum cholesterol levels, blood pressure, and ventricular hypertrophy [28].

Other measures for diabetic patients with esophageal dysfunction include adopting a low-fiber, low-fat diet with adequate fluid intake. Many patients report worsening symptoms after meals rich in fats, so reducing fat intake can help alleviate subjective complaints [43].

Gastric Involvement

In diabetic patients, various gastric function alterations can occur, ranging from a higher frequency of ulcers and erosions to gastroparesis and an increased risk of neoplastic pathology. The most common complication is delayed gastric emptying, which can affect up to one-third of all type 1 diabetes cases [44].

Gastroparesis

The cause of gastroparesis lies in vagal neuropathy, associated with dysfunction of interstitial cells of Cajal, along with the loss of neurons' ability to release nitric oxide [45]. This leads to a reduction in antral wave pressure, which can eventually halt gastric contractions altogether. Additionally, pyloric sphincter tone increases, contributing to the characteristic clinical manifestations of gastroparesis.

Oxidative stress also plays a role in the pathogenesis of gastroparesis. Heme oxygenase-1, an enzyme found in large quantities within macrophages in the gastric wall, is lost when glucose levels are high. This disrupts its ability to bind to a tyrosine kinase receptor, which is essential for stimulating peristalsis at this level [46]. The diagnosis of diabetic gastroparesis involves several steps. The initial suspicion arises when patients report early satiety, postprandial bloating, vomiting of undigested food, and, often, the presence of one or more microvascular complications [44]. Subsequently, other causes of delayed gastric emptying, such as pyloric stenosis, autoimmune diseases, or medications that reduce intestinal peristalsis, must be ruled out. The definitive diagnosis is confirmed through gastric emptying scintigraphy [47].

To manage gastroparesis induced by elevated blood glucose levels, prokinetic agents such as metoclopramide, domperidone, or erythromycin (a macrolide antibiotic that stimulates gastric emptying) can be prescribed. These drugs can be administered orally or intravenously, but the treatment duration should not exceed four weeks to avoid tachyphylaxis and other side effects such as diarrhea or cramps, which may limit their use [48].

Endoscopic and surgical methods can be an alternative for severe, treatment-refractory forms. Through interventional endoscopy, submucosal injection of a gel, submucosal dissection, and myotomy can be performed to alleviate the symptoms secondary to gastroparesis for up to 6 months in 50-80% of cases [49]. Surgical treatment may involve modifying the shape of the stomach by creating a bypass or implanting an electronic device that stimulates gastric peristalsis through high-frequency electrical impulses [50], or in extreme cases, a feeding jejunostomy can be installed [44].

Peptic ulcer disease

Infection with H. pylori is the main cause of chronic gastritis, gastric ulcer, and gastric cancer, significantly impacting the progression of these conditions, especially in countries where the prevalence of infection is high [51]. The association between diabetes and H. pylori infection is notable because there is a degree of chronic inflammation associated with insulin resistance, which could theoretically lead to more severe manifestations compared to individuals with normal blood glucose levels [52]. Bacterial colonization with H. pylori leads to the release of pro-inflammatory cytokines, which results in the phosphorylation of insulin receptors, complicating insulin action, as well as the activation of Toll-Like receptors by the lipopolysaccharides of the cell wall, which acts in concert with insulin resistance [53]. Additionally, an increase in hepatic insulin resistance can be observed in patients with diabetes and H. pylori, as the bacteria can stimulate the c-Jun/miR-203/SOCS3 signaling pathway [54]. This is confirmed by the correlation of higher glycated hemoglobin levels in diabetic patients with bacterial colonization by H. pylori [55]. Data published so far show a weak statistical association between severe forms of peptic ulcer at diabetic patients [56], but with a higher risk of bleeding [57]. This is due to the more challenging eradication of H. pylori from the gastric mucosa, as hyperglycemia causes a series of metabolic disturbances at the level of the gastric mucosa [58]. In healthy individuals, H. pylori derives its energy from amino acids such as alanine, arginine, and glutamate, which mostly come from protein hydrolysis [59]. In diabetic patients, it has been observed that the bacteria can consume D-glucose in particular, being capable of metabolizing sugars, and in the body's attempt to eliminate excess glucose, it can be expelled at the level of the gastric mucosa, leading to marked bacterial proliferation that is more difficult to eradicate compared to the healthy population.

This has been confirmed in cases where triple antibiotic therapy is administered [60]. In addition to the more frequent colonization with H. pylori, diabetic patients exhibit marked vulnerability of the gastric mucosa due to disturbances in the vascularization of the stomach secondary to atherosclerotic processes, a higher prevalence of pro-ulcerogenic factors (such as NSAID use and an unbalanced diet), as well as a decrease in protective gastric secretion correlated with reduced gastric motility. Consequently, ulcers occur more frequently in the diabetic population [61]. Thus, there is a bidirectional relationship concerning mucosal colonization with H. pylori and the presence of gastric ulcers associated with elevated blood glucose levels.

The first line of treatment for gastric ulcers in diabetic patients is represented by proton pump inhibitors, which can reduce symptoms and decrease gastric acid secretion but carry the risk of exacerbating glycemic imbalance in cases of prolonged treatment, with the risk correlating to the duration of treatment [62]. The treatment of diabetes with metformin is considered the first line of therapy, which, in addition to lowering blood glucose levels, can improve insulin resistance [63] by decreasing intestinal glucose absorption and reducing hepatic production. This allows for the mobilization of energy from hepatic deposits [64]. Moreover, at the gastric level, metformin can induce the release of nitric oxide, promoting blood flow and the production of prostaglandins, which facilitate mucosal healing and enhance healing chances in the presence of ulcers [65]. Additionally, its administration can lead to an increase in hydrochloric acid synthesis through the proliferation of acid-secreting cells, inhibiting H. pylori growth and reducing the risk of developing gastric ulcers and cancers [66].

Pioglitazone is a substance capable of stimulating insulin synthesis and tissue sensitivity to insulin, associated with reducing dyslipidemia in patients with type II diabetes by activating the PPAR-g receptor, which is found in the liver, stomach, and colon and is involved in tissue repair processes [67]. In laboratory animals, it has been observed to stimulate the healing of gastric ulcers through receptor activation, coupled with good angiogenesis, suppression of pro-inflammatory cytokines, and stimulation of COX-1 and nitric oxide synthesis through enzymatic action [68].

Glucagon-like peptide-1 (GLP-1) is a hormone derived from the incretin family that stimulates insulin release by binding to the GLP-1 receptor on pancreatic cells. It can have a blood glucose-lowering effect and cardioprotective activity. The administration of GLP-1 analogs has led to a reduction in myeloperoxidase activity and oxidative stress at the gastric wall, with decreased local IL-10 concentrations and increased angiogenesis, which stimulates and promotes local healing [69].

Gastric cancer

The relationship between gastric cancer and diabetes is close, as numerous biological processes can be influenced by elevated blood glucose levels and the factors that contribute to them. Thus, obesity, hyperglycemia, hyperinsulinemia, along with H. pylori infection, can lead to the development of gastric cancer [70]. Obesity can result in elevated insulin levels secondary to peripheral insulin resistance, associated with dynamic changes in the upper stomach, marked acid reflux, and the occurrence of gastroesophageal reflux with an increased risk of cardiac adenocarcinoma [71].

Hyperglycemia, alongside a chronic pro-inflammatory state due to oxidative stress, can activate the nuclear factor kappa B (NF-κB), promoting the development, progression, local invasion, and lymph node involvement of gastric neoplastic cells both indirectly and through endothelial dysfunction [72]. Secondary hyperinsulinemia leads to the activation of IGF-1 receptors, overstimulating the IGF II/IR-A pathways, which favor the survival and mitosis of neoplastic cells [73]. Malignantly transformed gastric cells show increased expression of insulin receptors, which can be found even in metastatic cells, and these receptors can stimulate the PI3K/Akt pathway, promoting growth, proliferation, and survival. Therefore, insulin and insulin receptors contribute to both the onset and progression of malignant gastric disease [74].

H. pylori infection is closely linked to gastric cancer and diabetes. For instance, a glycated hemoglobin level above 6 in patients with bacterial infection correlates with a higher risk of developing gastric cancer compared to the normal population due to atrophic, metaplastic, and dysplastic changes that persistent infection promotes through CagA and VacA, leading to cytoskeletal rupture and altered cell interconnections, affecting the epithelial-mesenchymal transition, as well as inhibiting cellular metabolism via the mTOR pathway [70].

As of now, the main treatment for gastric cancer remains surgical, with lymphadenectomy in associated stations being the only method that can increase survival rates. This surgical intervention can be associated with better glycemic control, with disease remission rates between 42.5% and 65.4% in patients who underwent total gastrectomy [75]. After gastrectomy, insulin resistance improves, fasting blood glucose levels normalize, and there is also a decrease in body mass index [76]. Regarding the type of reconstruction after gastric resection, remission of diabetes post-gastrectomy has been achieved with higher rates when a Roux-en-Y limb was used, and postoperative survival rates for patients with gastric cancer have also shown the best results [77]. A possible mechanism for these favorable outcomes may be the alteration in the secretion of ghrelin (a hormone that stimulates appetite, synthesized by X/A cells in the gastric wall), glucagon, and glucagon-like peptide 1 [78].

Metformin has a direct effect on gastric tumor cells, both insulin-dependent and independent. One of the mechanisms by which it acts on these cells is through the expression of activated T cells, which halts the local immunosuppressive environment and simultaneously modifies colonic microbiota [79]. Another advantage of using this molecule in patients with digestive cancers is the increased sensitivity of neoplastic tissues to chemotherapy, specifically 5-fluorouracil (5-FU) and paclitaxel [80]. The effect of this antidiabetic treatment has been particularly noted in the prophylaxis of gastric cancer; the longer the duration of use, especially if it exceeds two years, the risk can decrease by up to 21%, especially in younger

individuals of Asian descent [81]. These facts are confirmed by in vitro studies where concurrent administration with cisplatin, doxorubicin, and paclitaxel can induce apoptosis in gastric neoplastic cells through various pathways: activation of AMP-activated protein kinase (AMPK) with inhibition of cellular proliferation [82], blocking insulin receptors, compromising intracellular signal transmission, and accumulating intermediate glycolysis products that inhibit gluconeogenesis [83].

Other molecules with antitumor properties include glibenclamide, which can induce the formation of reactive oxygen species and induce cellular apoptosis [84], and ciglitazone, which stimulates the expression of protein p21 and suppresses cyclin D1 activity through PPAR-g, thereby inhibiting the growth of neoplastic gastric cells and initiating their apoptosis [85].

Intestinal and colonic involvement

Diabetic enteropathy

Diabetic enteropathy occurs as a consequence of alterations in the intestinal microbiota due to elevated glucose levels, oxidative stress, neuroinflammation, reduced nerve repair, and changes in the intestinal vascular structure [86]. These factors lead to impaired healing of the intestinal mucosa, marked apoptosis, and increased membrane permeability, along with decreased gastrointestinal motility [87]. As a result, there is a higher prevalence of diarrhea in individuals with elevated glucose levels compared to normal individuals, without the severity of symptoms being significantly influenced by the presence or absence of retinopathy, glycated hemoglobin levels, or the duration of diabetes [85]. Symptoms usually last for more than six weeks, often without abdominal pain or bloating. They most frequently occur in women with diabetes for over eight years, presenting at irregular intervals and abruptly following a normal stool or increased consistency. A characteristic aspect is the nocturnal occurrence of diarrhea, distinguishing it from other pathologies [88].

In diabetic patients with persistent diarrhea, it is necessary to rule out other infectious or non-infectious causes (such as celiac sprue, inflammatory bowel diseases). If no other causes are found, dietary modifications are recommended in combination with loperamide, an agonist of opioid receptors in the digestive tract [89]. In some cases, clonidine, an agonist of alpha-2 adrenergic receptors, can be administered to reduce the frequency of diarrheal stools, although it may have cardiovascular side effects [90]. It is crucial for patients with chronic diarrhea to compensate for significant fluid losses due to stool output, necessitating fluid administration and the temporary cessation of diuretic treatment, especially in warm weather [91]. If bacterial overgrowth is suspected as the cause of diarrhea in diabetic patients, the administration of rifaximin is recommended, which can reduce symptoms by up to 99%, or somatostatin analogs [92].

Metformin can cause diarrhea as an adverse reaction, as it reduces the absorption of bile salts; similarly, sweeteners that act as substitutes can attract water into the intestine through osmotic mechanisms. Additionally, gut flora can metabolize fatty acids into short-chain fatty acids that are strongly electronegative [93].

Another manifestation of diabetic enteropathy is chronic constipation, primarily affecting the nerve endings of the autonomic nervous system, leading to an inability to synchronize and mobilize the fecal bolus, along with the destruction of interstitial Cajal cells, resulting in decreased motility of the lower digestive tract [91,94].

The treatment of constipation in diabetic patients is primarily based on classic laxatives, along with supplementation of up to 30 grams of fiber per day, alongside adequate fluid intake [95]. Physical exercise of up to 150 minutes per week can reduce insulin requirements and improve chronic constipation [95,96]. It is important to note that in diabetic patients, there is a decrease in the variability of bacterial species in the colon, which may manifest as constipation. Probiotics and prebiotics can mitigate these effects by reducing inflammation, and certain species of Bifidobacterium may improve glucose tolerance and insulin synthesis while decreasing systemic inflammation [94]. Purgatives can deplete significant amounts of water from the body and should be avoided in diabetic patients. The administration of prucalopride, a 5-HT4 receptor agonist, stimulates the colonic wall, accelerating intestinal transit and the elimination of fecal matter, also promoting gastric emptying without significant adverse reactions [97,98].

Antidiabetic treatment can also lead to gastrointestinal adverse reactions such as constipation or diarrhea. Approximately 20% of patients using GLP-1 agonists experience constipation, which often occurs in patients who also use insulin preparations to control hyperglycemia. These reactions are dose-dependent, appear in the first week of treatment initiation, and are generally self-limiting [95].

Inflammatory bowel diseases

Inflammatory bowel diseases, represented by Crohn's disease and ulcerative colitis, can occur in patients with diabetes mellitus, which is an aggravating factor in their evolution, as it increases the risk of hospitalization and infections without altering the development of certain complications or influencing mortality [99]. However, a direct correlation between the onset of inflammatory bowel diseases and type II diabetes is not supported [100,101]. The pathogenesis of intestinal diseases is primarily determined by imbalances in the colonic microbiota, leading to a pro-inflammatory status that could interfere with carbohydrate metabolism. Similarities between the

two pathological entities appear in the context of reduced variability of bacterial species present, associated with high levels of Firmicutes and Bacteroidetes, which are also found in substantial amounts in patients with type II diabetes [102].

Antidiabetic treatments may have some influence on inflammatory bowel diseases. Metformin can have anti-inflammatory effects that alleviate the symptoms caused by ulcerative colitis and help maintain the integrity of the intestinal barrier, alongside restoring the microbiota [103]. Other agents used to normalize glucose levels, such as rosiglitazone, may also improve symptoms in mild forms of ulcerative colitis [104]. Furthermore, in patients with diabetes and inflammatory bowel disease, potential metabolic and physiological interactions must be considered when administering various treatments. Corticosteroids are the first-line treatment for moderate to severe forms, successfully inducing remission of the disease [105]. It is important to closely monitor blood glucose levels in diabetic patients or to use other classes that induce remission, as there may be decompensations due to glucose intolerance secondary to corticosteroid administration, with the risk being dose-dependent [106]. Up to 50% of patients with inflammatory bowel disease may develop high glucose levels during treatment [107].

Another approach to induce and maintain disease stability is biological treatment. Data regarding any changes in diabetic patients are controversial. Infliximab, a monoclonal antibody that inhibits TNF-alpha action, has been associated with increased signaling transduction of insulin receptors at the hepatic level, lowering glucose levels in laboratory animals [108]. Similar results have been observed in two autoimmune type diabetes patients who received such treatment for remission of acute Crohn's disease episodes [109]. Adalimumab, another monoclonal antibody acting against TNF, may also reduce glucose levels in laboratory animals with conditions similar to human obesity [110]. However, an analysis of 67,756 cases of patients receiving biological treatment compared to abatacept for rheumatoid arthritis revealed an increased risk of diabetes without a higher prevalence of obesity in the biological treatment group compared to the standard treatment [111].

Colorectal cancer

The link between colorectal cancer and hyperglycemia is a strong one, as the chronic exposure of colonic mucosal cells to elevated glucose levels and the changes occurring in the microbiota can lead to disturbances in cellular repair [112]. Complications that arise in diabetic patients, such as chronic kidney disease, neuropathy, and chronic infections, can influence treatment and outcomes regarding mortality, survival, and recurrence risk in patients with colon cancer [113].

From a pathophysiological standpoint, there is an increased activity of the alternative glucose metabolism pathway observed in the colonic mucosa, which influences mesenchymal transformation similarly to gastric cancer, alongside massive release of TNF-alpha. The higher and longer the glucose levels (measured by glycated hemoglobin), the greater the risk of developing colorectal cancer [114]. Another mechanism for malignant transformation of colonic cells under hyperglycemic conditions is through the activation of insulin receptors at this level, the PI3K-AKT-mTOR pathway, and the activation of VEGF, which stimulates angiogenesis and tumor invasion [115].

A number of genetic factors have been identified regarding the association between colon cancer and diabetes. TCF7L2 is a frequently encountered mutant gene in the East Asian population that may predispose to malignant invasion and neoplasia in colorectal cancer while also being a gene that predisposes to an increased risk of developing diabetes. Through its transcription, it forms transcription factor 4, which activates the WNT/β-catenin pathway, involving cyclin D1 and c-Myc in the pathogenesis of colorectal cancer [116]. GREM1 is another gene that predisposes to the development of diabetes and influences some patients' susceptibility to colon cancer by interrupting hsa-mir-185-3p, affecting the β-catenin pathway [117].

The treatment of patients with colon cancer is most often surgical, with metabolic peculiarities imposing a higher risk of adverse outcomes, influencing postoperative mortality, overall survival, and local recurrence risk, as well as postoperative complications such as the risk of post-anastomotic fistula and infections associated with invasive ventilation [118]. The risk of anastomotic fistula in colorectal surgery is pronounced due to chronic inflammation and the state of hyperglycemia, especially in patients whose surgical intervention is prolonged, subjecting the body to more significant stress. At the same time, these patients have more frequent general complications such as angiopathy, obesity, and dyslipidemia, which can interfere with local healing [119].

The influence of elevated glucose levels on postoperative evolution can significantly impact renal function, with a higher risk of developing AKI in the initial days due to micro- and macroangiopathy. The level of glycated hemoglobin correlates with this, alongside persistent dynamic ileus, which is prolonged in this cohort of patients due to the impairment of the myenteric plexuses [116]. The administration of erythromycin, metoclopramide, and cisapride does not significantly influence this complication [118,120]. Useful measures regarding the resumption of transit in these patients may include the use of epidural anesthesia in the perioperative period for adequate pain control, reducing the need for opioid analgesia, early mobilization, and utilizing minimally invasive methods [121].

Chemotherapy treatment in patients with colorectal cancer is represented by leucovorin, fluorouracil, and oxaliplatin for stages II and III. In cases where an elevated glucose level is observed, there is a resistance to 5-FU and oxaliplatin, alongside an accentuated toxicity profile [122], as a reduction in proliferation inhibition occurs with enhanced DNA replication [114]. Moreover, in metastatic cases of disease, tumor progression under treatment is also more likely for this cohort of patients, with more frequent adverse reactions [123].

Administration of Metformin to patients predisposed to developing colorectal cancer has been associated with an 11% reduction in risk due to its influence on the AMPK pathway [124]. In addition to this effect, an increase in overall survival is observed, especially in patients with metastatic disease, a benefit also seen in patients undergoing radio-chemotherapy treatment [125].

Other digestive manifestations

Anal incontinence

In patients with diabetes, there is a 1.5 times higher incidence of anal incontinence compared to individuals with normal glycemic levels. This condition is often associated with marked diabetic enteropathy and multiple bowel movements. If more than 21 bowel movements occur in one-week, anal incontinence can be up to 4.9 times more frequent [126]. Predisposing factors for this condition include peripheral neuropathy, which affects the rectum and external anal sphincter in women, reducing the sensation of defecation and weakening storage capacity [127]. Additionally, intestinal dysbiosis, along with antidiabetic treatment, can contribute to the occurrence of diarrhea [123].

Hemorrhoidal disease

Hemorrhoidal disease occurs more frequently in patients with diabetes due to vascular impairment and reduced venous tone at this level [128]. Metformin, with its anti-inflammatory and anti-atherosclerotic effects, may alleviate the severity of hemorrhoidal disease in diabetic patients by reducing local inflammation and fibrosis, as well as decreasing abdominal pressure through weight loss [129].

Conclusions

Elevated glucose levels predispose individuals to the exacerbation of potential digestive comorbidities, with one condition aggravating another in the context of acute decompensation, leading to a decreased quality of life and increased risks of complications and mortality. In the case of neoplastic gastric, colonic, and esophageal pathologies, there is interdependence, as common genes favor the onset, progression, and aggressiveness of these events. Elevated glycemic levels predispose patients to lower survival rates without adequate treatment. Among antidiabetic treatments, Metformin appears to have the best effects concerning digestive pathology, acting on the cellular metabolic pathways responsible for chronic inflammation, production of reactive oxygen species, and oncogenes. Therefore, the treatment of diabetic patients should focus not only on achieving adequate glycemic levels but also on managing potential complications within the gastrointestinal tract.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

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