gastrointestinal disorders

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Review

Diabetic Gastroparesis: Navigating Pathophysiology and Nutritional Interventions

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Abstract: Diabetic gastroparesis (DGP) delays gastric emptying in diabetes patients, notably impacting those with type 1 and long-standing type 2 diabetes. Symptoms include early satiety, fullness, appetite loss, bloating, abdominal pain, and vomiting, arising from slow stomach-to-intestine food movement. DGP's unpredictable nature complicates diagnosis and blood glucose management, leading to severe complications like dehydration, malnutrition, and bezoar formation. Understanding DGP's mechanisms is crucial for effective management. Vagal dysfunction, disturbances in the interstitial cells of Cajal, reduced neural nitric oxide synthase, and increased oxidative stress contribute to the complex pathophysiology. Accurate diagnosis demands a comprehensive approach, utilizing tools like gastric scintigraphy and the Gastric Emptying Breath Test. Considering the complex relationship between DGP and glycemia, managing blood glucose levels becomes paramount. Nutritional interventions, tailored to each patient, address malnutrition risks, emphasizing smaller, more frequent meals and liquid consistency. DGP's complex nature necessitates collaborative efforts for enhanced diagnostic strategies, improved pathophysiological understanding, and compassionate management approaches. This comprehensive approach offers hope for a future where individuals with DGP can experience improved well-being and quality of life.

Keywords: diabetic gastroparesis; nutritional intervention; pathophysiology; diabetes; diabetes complication

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1. Introduction

Diabetic gastroparesis (DGP) is a debilitating gastrointestinal disorder characterized by delayed gastric emptying in individuals with diabetes mellitus, particularly type 1 and long-standing type 2 diabetes. This condition, although not widely known, significantly impacts the quality of life of affected individuals. The symptoms of DGP, including early satiety, excessive fullness after meals, loss of appetite, bloating, abdominal pain, and vomiting, stem from the slowed or stalled movement of food from the stomach to the small intestine [1].

What makes DGP particularly challenging is its unpredictable nature. The severity of symptoms can vary widely among individuals, and it often occurs in the absence of

consistent patterns. This unpredictability not only complicates the diagnosis but also makes managing blood glucose levels exceptionally challenging for those with diabetes, as the absorption of ingested food becomes erratic. Furthermore, DGP can lead to serious complications such as dehydration, malnutrition, and the formation of bezoars—solid masses of undigested food that can obstruct the digestive tract. Consequently, individuals with DGP often face a reduced quality of life, experiencing persistent discomfort, nutritional deficiencies, and frequent hospitalizations due to complications [2,3].

In this context, understanding the mechanisms behind DGP, improving diagnostic techniques, and developing effective management strategies are critical areas of research. This exploration is not only vital for enhancing the lives of those already affected by DGP but also holds the potential to prevent its onset or progression in individuals with diabetes, significantly reducing the burden of this condition on both patients and the healthcare system.

2. Epidemiology

DGP is a prevalent complication affecting a significant proportion of individuals with diabetes mellitus, both type 1 and type 2. While exact prevalence rates can vary based on the studied population and diagnostic criteria, it is widely acknowledged that DGP represents a substantial burden within the diabetes community.

In a recent meta-analysis, it was found that approximately 9.3% of individuals with diabetes may experience the onset of gastroparesis during the course of their illness. This risk appears to be heightened in individuals with long-standing type 1 diabetes or type 2 diabetes lasting ten years or more [1,4]. This prevalence changes according to the geographical location, with a lower prevalence in North America (3.6%) and a higher prevalence in Asia (12.6%), Europe (16.5%), South America (16.4%), and Australia (17.7%) [4].

In terms of regional differences, emerging studies underscore the heightened susceptibility of certain populations, particularly those with elevated rates of diabetes, to the development of DGP. This vulnerability is further accentuated by disparities in healthcare access and awareness across regions, influencing both the diagnosis and prevalence rates of DGP. A compelling illustration of the regional nuances in diabetes prevalence comes from the Global Diabetes Map, which highlights China's critical diabetes situation. China not only ranks highest in both diagnosed and undiagnosed diabetes cases but also secures the second position in global diabetes health expenditure. Consequently, the burden of gastrointestinal dysfunction is pervasive among diabetic patients in the early or advanced stages of the disease. These findings underscore the imperative of considering regional factors in comprehending and addressing the prevalence of DGP. To address these disparities, targeted healthcare interventions and heightened awareness campaigns are crucial, especially in regions witnessing elevated diabetes rates [2,4].

DGP affects both men and women, although some studies indicate a higher incidence in females. In fact, in one of the most extensive population-based epidemiological studies, which included 3604 residents from Olmsted County, Minnesota, it was observed that the incidence of gastroparesis in women was four times greater than that in men [5]. The reasons behind this gender difference are not entirely clear and require further investigation [2,4].

Age also plays a significant role in the epidemiology of DGP. It is often observed that the risk of developing gastroparesis increases with age, particularly in individuals with diabetes of long duration. As the global population continues to age and the incidence of diabetes rises, the prevalence of DGP is expected to increase, posing a growing challenge for healthcare systems worldwide [4,6].

3. Pathophysiology

3.1. Gastric Motility Physiology

Gastric motility, a highly complex process, is regulated by a complex interplay of neural and hormonal signals. As ingested food fills the stomach, fundic compliance increases, creating a food reservoir without a simultaneous rise in pressure. In the initial filling phase, both pressure and peristaltic pumps remain inhibited, exhibiting no contrac-

tions. Subsequently, the filling phase transitions into a pumping phase characterized by a gradual tonic contraction of the fundus and an escalation of peristaltic contractions in the stomach. During this dynamic phase, a critical mechanism unfolds—the pylorus closes as the contraction wave approaches the distal stomach, essential for the mechanical digestion process known as trituration. This orchestrated phase promotes the thorough mixing of ingested food with gastric acid and pepsin, facilitating its transfer to the pylorus [7].

As the food undergoes trituration, it undergoes propulsion into the pyloric grinder through intensified contractions in the antrum. Following this, the pylorus relaxes to receive food from the proximal antrum. Pyloric contractions play a pivotal role by generating a robust negative pressure gradient of incompletely triturated food. Simultaneously, an anterograde positive pressure gradient propels chyme into the duodenum [8,9]. Central to this process is the enteric, or intrinsic, nervous system, often referred to as the "second brain". Comprising about a hundred million neurons, this complex network embedded in the gastrointestinal tract wall includes the myenteric plexus, primarily responsible for regulating gastric motility, and the submucosal plexus, which oversees gastric secretion and absorption. Both are modulated by the extrinsic nervous system, encompassing the parasympathetic and sympathetic components. The parasympathetic system stimulates non-sphincteric muscles and inhibits sphincter contraction, while the sympathetic system exerts opposing effects. Interstitial cells of Cajal, located between nerve endings and smooth muscle cells, act as pacemaker cells for gastrointestinal muscles, generating electrical signals that regulate smooth muscle contractions. The coordination between smooth muscle, interstitial cells of Cajal, and the enteric and extrinsic nervous systems is essential for proper gastric emptying [10]. Moreover, various hormones, such as gastrin, cholecystokinin (CCK), secretin, gastric inhibitory polypeptide (GIP), glucagon, vasoactive intestinal peptide (VIP), glucagon-like peptide-1 (GLP-1), motilin, and ghrelin, play pivotal roles in influencing gastrointestinal motility [11,12].

3.2. Diabetic Gastroparesis

The pathophysiology of DGP is complex and multifaceted, with various hypotheses pointing to potential factors like elevated blood glucose levels, vagal dysfunction, disturbances in the interstitial cells of the Cajal network, diminished expression of neural nitric oxide synthase in the myenteric plexus and increased oxidative stress (Figure 1). Studies in both animal models and humans have illuminated some underlying processes, but significant gaps in our understanding still exist. This complexity underscores the need for further research to unravel the complex mechanisms behind gastric motility dysfunction in diabetes [7].

Vagal innervation plays a pivotal role in modulating antral contractions, responsible for breaking down solid food into smaller particles and facilitating its passage through the pylorus. Under normal circumstances, the vagus nerve also stimulates pancreatic polypeptide secretion following a meal, ensuring the coordinated movement of food through the digestive tract. However, in individuals with DGP, this essential function is significantly compromised. In diabetic autonomic neuropathy, there's a correlation with antral hypomotility [11], diminished fasting proximal gastric tone, and decreased postprandial accommodation of the gastric fundus [13]. The blunted response of the vagus nerve in triggering pancreatic polypeptide secretion points to a malfunction in the neural signals that control gastrointestinal processes. Early studies in DGP revealed impaired pancreatic polypeptide response and reduced gastric secretion during sham feeding, indicating vagal dysfunction [14,15]. Histological examinations have identified alterations in both myelinated and unmyelinated vagal nerve fibers among DGP patients [16]. Additionally, the sympathetic component of the autonomic nervous system in DGP has shown histological changes in axon-dendritic structures and alterations in gene expression within prevertebral ganglia [17,18]. Most gastrointestinal peptide hormones typically exert an inhibitory effect on gastric emptying, suggesting that a reduction in their release cannot account for the reduced gastric emptying [8]. Instead, the impact of aberrant vagal signaling on gastric

function, particularly pyloric function, appears to be more pertinent. Pylorospasm, a consequence of vagal neuropathy described in DGP, is notable. Treatments specifically targeting the pylorus, such as G-POEM, have shown greater efficacy compared to conventional management, underscoring the relevance of addressing abnormal vagal signaling in managing DGP [19].

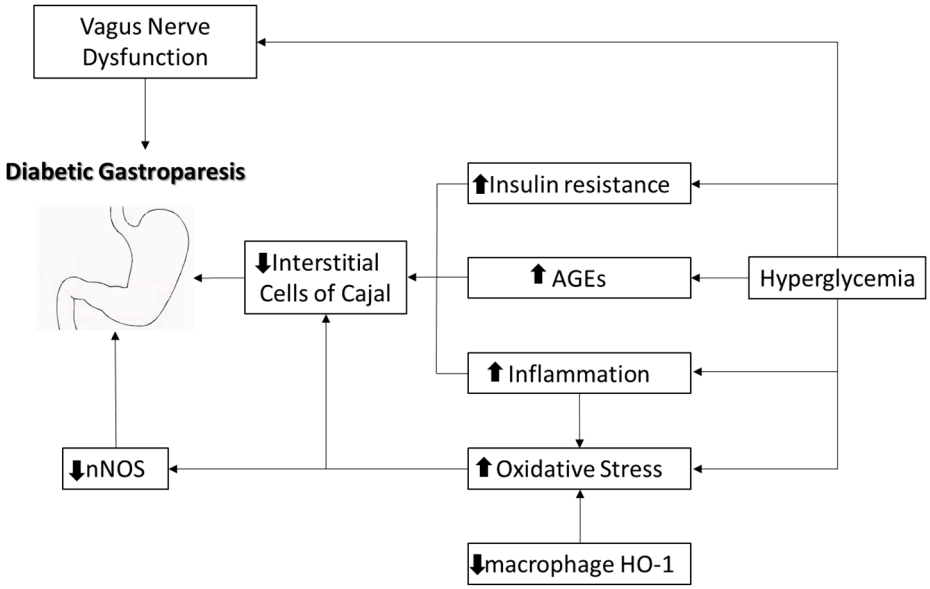

Figure 1. Main pathophysiological mechanisms associated with diabetic gastroparesis development. AGE—advanced glycation end-product.

Hyperglycemia exacerbates abnormally increased pyloric contractility, leading to reduced antral pressure waves, diminished antral motor activity, and increased pyloric pressure waves. As a consequence, patients often experience distressing symptoms such as early satiety, bloating, nausea, and vomiting [20,21].

Interstitial Cajal cell dysfunction serves as the "pacemaker" of the stomach by generating action potentials. Impaired insulin and IGF-1 signaling have been linked to damaged myenteric cholinergic neurons and ICCs in animal studies [22]. Additionally, DGP patients often exhibit reduced ICC numbers in antral biopsies, leading to abnormal gastric slow waves, potentially causing disordered motor function and symptoms [23–26]. Concurrently, a decrease in or loss of nNOS has been observed, contributing to the disrupted coordination of gastric motility [26,27].

In murine models of DGP, myopathy and depletion of interstitial cells of Cajal have been reported, preceding neuropathy. Human studies have also demonstrated the depletion of gastric interstitial cells of Cajal in up to 50% of patients with gastroparesis [28]. Other animal experiments have indicated that impaired gastric emptying results from decreased expression or inhibition of neural nitric oxide synthase [29]. These findings emphasize the multifaceted nature of DGP, involving complex interactions between interstitial cells of Cajal dysfunction, impaired signaling pathways, and disrupted neuronal coordination in the stomach's motility processes.

Enteric neurons and interstitial cells of Cajal are particularly vulnerable to hyperglycemia. When hyperglycemic episodes are frequent, or when hyperglycemia is persistent, shifts in the intracellular glucose metabolism of neurons occur, leading to the formation of advanced glycation end-products, osmotic and oxidative stress, as well as inflammation. Collectively, these processes result in cellular damage and, ultimately, cell death, a phenomenon commonly referred to as glucose neurotoxicity. While these mechanisms are primarily described in the peripheral nervous system, it is essential to note that similar processes are present in the enteric nervous system [30]. This heightened vulnerability to hyperglycemia further underscores the complex nature of DGP, where disruptions in multi-

ple pathways, including ICC dysfunction and neural damage, contribute to the complexity of the condition [30].

The nitrergic system, composed of inhibitory enteric neurons embedded in the gut wall musculature, assumes a pivotal role in the regulation of gastric motility [31]. These neurons express neuronal nitric oxide synthase (nNOS), an enzyme responsible for synthesizing and secreting nitric oxide (NO), a primary inhibitory neurotransmitter in the GI tract that induces relaxation of the stomach's smooth muscle [32]. The NO signaling involves three distinctive NOS isoform enzymes: endothelial NOS (eNOS), inducible NOS (iNOS), and neuronal NOS (nNOS) [33]. The term "nitrergic signaling" encompasses the release of NO from these enteric neurons, which collectively governs muscle tone in various GI structures, including the lower esophagus, antrum, pylorus, sphincter of Oddi, and anus. NO also plays a crucial role in regulating gastric accommodation and intestinal peristalsis. Dysfunction in the nitrergic system, as evidenced by reduced nNOS expression and/or NO release, is associated with defective smooth muscle relaxation in the GI tract, leading to gastroparesis [34,35]. Early studies provided evidence for the involvement of nitrergic nerves in gastric motility. These studies revealed that mice lacking neuronal nitric oxide synthase (nNOS) exhibited a dilated stomach with hypertrophy of the circular muscle layer, indicating the importance of nNOS in maintaining normal gastric function [36]. Additionally, experiments involving animals demonstrated that reduced expression of nNOS due to disease or pharmacological interference with nitric oxide synthase could lead to impaired gastric emptying [37,38]. Although limited patient data on the loss of enteric neurons or nervous function exist, immunohistochemistry data from a small case series indicated a decrease in nNOS and substance-P expression in the enteric nervous system of the stomach in diabetic patients compared to controls [26].

Several proposed mechanisms explain the decreased nNOS expression. Studies on non-obese diabetic (NOD) mice suggested a reversible loss of gastric nNOS expression, indicating down-regulation of nNOS without the loss of nitrergic neurons in the diabetic state [39]. Another study in streptozocin-induced diabetic rats found a reversible loss of nNOS after 4–8 weeks, which progressed to irreversible loss after 12 weeks, due to apoptosis. These findings demonstrate a biphasic loss of the nitrergic component, possibly induced by the accumulation of toxic substances or increased oxidative stress observed in both animal models and diabetic patients [40]. Moreover, the impaired neuromuscular function in the antrum of streptozocin-induced diabetic rats was attributed to the loss of dimerization of the active nNOS enzyme, further highlighting the complex mechanisms underlying gastric dysfunction in diabetes [31].

Oxidative stress is a significant factor contributing to the loss of nitrergic function.

In diabetes, persistent high blood glucose levels and mitochondrial dysfunction enhance the production of reactive oxygen species, intensifying oxidative stress [41,42]. Heme-oxygenase-1 (HO-1), up-regulated during oxidative stress, is an enzyme that catalyzes heme degradation into products such as carbon monoxide and biliverdin. These products are known for their antioxidative effects, offering protection against free radicals in the enteric nervous system. Studies in non-obese diabetic mice demonstrated that increased oxidative stress, resulting from the loss of macrophage HO-1 in the enteric nervous system, led to the loss of interstitial Cajal cells and delayed gastric emptying [43]. Another study in mice linked the development of diabetes with an increased number of macrophages and the up-regulation of HO-1 in the enteric nervous system. The progression of diabetes was marked by delayed gastric emptying, correlating with the loss of a subset of HO-1-positive macrophages. Interestingly, the induction of HO-1 reversed the delay in gastric emptying, indicating its potential as a therapeutic target [44]. Furthermore, in both mouse models and diabetic patients with gastroparesis, the depletion of HO-1 expressed by CD206+ M2 macrophages was observed, while the number of HO-1-negative M1 macrophages increased. HO-1 expression, up-regulated in response to oxidative stress in diabetic mice, appears to have a protective role against the development of gastroparesis. Consequently, the up-regulation of HO-1 expression has been suggested as a potential

strategy for managing gastroparesis, with research supporting this approach, showing a positive relationship between CD206+ cell expression and the number of interstitial Cajal cells in diabetic patients with gastroparesis [38].

3.3. Gender Difference

The gender difference in the occurrence of DGP has been linked to factors such as a naturally slower stomach in females, elevated levels of sex steroid hormones, diminished expression of neuronal nitric oxide, and potential alterations in serotonergic signaling. Additionally, there seems to be no correlation with the quantity of interstitial cells of Cajal in the antral and pyloric smooth muscle [45].

3.3.1. Sex Hormones

Sex hormones, particularly estrogen and progesterone, transcend their well-established roles in reproductive health to exert a profound influence on the intricate functioning of the gastrointestinal system [46–48]. The pervasive distribution of estrogen and progesterone receptors throughout the gastrointestinal tract, encompassing smooth muscle, mucosal layers, and endothelial tissues, underscores the systemic impact of these hormones. The presence of estrogen receptors along the brain–gut axis introduces a complex interplay between central and peripheral hormonal mechanisms that collectively shape gut function [49].

The menstrual cycle introduces a temporal dimension to these hormonal dynamics, with fluctuations in estrogen and progesterone levels. Studies have reported that during the luteal phase, characterized by elevated levels of these hormones, gastric emptying rates tend to be slower [50,51]. In-depth investigations, both in vitro and in vivo, further illuminate the inhibitory effects exerted by progesterone, either in isolation or in conjunction with estrogen, on gastrointestinal smooth muscle [52–54].

Pregnancy introduces its own set of complexities, with conflicting reports regarding its impact on gastric emptying. However, a consistent theme emerges in the form of changes in sex steroid hormones, particularly elevated levels of estradiol and progesterone, noted as gestational age advances. These hormonal fluctuations during pregnancy contribute to disturbances in gastrointestinal motility, potentially explaining common symptoms such as nausea, vomiting, and delayed gastric emptying [55–60].

The transition to menopause, characterized by a significant decline in estrogen and progesterone levels, marks another pivotal phase in the interplay between sex hormones and gastrointestinal function. Studies indicate that premenopausal women tend to exhibit slower gastric emptying rates compared to their postmenopausal counterparts, suggesting a direct association between menopausal status and gastric motility [61,62].

3.3.2. Nitric Oxide Signaling

The impact of gender on gastroparesis becomes apparent as estrogen, a key female sex hormone, is revealed to modulate the regulation of nNOS. Elevated levels of estradiol-17b (E2) in females correlate with increased NO levels, resulting in a more pronounced relaxation of gastric smooth muscle cells compared to males [63]. Studies involving diabetic rats and mice, particularly females, further underscore the vulnerability of the nitrergic system in the context of gastroparesis. Reduced levels of tetrahydrobiopterin (BH4), an essential cofactor for NO synthesis, are implicated in impaired NO generation and subsequent gastric motility issues. Intriguingly, BH4 supplementation in diabetic female rats has shown promise in restoring the impaired nitrergic system and accelerating gastric emptying, suggesting a potential therapeutic avenue for diabetes-induced gastroparesis [31,32,64]. In addition, studies evaluating nitrergic dysfunction and inflammation in normoglycemic diabetes-prone rats emphasize the role of aminoguanidine, a selective inhibitor of the iNOS enzyme, in counteracting inflammation-induced nitrergic dysfunction and preventing intestinal dysmotility, independent of hyperglycemia [45]. Furthermore, it has been suggested that variations in nNOS dimerization may contribute to the higher prevalence of females in this context [65]. This hypothesis derives from an examination of nitrergic

relaxation in healthy females that revealed intriguing nuances, with a more pronounced relaxation potentially attributed to the increased expression of the active dimeric form of nNOS alpha and heightened gastric BH4 content [66]. In the same investigation, it was reported that chronic hyperglycemia leads to a more pronounced reduction in both gastric pyloric BH4 content and active forms of nNOS specifically in females. This gender-specific modification contributes to a significant impairment of nitrergic relaxation, ultimately resulting in delayed gastric emptying [66].

3.3.3. Serotoninergic Signaling

The role of serotonin (5-HT) extends beyond its well-established function as a neurotransmitter in the brain, encompassing significant involvement in various gut functions. Surprisingly, over 90% of the body's serotonin is produced by enterochromaffin cells in the small intestine, impacting gut motility, secretion, and sensation [67,68]. The enteric nervous system's development and maintenance are also influenced by serotonin, with serotonergic neurons proving essential for mediating gastrointestinal propagating contractile complexes [69,70]. Research indicates that gender differences in serotonergic signaling regulate gastric emptying, and studies involving 5-HT receptor agonists/antagonists have shown promise in improving gut motility [71,72]. Notably, in healthy male subjects, the 5-HT4 agonist tegaserod accelerated gastric emptying and small intestinal transit [48]. Moreover, metoclopramide, functioning as both a 5-HT4 agonist and a dopamine D2 antagonist, enhances contractions in the esophagus, antrum, and small bowel, leading to an acceleration of gastric emptying [73]. Furthermore, gender differences in serotonin transporter gene polymorphisms, variations in serotonin synthesis rates, and disparities in serotonin synthesis rates have been noted [74]. Despite these valuable insights, the precise extent to which gender-related treatment responses to serotonin agents are tied to differences in serotonin synthesis or signaling in individuals with gastroparesis remains unclear. This underscores the need for further well-designed studies to unravel the complexities of this intriguing interplay and achieve a comprehensive understanding of the role of serotonin in gastrointestinal function and its implications for conditions like gastroparesis.

3.3.4. Interstitial Cells of Cajal

In a recent investigative study, the comparison of ICC in the antrum and pylorus smooth muscle was conducted among 38 individuals with severe refractory gastroparesis, encompassing both diabetic males and females [75]. Notably, the study, predominantly composed of females (66%, n = 25), revealed no statistically significant difference in the number of ICC between the two genders. However, distinct patterns emerged when examining ICC depletion in specific regions. In the antrum, 40% of females exhibited ICC depletion, mirroring the percentage observed in males (38%). Conversely, in the pylorus, 68% of females demonstrated ICC depletion, in contrast to 80% of males. These findings shed light on potential gender-related variations in the distribution of ICC in the context of severe refractory gastroparesis. In addition, the study prompts a crucial inquiry into the role of ICC as a potential marker for chronic injury leading to gastroparesis and underscores the need for larger-scale studies to validate and expand upon these initial observations.

4. Diagnosis

DGP presents a diagnostic challenge, demanding a comprehensive approach for accurate identification and management. The clinical diagnosis begins with a meticulous evaluation of the patient's medical history, focusing on symptoms such as early satiety, postprandial fullness, nausea, vomiting, and erratic blood glucose control, especially in individuals with a long-standing history of diabetes, particularly those with type 1 or longstanding type 2 diabetes [7,76,77]. A thorough physical examination is crucial, encompassing abdominal assessments to detect signs like distension or tenderness, alongside an evaluation of nutritional status. Exclusion of other conditions that mimic DGP symptoms, such as peptic ulcer disease or intestinal obstruction, involves tests like upper endoscopy,

imaging studies, and medication reviews to rule out potential causes. In the evaluation of suspected gastroparesis, it is imperative to exclude mechanical obstructions through diagnostic procedures such as upper endoscopy, computed tomography, or magnetic resonance enterography [78]. In cases where no obstructions are detected, specialized gastrointestinal function tests become instrumental in diagnosing disturbances associated with diabetic gastroenteropathy.

Specialized diagnostic tests play a pivotal role in confirming delayed gastric emptying and differentiating DGP from other motility disorders. Gastric scintigraphy (GES), considered the gold standard, evaluates gastric emptying non-invasively by employing a standard low-fat meal, tracking both solid and liquid phases. Delayed gastric emptying is diagnosed if there is greater than 60% retention at 2 h or 10% retention at 4 h. Mild, moderate, and severe classifications are made based on 10–15%, 16–35%, and >35% gastric retention after 4 h, respectively [79]. Notably, sex differences impact solid gastric emptying rates, with females being approximately 15% slower than males. GES limitations include variations in protocols across institutions, limited access to gamma-camera facilities, and radiation exposure concerns, restricting its use in specific populations, such as pregnant women or children.

The Gastric Emptying Breath Test (GEBT) offers a noninvasive approach to assess gastric emptying rates. Utilizing a ^{13}C-labeled substrate in a standardized meal, GEBT measures exhaled $^{13}CO_2$ at intervals (45, 90, 120, 150, 180, and 240 min) [6]. The ^{13}C substrate is absorbed in the duodenum, releasing $^{13}CO_2$ in breath samples. While GEBT is radiation-free, cost-effective, and suitable for certain populations, it remains an indirect measure of gastric emptying, with individual metabolism variations not fully understood.

The Wireless Motility Capsule (WMC) has served as a safe alternative to GES. This small wireless transmitting capsule records and transmits pH, pressure, and temperature data as it travels through the gastrointestinal tract. Gastric emptying time is determined by a pH shift as the capsule moves from the acidic stomach to the alkaline duodenum. The patient ingests the WMC after a standardized nutrient meal, and normal emptying should occur within 5 h. WMC pressure measurements can distinguish between patients with DGP and healthy individuals, demonstrating fewer contractions and motility indices in the former [80]. However, despite its historical significance, the WMC is no longer available.

Additionally, the Ambulatory Motilis 3D-Transit System, although holding promise for advancing our understanding of gastrointestinal motility, is currently not available in clinical practice. This innovative system monitors electromagnetic capsules as they traverse the gastrointestinal tract, furnishing detailed insights into gut contractile activity, movement velocity, orientation, and regional transit times. The system's capability to provide valuable anatomical information enables a comprehensive analysis of colonic motility, encompassing motor patterns and dynamics [80].

Finally, it is important to note that the diagnosis of diabetes presents a complex clinical landscape marked by challenges in establishing a clear association between delayed gastric emptying and symptomatic manifestations [81]. While delayed gastric emptying is often considered a hallmark of gastroparesis, the strength of its correlation with the daily symptoms experienced by individuals with diabetes mellitus remains elusive [82]. This diagnostic uncertainty is further compounded by the observation that a significant number of patients with delayed gastric emptying are asymptomatic, and that symptom profiles in diabetes mellitus patients with normal or delayed gastric emptying often exhibit striking similarities [83,84]. Moreover, therapeutic trials utilizing prokinetic agents for gastroparesis have revealed a lack of consistent correlation between improvements in gastric emptying and symptom relief [85]. In this context, exploring the intricacies of the diagnostic process becomes imperative, shedding light on the limitations of existing techniques and emphasizing the importance of considering subjective symptoms alongside objective measures during gastric emptying studies for a more nuanced and accurate diagnosis. Despite its traditional role in diagnosis, delayed gastric emptying suggests a potentially stronger relevance to glycemia and, conceivably, in guiding therapeutic

interventions [1,86]. Our evolving understanding prompts a nuanced perspective that goes beyond the conventional view of delayed gastric emptying as the hallmark feature.

5. Differential Diagnosis

DGP often coexists with complications such as retinopathy, neuropathy, nephropathy, and poor glycemic control [76,87,88]. In the realm of type 2 diabetes, individuals face an elevated risk of various organic gastrointestinal (GI) disorders, encompassing reflux esophagitis, gallstones, and GI malignancies. Consequently, the diagnostic process necessitates careful consideration of differential diagnoses, including gastric outlet obstruction, rumination syndrome, functional dyspepsia, chronic pancreatitis, and biliary colic.

The symptoms exhibited in DGP closely mirror those of gastric outlet obstruction, comprising nausea, vomiting, weight loss, abdominal bloating, early satiety, and abdominal discomfort. Intriguingly, these symptoms overlap with those of functional dyspepsia or indigestion, adding complexity to the diagnostic procedure [89]. While gastroesophageal reflux disease can sometimes be mistaken for gastroparesis, reflux typically manifests as a less prominent symptom in gastroparesis, where sensations of bloating and fullness take precedence. Patients with reflux primarily experience regurgitation immediately after food intake, distinguishing it from vomiting, which occurs hours after ingestion. Additionally, rumination syndrome should be contemplated in the list of differentials. Notably, other potential causes of unexplained vomiting encompass cyclic vomiting syndrome (CVS) and cannabinoid hyperemesis syndrome, further underscoring the need for a meticulous and comprehensive diagnostic approach to differentiate these conditions accurately [7].

6. Effects of Diabetic Gastroparesis on Glycemia

The gastrointestinal tract plays a crucial role in glucose homeostasis, with gastric emptying rates influencing blood glucose concentrations. While fasting blood glucose levels are regulated by insulin and glucagon secretion, hepatic and peripheral glucose uptake, and postprandial glucose levels are influenced by various factors. These factors include glucose absorption, disposal, endogenous glucose production, meal composition, gastric emptying rate, small intestine processes (such as glucose absorption and incretin release), insulin secretion, and hepatic and peripheral glucose disposal [90–92]. The gastric emptying rate accounts for about 35% of the initial rise in postprandial glucose levels, contributing significantly to both early and overall postprandial glycemia [93,94]. Notably, patients with gastroparesis in Type 1 diabetes require reduced early postprandial insulin compared to those with a normal gastric emptying rate [95]. In intervention studies with Type 2 diabetes patients, inhibiting gastric emptying with opiates markedly decreased glycemic excursions, while prokinetic erythromycin administration had opposite effects [96]. Understanding the relationship between slowing gastric emptying and reductions in glycemia is crucial. Precise evaluation using intraduodenal glucose infusions spanning physiological rates demonstrated a nonlinear glycemic response, emphasizing the significance of even modest changes in intestinal glucose flux. Moreover, studies indicate that accelerated gastric emptying leads to postprandial hyperglycemia, while abnormally delayed emptying might predispose individuals to hypoglycemia. Therefore, measuring gastric emptying in insulin-treated diabetes patients with unexplained hypoglycemic episodes, particularly in the early postprandial period, is vital. Adjustments in insulin regimens or therapies to enhance gastric emptying predictability, typically by accelerating it, should be considered based on these measurements [97,98].

7. Nutritional Management of Diabetic Gastroparesis

DGP is a clinical condition characterized by an increased risk of malnutrition, both in quantitative and qualitative terms. Data from The NIDDK Gastroparesis Clinical Research Consortium (GpCRC) in 2011 revealed that more than 60% of the 305 patients enrolled in the study experienced malnutrition, failing to meet the minimum required levels of calories, and many of them presented severe vitamin deficiencies. This registry encompasses

all patients with gastroparesis, regardless of the presence of type 1 or type 2 diabetes. Particularly in type 2 diabetic individuals, the data showed a significant number of patients who were overweight, contrary to the common idea that identifies underweight as the sole hallmark of malnutrition. According to the study results, only a very small percentage of gastroparetic patients received nutrition counseling from a qualified dietitian or followed a suggested diet to minimize gastrointestinal discomfort [99]. All these data underscore the crucial importance of nutritional assessment in all individuals affected by gastroparesis, with special attention to diabetic individuals due to implications for glucose management.

In the absence of evidence-based guidelines, nutritional management of DGP relies on expert recommendations, observational studies, and clinical consensus. Initially, all patients diagnosed with DGP should undergo an assessment for malnutrition. A BMI < 20 kg/m^2 or unintentional weight loss of 5–10% of body weight within the last 3–6 months are considered severe clinical markers of malnutrition [100,101]. Being overweight, as discussed below, does not exclude the presence of a risk or actual malnutrition. In diabetic individuals, the presence of early morning satiety could be an indirect sign of gastroparesis. To avoid excluding overweight individuals from nutritional surveillance, a weight goal, above which clinical intervention must be performed, should be identified for all individuals affected by DGP, leading to a specific nutritional plan tailored to each patient. One of the general recommendations is to avoid large meals. For individuals with DGP, six or eight meals during the day are suggested. Large meals, indeed, both slow gastric emptying and reduce lower esophageal sphincter pressure. Food consistency is crucial. Unlike solids, liquid meals do not require antral contraction to pass through the stomach, emptying simply by gravity. Moreover, well-prepared liquid meals can be highly caloric. If feasible, transitioning from solid to liquid meals could be suggested for all gastroparetic patients. Consuming liquid meals in the later part of the day could alleviate gastroparetic symptoms. Parrish et al. suggest in their work a specific semi-liquid meal pattern combining liquid foods and liquid supplements. Moreover, they suggest enhancing the protein and caloric load, flavor, and palatability of liquid foods [102]. Experts also recommend avoiding a supine position in the first hours after a meal, as antigravity effects and duodenal compression by the spine could immediately worsen gastroparetic symptoms. For the same reason, elevating the head by 6–8 cm during sleep is suggested to minimize reflux. Patients with DGP are prone to the formation of bezoars due to their incapability to properly eliminate fibers. Generally, fibers are contraindicated in patients with DGP, although their possible effect in minimizing the glycemic index of foods is recognized. Some researchers are exploring technological solutions to improve gastric tolerance to fibers in gastroparetic individuals [103]. Suresh et al. have recently demonstrated that some fibers characterized by low viscosity (PHGG—partially hydrolyzed guar gum or Arabic gum) are better tolerated in terms of gastrointestinal symptoms than high viscosity ones (psyllium husk) in people affected by DGP presenting the same effects in mitigating glycemic index. These results seem encouraging in a new definition of the role of fibers in DGP [103]. Fats, in general, reduce gastric emptying, although they may be better tolerated in liquid form. Limiting their consumption to general dietary recommendations in people with diabetes, based on the patients' gastric tolerance, could be encouraged. Another aspect to consider is that hyperglycemia (glycemia > 200 mg/dL) itself inhibits gastric emptying. Trying to avoid glycemic variability and adapting insulin administration following a basal-bolus regimen to the nutritional habits of the patient affected by DGP is a fundamental goal for diabetologists, also aiming to improve the quality of life and reduce gastric symptoms in patients. To date, there are no recommendations for choosing specific insulin analogs over others. In summary, the main nutritional suggestions for diabetic individuals experiencing gastroparesis are as follows (Figure 2) [102]:

- Eating smaller and more frequent meals;
- Eating slowly (30 min meals);
- Avoiding the supine position for at least the first hour after a meal;
- Sleeping with the head elevated 6–8 inches from the bed to minimize reflux;

- Avoiding tight clothes that could compress the abdomen;
- Avoiding meals in the later part of the day;
- Avoiding fats and fibers;
- Avoiding chewing gums that increase air swallowing;
- Avoiding CATS: caffeine, alcohol, tobacco, and stress;
- Avoiding all foods that can reduce lower esophageal sphincter pressure: peppermint, chocolate, fat, and caffeine.

Figure 2. Main nutritional interventions in patients with diabetic gastroparesis.

Some experts have suggested a specific semi-liquid dietary plan divided into six meals, also indicating carbohydrate counts to help patients choose the correct rapid insulin analog dose, minimizing glycemic variability [102]. Finally, it is possible to consider enteral nutrition if patients with DGP fail to maintain the weight goal, continue to lose weight, or experience multiple hospitalizations for refractory gastric symptoms, which could lead to dehydration and starvation. As is well known, enteral nutrition represents the best option in terms of artificial nutrition, ensuring patients' both balanced nutrition and hydration and a reliable means of drug delivery (e.g., antiemetic or prokinetic), preserving the functionality of the gastrointestinal tube and helping diabetologists and patients themselves better control glycemic variability due to a direct correlation between nutrients, glycemic variation, and administered insulin doses. Parenteral nutrition could be reserved only in selected cases, considering the high rate of complications associated with its use in diabetic individuals. Nutritional management of patients affected by DGP continues to pose a difficult clinical challenge for diabetologists and nutritionists who must balance a proper diet in both qualitative and quantitative terms, glycemic control, and gastric symptoms to enhance the quality of life [99].

8. Conclusions

In summary, DGP presents a multifaceted challenge, intertwining complex pathophysiology, diverse symptoms, diagnostic intricacies, and the imperative need for tailored nutritional interventions. The understanding of delayed gastric emptying, coupled with

the spectrum of symptoms, underscores the necessity for nuanced diagnostic approaches. Nutritional intervention emerges as a crucial component in managing symptoms and enhancing the quality of life for affected individuals, together with the need for personalized approaches guided by expert recommendations. As we navigate the complexities of this condition, collaboration between researchers, clinicians, and patients remains paramount, offering hope for a future with more effective and compassionate management of DGP.

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References

1. Bharucha, A.E.; Kudva, Y.C.; Prichard, D.O. Diabetic Gastroparesis. *Endocr. Rev.* **2019**, *40*, 1318–1352. [CrossRef]
2. Ahmed, M.S.O.; Forde, H.; Smith, D. Diabetic gastroparesis: Clinical features, diagnosis and management. *Ir. J. Med. Sci.* **2023**, *192*, 1687–1694. [CrossRef]
3. Zahid, S.A.; Tated, R.; Mathew, M.; Rajkumar, D.; Karnik, S.B.; Pramod Roy, A.; Jacob, F.P.; Baskara Salian, R.; Razzaq, W.; Shivakumar, D.; et al. Diabetic Gastroparesis and its Emerging Therapeutic Options: A Narrative Review of the Literature. *Cureus* **2023**, *15*, e44870. [CrossRef]
4. Li, L.; Wang, L.; Long, R.; Song, L.; Yue, R. Prevalence of gastroparesis in diabetic patients: A systematic review and meta-analysis. *Sci. Rep.* **2023**, *13*, 14015. [CrossRef]
5. Jung, H.K.; Choung, R.S.; Locke, G.R., 3rd; Schleck, C.D.; Zinsmeister, A.R.; Szarka, L.A.; Mullan, B.; Talley, N.J. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology* **2009**, *136*, 1225–1233. [CrossRef]
6. Pafundi, P.C.; Garofalo, C.; Galiero, R.; Borrelli, S.; Caturano, A.; Rinaldi, L.; Provenzano, M.; Salvatore, T.; De Nicola, L.; Minutolo, R.; et al. Role of Albuminuria in Detecting Cardio-Renal Risk and Outcome in Diabetic Subjects. *Diagnostics* **2021**, *11*, 290. [CrossRef]
7. Petri, M.; Singh, I.; Baker, C.; Underkofler, C.; Rasouli, N. Diabetic gastroparesis: An overview of pathogenesis, clinical presentation and novel therapies, with a focus on ghrelin receptor agonists. *J. Diabetes Complicat.* **2021**, *35*, 107733. [CrossRef]
8. Goyal, R.K.; Guo, Y.; Mashimo, H. Advances in the physiology of gastric emptying. *Neurogastroenterol. Motil.* **2019**, *31*, e13546. [CrossRef] [PubMed]
9. Ibba Manneschi, L.; Pacini, S.; Corsani, L.; Bechi, P.; Faussone-Pellegrini, M.S. Interstitital cells of Cajal in the human stomach: Distribution and relationship with enteric innervation. *Histol. Histopathol.* **2004**, *19*, 1153–1164. [PubMed]
10. Harvey, R.F. Hormonal control of gastrointestinal motility. *Am. J. Dig. Dis.* **1975**, *20*, 523–539. [CrossRef] [PubMed]
11. Camilleri, M.; Bharucha, A.E.; Farrugia, G. Epidemiology, mechanisms, and management of diabetic gastroparesis. *Clin. Gastroenterol. Hepatol.* **2011**, *9*, 5–12. [CrossRef] [PubMed]
12. Dockray, G.J. Gastrointestinal hormones and the dialogue between gut and brain. *J. Physiol.* **2014**, *592*, 2927–2941. [CrossRef] [PubMed]
13. Samsom, M.; Roelofs, J.M.; Akkermans, L.M.; van Berge Henegouwen, G.P.; Smout, A.J. Proximal gastric motor activity in response to a liquid meal in type I diabetes mellitus with autonomic neuropathy. *Dig. Dis. Sci.* **1998**, *43*, 491–496. [CrossRef] [PubMed]
14. Gaddipati, K.V.; Simonian, H.P.; Kresge, K.M.; Boden, G.H.; Parkman, H.P. Abnormal ghrelin and pancreatic polypeptide responses in gastroparesis. *Dig. Dis. Sci.* **2006**, *51*, 1339–1346. [CrossRef]
15. Buysschaert, M.; Donckier, J.; Dive, A.; Ketelslegers, J.M.; Lambert, A.E. Gastric acid and pancreatic polypeptide responses to sham feeding are impaired in diabetic subjects with autonomic neuropathy. *Diabetes* **1985**, *34*, 1181–1185. [CrossRef]
16. Guy, R.J.; Dawson, J.L.; Garrett, J.R.; Laws, J.W.; Thomas, P.K.; Sharma, A.K.; Watkins, P.J. Diabetic gastroparesis from autonomic neuropathy: Surgical considerations and changes in vagus nerve morphology. *J. Neurol. Neurosurg. Psychiatry* **1984**, *47*, 686–691. [CrossRef]
17. Schmidt, R.E.; Green, K.G.; Snipes, L.L.; Feng, D. Neuritic dystrophy and neuronopathy in Akita (Ins2(Akita)) diabetic mouse sympathetic ganglia. *Exp. Neurol.* **2009**, *216*, 207–218. [CrossRef]

18. Carroll, S.L.; Byer, S.J.; Dorsey, D.A.; Watson, M.A.; Schmidt, R.E. Ganglion-specific patterns of diabetes-modulated gene expression are established in prevertebral and paravertebral sympathetic ganglia prior to the development of neuroaxonal dystrophy. *J. Neuropathol. Exp. Neurol.* **2004**, *63*, 1144–1154. [CrossRef]
19. Grover, M.; Farrugia, G.; Stanghellini, V. Gastroparesis: A turning point in understanding and treatment. *Gut* **2019**, *68*, 2238–2250. [CrossRef]
20. Tashima, K.; Nishijima, M.; Fujita, A.; Kubomi, M.; Takeuchi, K. Acid secretory changes in streptozotocin-diabetic rats: Different responses to various secretagogues. *Dig. Dis. Sci.* **2000**, *45*, 1352–1358. [CrossRef] [PubMed]
21. Camilleri, M.; Malagelada, J.R. Abnormal intestinal motility in diabetics with the gastroparesis syndrome. *Eur. J. Clin. Investig.* **1984**, *14*, 420–427. [CrossRef]
22. Yang, S.; Wu, B.; Sun, H.; Sun, T.; Han, K.; Li, D.; Ji, F.; Zhang, G.; Zhou, D. Impaired insulin/IGF-1 is responsible for diabetic gastroparesis by damaging myenteric cholinergic neurones and interstitial cells of Cajal. *Biosci. Rep.* **2017**, *37*, BSR20170776. [CrossRef] [PubMed]
23. Forster, J.; Damjanov, I.; Lin, Z.; Sarosiek, I.; Wetzel, P.; McCallum, R.W. Absence of the interstitial cells of Cajal in patients with gastroparesis and correlation with clinical findings. *J. Gastrointestig. Surg.* **2005**, *9*, 102–108. [CrossRef]
24. Grover, M.; Bernard, C.E.; Pasricha, P.J.; Lurken, M.S.; Faussone-Pellegrini, M.S.; Smyrk, T.C.; Parkman, H.P.; Abell, T.L.; Snape, W.J.; Hasler, W.L.; et al. Clinical-histological associations in gastroparesis: Results from the Gastroparesis Clinical Research Consortium. *Neurogastroenterol. Motil.* **2012**, *24*, 531–539. [CrossRef]
25. Grover, M.; Farrugia, G.; Lurken, M.S.; Bernard, C.E.; Faussone-Pellegrini, M.S.; Smyrk, T.C.; Parkman, H.P.; Abell, T.L.; Snape, W.J.; Hasler, W.L.; et al. Cellular changes in diabetic and idiopathic gastroparesis. *Gastroenterology* **2011**, *140*, 1575–1585. [CrossRef] [PubMed]
26. Iwasaki, H.; Kajimura, M.; Osawa, S.; Kanaoka, S.; Furuta, T.; Ikuma, M.; Hishida, A. A deficiency of gastric interstitial cells of Cajal accompanied by decreased expression of neuronal nitric oxide synthase and substance P in patients with type 2 diabetes mellitus. *J. Gastroenterol.* **2006**, *41*, 1076–1087. [CrossRef]
27. He, C.L.; Soffer, E.E.; Ferris, C.D.; Walsh, R.M.; Szurszewski, J.H.; Farrugia, G. Loss of interstitial cells of Cajal and inhibitory innervation in insulin-dependent diabetes. *Gastroenterology* **2001**, *121*, 427–434. [CrossRef]
28. Young, R.L.; Chia, B.; Isaacs, N.J.; Ma, J.; Khoo, J.; Wu, T.; Horowitz, M.; Rayner, C.K. Disordered control of intestinal sweet taste receptor expression and glucose absorption in type 2 diabetes. *Diabetes* **2013**, *62*, 3532–3541. [CrossRef] [PubMed]
29. Camilleri, M. Gastrointestinal hormones and regulation of gastric emptying. *Curr. Opin. Endocrinol. Diabetes Obes.* **2019**, *26*, 3–10. [CrossRef]
30. Meldgaard, T.; Olesen, S.S.; Farmer, A.D.; Krogh, K.; Wendel, A.A.; Brock, B.; Drewes, A.M.; Brock, C. Diabetic enteropathy: From molecule to mechanism-based treatment. *J. Diabetes Res.* **2018**, *2018*, 3827301. [CrossRef]
31. Gangula, P.R.; Maner, W.L.; Micci, M.A.; Garfield, R.E.; Pasricha, P.J. Diabetes induces sex-dependent changes in neuronal nitric oxide synthase dimerization and function in the rat gastric antrum. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2007**, *292*, G725–G733. [CrossRef]
32. Gangula, P.R.; Sekhar, K.R.; Mukhopadhyay, S. Gender bias in gastroparesis: Is nitric oxide the answer? *Dig. Dis. Sci.* **2011**, *56*, 2520–2527. [CrossRef]
33. Daff, S. NO synthase: Structures and mechanisms. *Nitric Oxide* **2010**, *23*, 1–11. [CrossRef]
34. Yamamoto, I.; Fujimura, M.; Kihara, N.; Kumano, K.; Yamada, T.; Yamamoto, H.; Fujimiya, M. Nitric oxide formation in the dog sphincter of Oddi from nitric oxide donors as measured with in vivo micro-dialysis. *Aliment. Pharmacol. Ther.* **2000**, *14*, 1095–1101. [CrossRef]
35. Takahashi, T. Pathophysiological significance of neuronal nitric oxide synthase in the gastrointestinal tract. *J. Gastroenterol.* **2003**, *38*, 421–430. [CrossRef]
36. Huang, P.L.; Dawson, T.M.; Bredt, D.S.; Snyder, S.H.; Fishman, M.C. Targeted disruption of the neuronal nitric oxide synthase gene. *Cell* **1993**, *75*, 1273. [CrossRef]
37. Plourde, V.; Quintero, E.; Suto, G.; Coimbra, C.; Taché, Y. Delayed gastric emptying induced by inhibitors of nitric oxide synthase in rats. *Eur. J. Pharmacol.* **1994**, *256*, 125–129. [CrossRef]
38. Takahashi, T.; Nakamura, K.; Itoh, H.; Sima, A.A.; Owyang, C. Impaired expression of nitric oxide synthase in the gastric myenteric plexus of spontaneously diabetic rats. *Gastroenterology* **1997**, *113*, 1535–1544. [CrossRef] [PubMed]
39. Watkins, C.C.; Sawa, A.; Jaffrey, S.; Blackshaw, S.; Barrow, R.K.; Snyder, S.H.; Ferris, C.D. Insulin restores neuronal nitric oxide synthase expression and function that is lost in diabetic gastropathy. *J. Clin. Investig.* **2000**, *106*, 803. [CrossRef] [PubMed]
40. Cellek, S. Point of NO return for nitrergic nerves in diabetes: A new insight into diabetic complications. *Curr. Pharm. Des.* **2004**, *10*, 3683–3695. [CrossRef] [PubMed]
41. Caturano, A.; D'Angelo, M.; Mormone, A.; Russo, V.; Mollica, M.P.; Salvatore, T.; Galiero, R.; Rinaldi, L.; Vetrano, E.; Marfella, R.; et al. Oxidative Stress in Type 2 Diabetes: Impacts from Pathogenesis to Lifestyle Modifications. *Curr. Issues Mol. Biol.* **2023**, *45*, 6651–6666. [CrossRef] [PubMed]
42. Galiero, R.; Caturano, A.; Vetrano, E.; Beccia, D.; Brin, C.; Alfano, M.; Di Salvo, J.; Epifani, R.; Piacevole, A.; Tagliaferri, G.; et al. Peripheral Neuropathy in Diabetes Mellitus: Pathogenetic Mechanisms and Diagnostic Options. *Int. J. Mol. Sci.* **2023**, *24*, 3554. [CrossRef] [PubMed]

43. Choi, K.M.; Gibbons, S.J.; Nguyen, T.V.; Stoltz, G.J.; Lurken, M.S.; Ordog, T.; Szurszewski, J.H.; Farrugia, G. Heme oxygenase-1 protects interstitial cells of Cajal from oxidative stress and reverses diabetic gastroparesis. *Gastroenterology* **2008**, *135*, 2055–2064. [CrossRef] [PubMed]
44. Choi, K.M.; Kashyap, P.C.; Dutta, N.; Stoltz, G.J.; Ordog, T.; Shea Donohue, T.; Bauer, A.J.; Linden, D.R.; Szurszewski, J.H.; Gibbons, S.J.; et al. CD206-positive M2 macrophages that express heme oxygenase-1 protect against diabetic gastroparesis in mice. *Gastroenterology* **2010**, *138*, 2399–2409. [CrossRef] [PubMed]
45. Gonzalez, Z.; Loganathan, P.; Sarosiek, I.; McCallum, R.W. Gender-Related Differences in Gastroparesis. *Am. J. Med. Sci.* **2020**, *360*, 474–483. [CrossRef] [PubMed]
46. Yang, X.; Guo, Y.; He, J.; Zhang, F.; Sun, X.; Yang, S.; Dong, H. Estrogen and estrogen receptors in the modulation of gastrointestinal epithelial secretion. *Oncotarget* **2017**, *8*, 97683–97692. [CrossRef] [PubMed]
47. Zia, J.K.; Heitkemper, M.M. Upper gastrointestinal tract motility disorders in women, gastroparesis, and gastroesophageal reflux disease. *Gastroenterol. Clin. N. Am.* **2016**, *45*, 239–251. [CrossRef]
48. Degen, L.P.; Phillips, S.F. Variability of gastrointestinal transit in healthy women and men. *Gut* **1996**, *39*, 299–305. [CrossRef]
49. Jiang, Y.; Greenwood-Van Meerveld, B.; Johnson, A.C.; Travagli, R.A. Role of estrogen and stress on the brain-gut axis. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2019**, *317*, G203–G209. [CrossRef]
50. Petring, O.U.; Flachs, H. Inter- and intrasubject variability of gastric emptying in healthy volunteers measured by scintigraphy and paracetamol absorption. *Br. J. Clin. Pharmacol.* **1990**, *29*, 703–708. [CrossRef]
51. Gill, R.C.; Murphy, P.D.; Hooper, H.R.; Bowes, K.L.; Kingma, Y.J. Effect of the menstrual cycle on gastric emptying. *Digestion* **1987**, *36*, 168–174. [CrossRef]
52. Crimmins, S.; Smiley, R.; Preston, K.; Yau, A.; Mccallum, R.; Ali, M.S. Increased Expression of Pyloric ERβ Is Associated with Diabetic Gastroparesis in Streptozotocin-Induced Male Diabetic Rats. *Gastroenterol. Res.* **2016**, *9*, 39–46. [CrossRef]
53. Bruce, L.A.; Behsudi, F.M. Differential inhibition of regional gastrointestinal tissue to progesterone in the rat. *Life Sci.* **1980**, *27*, 427–434. [CrossRef]
54. Davis, M.; Ryan, J.P. Influence of progesterone on guinea pig gallbladder motility in vitro. *Dig. Dis. Sci.* **1986**, *31*, 513–518. [CrossRef]
55. O'Sullivan, G.M.; Sutton, A.J.; Thompson, S.A.; Carrie, L.E.; Bullingham, R.E. Noninvasive measurement of gastric emptying in obstetric patients. *Anesth. Analg.* **1987**, *66*, 505–511. [CrossRef]
56. Davison, J.S.; Davison, M.C.; Hay, D.M. Gastric emptying time in late pregnancy and labour. *J. Obstet. Gynaecol. Br. Commonw.* **1970**, *77*, 37–41. [CrossRef] [PubMed]
57. Davison, J.S. Letter: Gastric emptying in labour. *Lancet* **1975**, *2*, 227–228. [CrossRef] [PubMed]
58. Simpson, K.H.; Stakes, A.F.; Miller, M. Pregnancy delays paracetamol absorption and gastric emptying in patients undergoing surgery. *Br. J. Anaesth.* **1988**, *60*, 24–27. [CrossRef] [PubMed]
59. Ryan, J.P.; Bhojwani, A.; Wang, M.B. Effect of pregnancy on gastric motility in vivo and in vitro in the guinea pig. *Gastroenterology* **1987**, *93*, 29–34. [CrossRef] [PubMed]
60. Chiloiro, M.; Darconza, G.; Piccioli, E.; De Carne, M.; Clemente, C.; Riezzo, G. Gastric emptying and orocecal transit time in pregnancy. *J. Gastroenterol.* **2001**, *36*, 538–543. [CrossRef] [PubMed]
61. Datz, F.; Christian, P.; Moore, J. Differences in gastric emptying rates between menstruating and postmenopausal women. *J. Nucl. Med.* **1987**, *28*, 604–605.
62. Hutson, W.R.; Roehrkasse, R.L.; Wald, A. Influence of gender and menopause on gastric emptying and motility. *Gastroenterology* **1989**, *96*, 11–17. [CrossRef]
63. Al-Shboul, O.A.; Nazzal, M.S.; Mustafa, A.G.; Al-Dwairi, A.N.; Alqudah, M.A.; Abu Omar, A.; Alfaqih, M.A.; Alsalem, M.I. Estrogen relaxes gastric muscle cells via a nitric oxide- and cyclic guanosine monophosphate-dependent mechanism: A sex-associated differential effect. *Exp. Ther. Med.* **2018**, *16*, 1685–1692. [CrossRef] [PubMed]
64. Showkat Ali, M.; Tiscareno-Grejada, I.; Locovei, S.; Smiley, R.; Collins, T.; Sarosiek, J.; McCallum, R. Gender and estradiol as major factors in the expression and dimerization of nNOSα in rats with experimental diabetic gastroparesis. *Dig. Dis. Sci.* **2012**, *57*, 2814–2825. [CrossRef] [PubMed]
65. Krishnasamy, S.; Abell, T.L. Diabetic Gastroparesis: Principles and Current Trends in Management. *Diabetes Ther.* **2018**, *9* (Suppl. S1), 1–42. [CrossRef]
66. Gangula, P.R.; Mukhopadhyay, S.; Ravella, K.; Cai, S.; Channon, K.M.; Garfield, R.E.; Pasricha, P.J. Tetrahydrobiopterin (BH4), a cofactor for nNOS, restores gastric emptying and nNOS expression in female diabetic rats. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2010**, *298*, G692–G699. [CrossRef] [PubMed]
67. van Lelyveld, N.; Ter Linde, J.; Schipper, M.; Samsom, M. Serotonergic signalling in the stomach and duodenum of patients with gastroparesis. *Neurogastroenterol. Motil.* **2008**, *20*, 448–455. [CrossRef] [PubMed]
68. Spohn, S.N.; Mawe, G.M. Non-conventional features of peripheral serotonin signalling—The gut and beyond. *Nat. Rev. Gastroenterol. Hepatol.* **2017**, *14*, 412–420. [CrossRef] [PubMed]
69. Neal, K.B.; Parry, L.J.; Bornstein, J.C. Strain-specific genetics, anatomy and function of enteric neural serotonergic pathways in inbred mice. *J. Physiol.* **2009**, *587*, 567–586. [CrossRef] [PubMed]
70. Gershon, M.D. 5-HT4-mediated neuroprotection: A new therapeutic modality on the way? *Am. J. Physiol. Gastrointest. Liver Physiol.* **2016**, *310*, G766–G767. [CrossRef]

71. Tack, J.; Broekaert, D.; Coulie, B.; Fischler, B.; Janssens, J. Influence of the selective serotonin re-uptake inhibitor, paroxetine, on gastric sensorimotor function in humans. *Aliment. Pharmacol. Ther.* **2003**, *17*, 603–608. [CrossRef] [PubMed]
72. Coleman, N.S.; Marciani, L.; Blackshaw, E.; Wright, J.; Parker, M.; Yano, T.; Yamazaki, S.; Chan, P.Q.; Wilde, K.; Gowland, P.A.; et al. Effect of a novel 5-HT3 receptor agonist MKC-733 on upper gastrointestinal motility in humans. *Aliment. Pharmacol. Ther.* **2003**, *18*, 1039–1048. [CrossRef] [PubMed]
73. Waseem, S.; Moshiree, B.; Draganov, P.V. Gastroparesis: Current diagnostic challenges and management considerations. *World J. Gastroenterol.* **2009**, *15*, 25–37. [CrossRef] [PubMed]
74. Nishizawa, S.; Benkelfat, C.; Young, S.N.; Leyton, M.; Mzengeza, S.; de Montigny, C.; Blier, P.; Diksic, M. Differences between males and females in rates of serotonin synthesis in human brain. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 5308–5313. [CrossRef] [PubMed]
75. Bashashati, M.; McCallum, R.W. Is Interstitial Cells of Cajal−opathy Present in Gastroparesis? *J. Neurogastroenterol. Motil.* **2015**, *21*, 486–493. [CrossRef] [PubMed]
76. Farmer, A.D.; Kadirkamanathan, S.S.; Aziz, Q. Diabetic gastroparesis: Pathophysiology, evaluation and management. *Br. J. Hosp. Med.* **2012**, *73*, 451–456. [CrossRef] [PubMed]
77. Camilleri, M.; Iturrino, J.; Bharucha, A.E.; Burton, D.; Shin, A.; Jeong, I.D.; Zinsmeister, A.R. Performance characteristics of scintigraphic measurement of gastric emptying of solids in healthy participants. *Neurogastroenterol. Motil.* **2012**, *24*, 1076-e562. [CrossRef]
78. Parkman, H.P.; Hasler, W.L.; Fisher, R.S.; American Gastroenterological Association. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. *Gastroenterology* **2004**, *127*, 1592–1622. [CrossRef]
79. Young, C.F.; Moussa, M.; Shubrook, J.H. Diabetic Gastroparesis: A Review. *Diabetes Spectr.* **2020**, *33*, 290–297. [CrossRef]
80. Meldgaard, T.; Keller, J.; Olesen, A.E.; Olesen, S.S.; Krogh, K.; Borre, M.; Farmer, A.; Brock, B.; Brock, C.; Drewes, A.M. Pathophysiology and management of diabetic gastroenteropathy. *Therap. Adv. Gastroenterol.* **2019**, *12*, 1–17. [CrossRef]
81. Vijayvargiya, P.; Jameie-Oskooei, S.; Camilleri, M.; Chedid, V.; Erwin, P.J.; Murad, M.H. Association between delayed gastric emptying and upper gastrointestinal symptoms: A systematic review and meta-analysis. *Gut* **2019**, *68*, 804–813. [CrossRef]
82. Teigland, T.; Iversen, M.M.; Sangnes, D.A.; Dimcevski, G.; Søfteland, E. A longitudinal study on patients with diabetes and symptoms of gastroparesis—Associations with impaired quality of life and increased depressive and anxiety symptoms. *J Diabetes Complicat.* **2018**, *32*, 89–94. [CrossRef] [PubMed]
83. Freeman, R. Diabetic autonomic neuropathy. *Handb. Clin. Neurol.* **2014**, *126*, 63–79.
84. Khayyam, U.; Sachdeva, P.; Gomez, J.; Ramzan, Z.; Smith, M.S.; Maurer, A.H.; Fisher, R.S.; Parkman, H.P. Assessment of symptoms during gastric emptying scintigraphy to correlate symptoms to delayed gastric emptying. *Neurogastroenterol. Motil.* **2010**, *22*, 539–545. [CrossRef]
85. Janssen, P.; Harris, M.S.; Jones, M.; Masaoka, T.; Farré, R.; Törnblom, H.; Van Oudenhove, L.; Simrén, M.; Tack, J. The relation between symptom improvement and gastric emptying in the treatment of diabetic and idiopathic gastroparesis. *Am. J. Gastroenterol.* **2013**, *108*, 1382–1391. [CrossRef]
86. Caturano, A.; Galiero, R.; Pafundi, P.C. Metformin for Type 2 Diabetes. *JAMA* **2019**, *322*, 1312. [CrossRef] [PubMed]
87. Salvatore, T.; Galiero, R.; Caturano, A.; Vetrano, E.; Loffredo, G.; Rinaldi, L.; Catalini, C.; Gjeloshi, K.; Albanese, G.; Di Martino, A.; et al. Coronary Microvascular Dysfunction in Diabetes Mellitus: Pathogenetic Mechanisms and Potential Therapeutic Options. *Biomedicines* **2022**, *10*, 2274. [CrossRef]
88. Salvatore, T.; Galiero, R.; Caturano, A.; Vetrano, E.; Rinaldi, L.; Coviello, F.; Di Martino, A.; Albanese, G.; Colantuoni, S.; Medicamento, G.; et al. Dysregulated Epicardial Adipose Tissue as a Risk Factor and Potential Therapeutic Target of Heart Failure with Preserved Ejection Fraction in Diabetes. *Biomolecules* **2022**, *12*, 176. [CrossRef] [PubMed]
89. Shin, A.S.; Camilleri, M. Diagnostic assessment of diabetic gastroparesis. *Diabetes* **2013**, *62*, 2667–2673. [CrossRef]
90. Woerle, H.J.; Albrecht, M.; Linke, R.; Zschau, S.; Neumann, C.; Nicolaus, M.; Gerich, J.; Göke, B.; Schirra, J. Importance of changes in gastric emptying for postprandial plasma glucose fluxes in healthy humans. *Am. J. Physiol. Endocrinol. Metab.* **2008**, *294*, E103–E109. [CrossRef]
91. Caturano, A.; Acierno, C.; Nevola, R.; Pafundi, P.C.; Galiero, R.; Rinaldi, L.; Salvatore, T.; Adinolfi, L.E.; Sasso, F.C. Non-Alcoholic Fatty Liver Disease: From Pathogenesis to Clinical Impact. *Processes* **2021**, *9*, 135. [CrossRef]
92. Woerle, H.J.; Meyer, C.; Dostou, J.M.; Gosmanov, N.R.; Islam, N.; Popa, E.; Wittlin, S.D.; Welle, S.L.; Gerich, J.E. Pathways for glucose disposal after meal ingestion in humans. *Am. J. Physiol. Endocrinol. Metab.* **2003**, *284*, E716–E725. [CrossRef]
93. Horowitz, M.; Edelbroek, M.A.; Wishart, J.M.; Straathof, J.W. Relationship between oral glucose tolerance and gastric emptying in normal healthy subjects. *Diabetologia* **1993**, *36*, 857–862. [CrossRef]
94. Jones, K.L.; Horowitz, M.; Carney, B.I.; Wishart, J.M.; Guha, S.; Green, L. Gastric emptying in early noninsulin-dependent diabetes mellitus. *J. Nucl. Med.* **1996**, *37*, 1643–1648.
95. Ishii, M.; Nakamura, T.; Kasai, F.; Onuma, T.; Baba, T.; Takebe, K. Altered postprandial insulin requirement in IDDM patients with gastroparesis. *Diabetes Care* **1994**, *17*, 901–903. [CrossRef] [PubMed]
96. Gonlachanvit, S.; Hsu, C.W.; Boden, G.H.; Knight, L.C.; Maurer, A.H.; Fisher, R.S.; Parkman, H.P. Effect of altering gastric emptying on postprandial plasma glucose concentrations following a physiologic meal in type-II diabetic patients. *Dig. Dis. Sci.* **2003**, *48*, 488–497. [CrossRef] [PubMed]

97. Perano, S.J.; Rayner, C.K.; Kritas, S.; Horowitz, M.; Donaghue, K.; Mpundu-Kaambwa, C.; Giles, L.; Couper, J.J. Gastric emptying is more rapid in adolescents with type 1 diabetes and impacts on postprandial glycemia. *J. Clin. Endocrinol. Metab.* **2015**, *100*, 2248–2253. [CrossRef] [PubMed]
98. Rayner, C.K.; Horowitz, M. New management approaches for gastroparesis. *Nat. Clin. Pract. Gastroenterol. Hepatol.* **2005**, *2*, 454–493. [CrossRef] [PubMed]
99. Parkman, H.P.; Yates, K.P.; Hasler, W.L.; Nguyen, L.; Pasricha, P.J.; Snape, W.J.; Farrugia, G.; Calles, J.; Koch, K.L.; Abell, T.L.; et al. Dietary intake and nutritional deficiencies in patients with diabetic or idiopathic gastroparesis. *Gastroenterology* **2011**, *141*, 486–498. [CrossRef] [PubMed]
100. Sadiya, A. Nutritional therapy for the management of diabetic gastroparesis: Clinical review. *Diabetes Metab. Syndr. Obes.* **2012**, *5*, 329–335. [CrossRef] [PubMed]
101. Di Francia, R.; Rinaldi, L.; Cillo, M.; Varriale, E.; Facchini, G.; D'Aniello, C.; Marotta, G.; Berretta, M. Antioxidant diet and genotyping as tools for the prevention of liver disease. *Eur. Rev. Med. Pharmacol. Sci.* **2016**, *20*, 5155–5163. [PubMed]
102. Parrish, C.S.; Pastors, J.G. Nutritional Management of Gastroparesis in People with Diabetes. *Diabetes Spectr.* **2007**, *20*, 231–234. [CrossRef]
103. Suresh, H.; Zhou, J.; Ho, V. The Short-Term Effects and Tolerability of Low-Viscosity Soluble Fibre on Gastroparesis Patients: A Pilot Clinical Intervention Study. *Nutrients* **2021**, *13*, 4298. [CrossRef] [PubMed]