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The Duodenum: Its Role as a Metabolic Center and Clinical Implications

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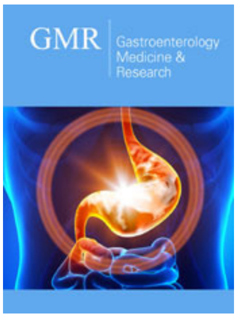

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Abstract

Common metabolic diseases, such as type 2 diabetes (T2DM), obesity, and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), have become a global health burden. In recent years, the glucoregulatory function of the duodenum has been more clearly understood, with studies indicating that changes in the morphology and function of the duodenal mucosa may significantly contribute to the development of metabolic diseases. Interventions such as Roux-en-Y gastric bypass and Duodenal Mucosal Resurfacing (DMR) have demonstrated significant improvements in glycemic control, suggesting that targeting the duodenum may offer novel therapeutic approaches for managing metabolic diseases.

Introduction

Metabolic diseases, like Type 2 Diabetes (T2DM), Metabolic-Associated Fatty Liver Disease (MASLD), and obesity, pose significant challenges to the global health systems and have reached epidemic proportions [1,2]. It is predicted that by 2030, 48.9% of adults in the United States will be classified as obese, and 24.2% will be severely obese [3]. The prevalence of MASLD and T2D has also been increasing worldwide and is expected to continue to rise if current trends are left unchecked [4,5]. These conditions often coexist and synergistically contribute to the progression of each other suggesting a common pathophysiological pathway [6]. In recent years, the link between T2DM, obesity and MASLD has become increasingly evident. Several key pathophysiological mechanisms, including insulin resistance, inflammation, and lipotoxicity, underpin the complex interplay between these conditions [7]. As researchers strive to uncover the root causes of metabolic disorders and identify potential therapeutic targets, a growing body of studies has focused on exploring the role of the duodenum in regulating glucose homeostasis.

Studies have shown that the duodenum maintains energy and glucose homeostasis, through nutrient-sensing and gut microbiome metabolites. In turn, signals via endocrine, paracrine, and enteric nervous system mechanisms orchestrate the metabolic response by modulating hepatic and peripheral muscle insulin resistance, hepatic gluconeogenesis, and metabolic rate [8,9]. Different animal studies have described the changes of duodenal mucosa in response in changes in diet triggering insulin resistance [10,11]. Consequently, these factors are believed to be pivotal in the improvement in hyperglycemia, insulin resistance, as well as MASLD after certain bariatric procedures including duodenal bypass [12] and novel endoscopic therapies such as Duodenal Mucosal Resurfacing (DMR) [13,14]. We aimed to write this review article to explore the duodenum's role as a metabolic center and discuss its potential clinical implications for patients.

Discussion

Understanding the duodenal histology

The duodenum's wall consists of four layers similar to those found throughout the Gastrointestinal (GI) tract. These layers, from innermost to outermost, are the mucosa, submucosa, muscularis and serosa. The mucosal layer lines the inner surface of the duodenum and comprises the intestinal epithelium, lamina propria, and mucosal muscle layer. The intestinal epithelium is a single layer of columnar epithelial cells with two distinct parts: villi and crypts. The crypts are tubular invaginations found in the epithelial lining of the small intestine, and the villi are slender, finger-like projections that protrude into the lumen. Each villus contains a central core consisting of an artery and a vein, a strand of muscle, a centrally located (lacteal), and connective tissue that adds support to the structures [15,16].

The duodenum acts as a metabolic signaling hub

The duodenum has been long recognized for not just its crucial role in digestion, but also for its broader significance as a metabolic hub, orchestrating nutrient absorption, and hormones secretion [17]. Recent investigations have delved into its involvement in insulin action and, therefore, insulin resistance states, a fundamental factor in various metabolic disorders such as T2DM and MASLD [18]. Previous studies have reported that in rodents fed a high-fat and high-sugar diet, the duodenal mucosa proliferated and triggered signals associated with insulin resistance. This suggests that dysregulation of duodenum-mediated signaling may be a key contributing factor to metabolic diseases [19-21].

In addition, the duodenum is home to a complex ecosystem of microorganisms known as the gut microbiota. The gut microbiota has been recognized to play a crucial role in maintaining gut health and regulating metabolism, by modulating immune responses and maintaining gut barrier integrity. Dysbiosis, induced by factors like diet and genetics, can lead to metabolic disturbances, including insulin resistance and type 2 diabetes [22]. Diabetes in turn causes different alterations in the duodenum. Past research has indicated that diabetic rats exhibit increased diameter, weight, and length of the duodenum compared to normal controls [10,23]. Additionally, diabetic rats tend to have elongated duodenal villi, resulting in thickening of the duodenal mucosa [11]. These alterations in duodenal mucosal growth in diabetic rats were primarily attributed to the diabetic condition itself rather than food intake [11,24]. Interestingly, insulin was found to reserve the increase in the villus length caused by diabetes [24,25].

Clinical Implications

In humans, the metabolic effects of the duodenum might be evident in the rapid and significant metabolic improvements observed after Roux-en-Y gastric bypass, where the duodenum is bypassed. These improvements are often noticed within days of the procedure before substantial weight loss occurs. gastric bypass restored glucose, insulin, and glycated Hemoglobin (HbA1c) to normal levels in 91% of patients with T2DM, which was maintained up to 14 years post-surgery [26]. Additionally, there is a clear and measurable insulin-sensitizing effect within the first 2 weeks post-surgery that persists over time [27-30]. This further supports the hypothesis that duodenal dysfunction, is at the core pathophysiology of certain metabolic diseases.

The metabolic effects of the duodenum are also apparent in the Duodenal Mucosal Resurfacing (DMR) procedure. DMR is a minimally invasive endoscopic procedure that involves creating a circumferential mucosal lift and performing hydrothermal ablation of the duodenal mucosa [31]. The hot fluid makes the mucosa necrotic and shedding, and then new mucosa grows. The initial safety trial in humans demonstrated that DMR is safe and effective in improving glycemic control, with the degree of improvement being proportional to the length of the ablated duodenal mucosal segment [13,32]. It also has shown promise in treating metabolic diseases like Type 2 Diabetes (T2D) and nonalcoholic fatty liver disease. However, the precise mechanisms underlying DMR's effects on glycemic improvement in T2D patients are yet to be fully elucidated. Current research explores changes in duodenal morphology, intestinal cells, nerves, glucose transporters, and gut microbiota to understand DMR's mechanisms in improving glycemic parameters in T2D [20,32-35].

Conclusion

The duodenum plays a pivotal role in regulating metabolic processes, influencing both energy and glucose homeostasis. Emerging evidence underscores its significance as a metabolic hub, where dysfunction in its morphology and signaling pathways can contribute to the development and progression of metabolic diseases such as T2DM, obesity, and MASLD. Recent therapeutic approaches, including Roux-en-Y gastric bypass and Duodenal Mucosal Resurfacing (DMR), highlight the potential for targeting the duodenum in the treatment of these conditions, with promising results in improving glycemic control and reducing insulin resistance. However, the precise mechanisms by which the duodenum exerts these effects remain to be fully understood, and further research is needed to clarify the underlying processes. Ultimately, a better understanding of the duodenum's role in metabolism could pave the way for innovative, more effective treatments for metabolic diseases, offering hope for millions of individuals affected worldwide.

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