Dumping Syndrome after Bariatric Surgery

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Dumping syndrome (DS) is a collection of gastrointestinal (GI) and vasomotor symptoms arising postprandially because of prompt gastric emptying. This can develop due to any changes in gastric anatomy or innervation during esophageal, gastric, or bariatric surgery. Due to the increase in the number of bariatric operations and innovative surgeries performed internationally, bariatric surgery has emerged as the most common cause of this disease entity. 25–50% of all gastric surgery patients experience dumping symptoms after their procedures. Patients who have had Roux-en-Y gastric bypass (RYGB) are at an extremely high risk (up to 40%) of developing dumping syndrome postoperatively. The goal of this review is to provide an insightful evaluation of the most recent literature on the overlooked scientific and clinical elements of dumping syndrome, such as diagnostic aspects, pathogenesis, terminology, and management. More research is needed to establish guidelines and terms used to properly document and manage dumping syndrome.

Keywords: bariatric surgery; dumping syndrome; quality of life

Introduction

Dumping syndrome (DS) is a group of gastrointestinal (GI) and vasomotor symptoms that appear postprandially due to rapid gastric emptying. Any changes in gastric anatomy or innervation during esophageal, gastric, or bariatric surgery can result in this syndrome [1]. DS is a collection of symptoms rather than a single ailment, and it can be divided into early and late variants based on the onset of symptoms and the time since a meal. Early dumping symptoms appear 10–30 minutes postprandially, and late dumping symptoms appear 1–3 hours afterward [2]. Moreover, DS is a spectrum condition in which people may have early, late, or dumping symptoms [3]. Serious complications of dumping syndrome may include rapid weight loss and malnutrition; however, these conditions are generally treatable [3, 4]. Unfortunately, DS is frequently misidentified [4], and despite its consequences and prevalence, there is little guidance on how to recognize and manage this illness. Therefore, we made efforts to gather a comprehensive, instructive review of the newest studies on the underrepresented DS scientific basic and clinical parts in this article.

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Prevalence

DS has long been recognized as a prevalent adverse outcome of esophageal and gastric surgeries [5]. In general, 25–50% of all gastric surgery patients experience DS symptoms after their procedures; however, only 10% of them experience symptoms severe and persistent enough to warrant a diagnosis of DS [1]. DS occurs in around 20% of individuals after vagotomy with pyloroplasty and 50% of those undergoing esophagectomy for esophageal cancer [4, 6]. In gastric cancer patients, those who underwent pylorus preserving gastrectomy (PPG) experienced the lowest incidence of early dumping syndrome symptoms, with distal gastrectomy with Roux-en Y reconstruction (DGRY), distal gastrectomy with Billroth I reconstruction (DGB1), and proximal gastrectomy (PG)/total gastrectomy (TG) following in ascending order. Post-gastrectomy, a significantly higher number of individuals developed early dumping syndrome compared to late dumping syndrome [7]. PPG and PG represent the two predominant function-preserving surgical approaches for stomach cancer, aimed at preventing complications such as dumping syndrome [8]. With the onset of the obesity pandemic over the last two decades, the frequency of various forms of bariatric surgery has increased, resulting in a rise in the number of reported instances of DS, including operations that result in DS symptoms that can be difficult to cope with and cure [3]. Various bariatric surgeries are used nowadays, including restrictive and malabsorptive techniques. Roux-en-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy (LSG), biliopan-

creatic diversion, vertical banded gastroplasty, and laparoscopic adjustable gastric band are examples. DS is known to be more prevalent after RYGB and partial gastrectomy. Patients who have had RYGB are at an extremely high risk of developing DS postoperatively, with reports indicating a 40% chance [4, 9]. According to a 2017 study by Ahmad *et al*. [10], the prevalence of DS after laparoscopic sleeve gastrectomy is 26.5%. There are now additional individuals with DS because of the rapid acceptance of bariatric surgeries.

The prevalence of DS in pregnant women following bariatric surgery is unknown, and limited studies have been conducted on the maternal and perinatal consequences of bariatric surgery. Basbug *et al*.'s study [11] looked at the effect of pregnancy following LSG and reported symptoms of DS in pregnant women who had had LSG. The outcomes were as follows: Early DS was found in 75% of the early pregnancy group (those who were pregnant within 18 months of having LSG) and 13.3% of the late pregnancy group (those who were pregnant after 18 months of LSG) whereas late DS were found in 12.5% of the early pregnancy group and 6.7% of the late pregnancy group [11].

Terminology

The terminology used to describe late DS has been debated. Multiple terms have been used in clinical settings, and there is no clear consensus on the definition of DS. Late dumping has been referred to by various names, including hypoglycemia, reactive hypoglycemia, and post bariatric hypoglycemia (PBH) [4, 12]. Such confusion can be attributed to the variety of definitions and clinical characteristics of DS. The lack of a standardized definition and description of DS diagnostic criteria restricts accurate scientific reporting [13]. The term "late DS" is proposed to characterize the onset of hypoglycemic symptoms in these patients.

This nomenclature is misleading, nevertheless, because these symptoms and the pathophysiology that underlies them are not related to the mechanical or physical processes that 'dump' ingested nutrients, even though these processes are still poorly understood. Instead, changes in postprandial carbohydrate absorption and the ensuing hormonal adjustments in incretin and insulin release are more likely to be responsible for symptoms. As a result, it was suggested that the term "postprandial reactive (hypoglycemic) syndrome" be used instead [14]. Opponents of this definition argued that simplifying the series of events leading to reactive hypoglycemia was undesirable.

Late hypoglycemia requires early postprandial hyperglycemia. The discovery that early hyperglycemia is accompanied by an increase in pulse rate and hemoglobin concentration, as well as the therapeutic value of acarbose, the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin, and substances that make food viscous (such as guar gum, pectin, and glucomannan), supports the chain of events that leads to late hypoglycemia [15]. Several cohort studies of bariatric surgery patients showed a link between (early) DS and hypoglycemia [16, 17, 18]. The idiom DS, which contains an early and late component, covers this sequence.

To date, the symptoms of DS have been observed and classified as early and late, but there is still much misunderstanding about the terminology used to characterize these symptoms. Because DS has been found to have a substantial impact on the quality of life of individuals who have it, additional study is needed to define guidelines and terms used to adequately document and manage DS symptoms.

Pathophysiology

The pathophysiological processes underlying the development of the DS are obscure [2]. Extensive research on the subject has yielded a plethora of possible etiological variables, the most important of which is the well-known rapid emptying of liquids from the stomach. When a large volume of hyperosmolar fluid enters the small intestine, the osmotic shift of plasma fluid into the intestinal lumen can produce a decrease in circulating plasma volume and hemoconcentration. Research using cross-circulation in animals led to the conclusion that DS is caused by a hormone pathway [19].

Early Dumping

Post-operative dumping symptoms are commonly associated with gastric surgery like LSG, total or partial gastrectomy, fundoplication, and esophageal resection. Both gastric and esophageal procedures reduce the capacity of the stomach to retain food or demolish the pyloric barrier mechanism. Gastric procedures often lower gastric capacity, whereas esophageal surgeries are typically performed together with a vagotomy. As a result, the capacity of the stomach to retain food decreases. Consequently, gastric contents pass rapidly to the duodenum with incomplete digestion. These nutrients have a hyperosmolar feature that causes fluids to shift from the vascular compartment to the intestinal lumen, causing hypotension, lightheadedness, and occasionally syncope [2]. Furthermore, the process of fluid shifting fosters duodenal distension, which causes bowel contraction, as well as diarrhea and abdominal bloating. However, volume shifts are unlikely to be the primary mechanism, as intravenous fluid replacement was ineffective in preventing early DS symptoms [19].

Early DS may also be influenced by GI peptide hormones such as neurotensin, vasoactive agents like vasoactive intestinal peptide (VIP), incretins like glucagon-like peptide-1 (GLP-1) and peptide YY, a gastric inhibitory polypeptide, and glucose control hormones (insulin and glucagon) [20]. Due to fluid shifts, duodenal and jejunal distension may trigger the release of these hormones. Increased secretion of these hormones has been linked to changes in GI motility, secretion, and circulation. VIP and neurotensin, for example, cause splanchnic vasodilation, which causes

hypotension and systemic hemoconcentration [1]. As a result, the hormones trigger GI and cardiovascular events.

Late Dumping

Late dumping occurs because of reactive hypoglycemia [21]. The swift movement of undigested food to the intestine triggers the release of a significant amount of insulin into the bloodstream due to the high glucose levels found in unprocessed carbohydrates. Some of the hormones may have a role in the modulation of this process. Two hormones are crucial in the development of late dumping symptoms: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide or gastric inhibitory polypeptide (GIP) [22]. An increased GLP-1 release has been found in patients after RYGB, and a positive correlation has been observed between increasing GLP-1 levels and insulin release [23]. Another study found that GLP-1 antagonists may help manage glucose levels for individuals who have postprandial hypoglycemia after gastric bypass surgery [24]. As a result, it appears that an enhanced endogenous GLP-1 response is the key mediator of the hyperinsulinemic, and hypoglycemic impact found in late DS [23]. However, the specific mechanism by which GLP-1 contributes to glucose homeostasis and late DS is likely to be intricate and remains unknown.

According to recent research, the sodium-glucose cotransporter 1 (SGLT-1) is responsible for most of the glucose absorption in the small intestine. Furthermore, these findings imply that intestine SGLT-1 is involved in the pathogenesis of reactive hypoglycemia [25, 26]. *In vitro* studies demonstrate that sodium-glucose cotransporter-1 (SGLT1)-mediated glucose absorption is essential for GLP-1 and GIP production [27, 28, 29]. Patients who are morbidly obese have increased SGLT1 expression and postprandial glucose absorption in their proximal gut [30]. Nguyen *et al*. [31] discovered that after RYGB, the intestinal glucose transporter SGLT-1 was increased. These findings lend credence to the notion that SGLT-1 inhibition could be used to treat the symptoms of late DS.

The recent discovery that bile acids have a function in the synthesis of GLP-1 and other gut hormones including peptide YY (PYY) suggests that they may contribute to the pathophysiology of both disorders [32]. Bile acids have been demonstrated to promote GLP-1 excretion via binding to the G protein-coupled bile acid receptor (GPBAR-1), also known as TGR5, which is located on enteroendocrine L-cells [33]. Some patients have reported altered bile acids metabolism following cholecystectomy due to increased enterohepatic recycling of bile acids and higher plasma bile acids [34]. The metabolism of bile acids changes and its concentration in the systemic circulation rises during RYGB, biliopancreatic diversion, and perhaps LSG [35].

van Furth *et al*. [36] conducted a large cohort research to determine whether cholecystectomy enhanced the incidence of both early and late syndromes. The study found that patients who have had a previous cholecystectomy are more likely to develop early and late DS, showing that changed kinetics of circulating bile acid concentration play a role in the development of both disorders.

Mulla *et al*. [37] conducted a study that established a novel concept that fibroblast growth factor 19 (FGF-19) may be a major contributor to PBH, presumably via bile acid-Farnesoid-X receptor-fibroblast growth factor 19 (FXR-FGF-19) axis modification. The intestinally generated hormone FGF-19 was the protein that showed the most magnitude difference in this experiment; FGF-19 was elevated at all intervals and was 2.4 times higher in PBH compared to asymptomatic after 120 minutes following a mixed meal. FGF-19 increases do not appear to be a direct result of elevated plasma incretins since GLP-1/PYY infusion did not enhance FGF-19 levels immediately and exendin 9–39 (GLP-1 receptor antagonist) did not decrease FGF-19 levels in healthy or asymptomatic post-RYGB people [37].

Symptoms

There are two types of DS symptoms: early and late dumping including both gastrointestinal and vasomotor symptoms. GI symptoms include abdominal pain, bloating, borborygmi, nausea, and diarrhea. Vasomotor symptoms involve sweating, flushing, palpitations, dizziness, tachycardia, hypotension, and an intense desire to lie down. Early DS, within an hour after eating, is characterized by both GI and vasomotor symptoms. Late dumping, however, presents vasomotor symptoms only and is often referred to as "reactive hypoglycemia" [2, 3, 4].

Late DS symptoms appear within 1–3 hours after a meal and are caused by reactive hypoglycemia (or hyperinsulinemic hypoglycemia). The fast passage of carbohydrates to the small intestine initiates the hyperinsulinemia reaction and its consequent hypoglycemia [4, 5]. Late dumping symptoms associated with neuroglycopenia include weariness, weakness, confusion, hunger, and syncope, whereas those connected with autonomic/adrenergic reactivity include perspiration, palpitations, tremors, and irritability [10]. Clinical signs of hypoglycemia can occur three months to a year following surgery, which could be explained by the increased insulin sensitivity associated with weight loss [12].

Early DS is the most frequent form of DS. Even though research has not yet determined which type of DS is more common, studies focusing on glucose tolerance tests reveal a high incidence of elevated pulse rate and a lower incidence of hypoglycemia. A high pulse rate indicates early DS, while hypoglycemia indicates late DS, indicating that early DS is the commonest dumping type. Furthermore, early DS can occur alone or in conjunction with late dumping [4]. In extreme cases, DS can lead to a major decline in quality of life. To avoid unpleasant symptoms, patients suffering from severe dumping typically decrease their meal consumption. This could lead to weight loss and, ultimately,

malnutrition [11]. It is not usually straightforward to distinguish between the two types of dumping symptoms. In other circumstances, early dumping symptoms may have faded before late dumping symptoms emerged [13].

According to research, DS symptoms are typically exhausting and emotionally upsetting. Patients with moderate to severe early and late dumping symptoms have a significantly lower health-related quality of life (HRLQ), in addition to anxiety and depression. Emous *et al*. [12] found that RYGP surgery patients with early and late dumping had substantially lower scores on the standardized questionnaires RAND-36 and hospital anxiety and depression scale (HADS) quality of life scores than those without dumping. Klevebro *et al*. [14] found that after transthoracic esophagectomy, patients reported mild to severe dumping symptoms, with "need to lie down", "diarrhea", and "stomach cramps" being the most common. They also discovered that increasing dumping symptoms were associated with a decline in all aspects of HRLQ except physical functioning [14].

Another factor contributing to the variability of DS symptoms is the type of surgery that caused them. According to Ahmad *et al*.'s study [10], 84.8% of LSG and 84.7% of LRYGB had early DS, while only 36% of LSG and 28% of LRYGB had late DS. In terms of the prevalence of dumping symptoms associated with the consumption of sweets, drinking within 30 minutes of a meal, and alcohol use, 27% of LSG and 44.4% of LRYGB, 34.3% of LSG and 35.5% of LRYGB, and 14.5% of LSG and 17.3% of LRYGB, respectively, reported symptoms of DS [8]. Furthermore, patients undergoing LRYGB with a larger gastrojejunal anastomosis are more likely to develop DS than patients undergoing LSG or LRYGB with a calibrated manual anastomosis [9]. The most common dumping symptoms reported in patients who had undergone esophagectomy were diarrhea, abdominal cramping, dizziness, diaphoresis, and nausea, defining "post-esophagectomy dumping syndrome" with early DS [13]. This highlights how different surgical procedures might cause varying DS symptoms.

In general, the multiple symptoms caused by DS can have a substantial negative impact on a patient's life, needing additional medical assistance and nutritional guidance to alleviate the clinical repercussions [16].

Diagnosis

Patients who have undergone surgery or display typical symptoms of dumping syndrome should be considered as possibly having the condition [38]. To confirm DS diagnosis in symptomatic patients, three questionnaires based on symptoms are utilized: Arts, Sigstad's score, and the Dumping Symptom Rating Scale [5].

The Sigstad's score distinguishes between patients with and without DS, whereas the Arts questionnaire distinguishes between early and late dumping symptoms. Both questionnaires are therapy-sensitive. However, the diagnostic accuracy of Sigstad's scoring questionnaire in bariatric patients or following upper GI cancer surgery or peptic ulcer surgery is similar and not well established [39]. The score can only be used to diagnose early DS following peptic ulcer surgery.

Arts *et al*. [40] designed a non-validated questionnaire to assess the severity of dumping symptoms in 2009. It was successful in showing improvement in severity with the use of somatostatin analogs and was useful in discriminating between early and late dumping symptoms. The questionnaire assigned 8 symptoms for early dumping and 6 symptoms for late dumping, and the symptoms were scored using a 4-point Likert scale [40]. No thresholds (late or early) were chosen for any of the sub-scores. Consequently, although this score quantifies symptoms, its effectiveness in distinguishing between early and late DS remains uncertain.

The Dumping Symptom Rating Scale is a questionnaire created by a multidisciplinary team of specialists [41]. The scale comprises nine symptoms associated with early Dumping Syndrome (DS), one related to fluid intake, and another linked to the consumption of sweetened beverages. A summary score is derived by summing the individual severity (on a scale of 1–9) and frequency (on a scale of 1–8) ratings for each symptom. A substantial patient cohort was utilized to assess content, internal consistency, and construct validity, although the test-retest reliability showed variability. The components of the GI Symptom Rating Scale have varying relationships. Furthermore, the response of this scale to therapy has not been studied [42, 43].

Plasma glucose measurement can also be used as a diagnostic test, albeit its diagnostic value is modest [44]. Nevertheless, this test might prove more beneficial if conducted on patients exhibiting symptoms of late dumping. Some clinicians use a cut-off point value of below 2.8 mmol/L to identify hypoglycemia following gastric surgery, while others use a cut-off value of below 3.3 mmol/L [45]. Continuous glucose monitoring (CGM) can help identify and assess difficult instances of dumping. CGM, on the other hand, has not been compared to the diagnostic accuracy of provocative tests or diagnostic questionnaires, nor has it been used to predict therapy outcomes.

Digital technologies hold immense potential to aid, enhance, and transform nutrition and food management in daily life, thereby elevating the life quality and safety of individuals impacted. This is accomplished through better data gathering and analysis from multiple sources [46]. Promising methods encompass automated image-based food analysis, CGM visualization of food impact, digital receipts for enhanced grocery selection, integrated platforms merging multiple data sources, and sophisticated data analysis techniques to refine prediction algorithms and decision support systems.

One of the long-term consequences of bariatric surgery is increased glucose variability (GV) [47]. This represents several glucose variations throughout the day, frequently

surpassing the hypoglycemic threshold [48], particularly in patients with type 2 diabetic mellitus (T2DM), which reverses following bariatric surgery according to recently validated criteria [49]. Non-diabetic people can also suffer from this complication Hypoglycemia can develop both after RYGB and after LSG [50, 51]. T2DM patients, on the other hand, usually report elevated GV, which is frequently associated with oxidative stress [51] .GM devices provide a detailed picture of glucose changes throughout the day, enabling the quantification of GV and the detection of asymptomatic hypoglycemia [48]. Honka *et al*. [49], on the other hand, demonstrated that the mixed meal tolerance test (MMTT) is more reliable than CGM assessment in detecting postprandial clinical hypoglycemia in post-GB patients, emphasizing the importance of individual factors such as carbohydrate restriction and eating habits on CGM results. Kefurt *et al*. [50] discovered that CGM detected hypoglycemia more accurately than MMTT in patients undergoing RYGB. In a case study of two patients with post-RYGB hypoglycemia, Lembo *et al*. [51] used CGM to document both postprandial and nocturnal hypoglycemic episodes.

Based on this, Lupoli *et al*. [45] undertook a study employing the CGM system to analyze glycemic patterns in both RYGB and LSG patients, to determine if the presence of T2DM before bariatric surgery affects glycemic patterns after surgery. This study discovered that RYGB has a greater GV and a higher number of hypoglycemic episodes, which are usually postprandial and symptomatic, whereas LSG has hypoglycemia which happens more frequently during nocturnal fasting and is normally asymptomatic. They also discovered that the existence of pre-surgery diabetes predicted glucose fluctuation ($p = 0.002$) [45].

The stomach emptying study serves as a non-invasive and safe diagnostic method. It involves consuming a bland meal that contains a small amount of radioactive substance, followed by monitoring the stomach's emptying rate hourly over four hours. This test has multiple limitations. Firstly, it is not suitable to follow a total gastrectomy. Secondly, conditions such as functional dyspepsia, among others, can also cause rapid stomach emptying, not just DS [52]. Additionally, although early rapid stomach emptying can trigger symptoms of Dumping Syndrome (DS), such as nausea, these symptoms may in turn slow down gastric emptying. This can lead to an overall gastric emptying rate that falls within the normal range, as demonstrated in a previous study [53]. Considering these constraints, gastric emptying tests seem to have limited utility in identifying Dumping Syndrome. The test also has low sensitivity and specificity. Provocation tests may have better diagnostic accuracy [38]. There are two options: the oral glucose tolerance test (OGTT) and the mixed meal tolerance test (MMTT) [43]. Currently, the OGTT is the most widely utilized diagnostic test for DS [40, 46]. The OGTT requires the consumption of a glucose solution containing either 50 or 75 grams of sugar, followed by monitoring blood glucose levels, hematocrit, pulse, and blood pressure at 30-minute intervals over three hours [5]. Early DS is indicated by a 3% increase in hematocrit and/or a 10-minute increase in pulse rate, with the latter being the most sensitive indicator [54], whereas hypoglycemia signals late DS [5]. The absence of hypoglycemia does not rule out the possible existence of DS, as early DS can exist in the absence of late DS. The modified OGTT offers high specificity for DS but limited sensitivity [4]. Even if no symptoms of late DS are present, the OGTT may detect hypoglycemia following gastric bypass surgery [55]. Consequently, the test's accuracy will most likely be low. In evaluations of non-diabetic patients before and after bariatric surgery, most of whom had gastric bypass, hypoglycemia was observed. However, none of the patients reported symptoms of hypoglycemia, suggesting limited specificity of the test [56]. Consequently, it is suggested that the measurement of hypoglycemia in bariatric surgery patients is significant only when it coincides with symptoms that are alleviated by the consumption of carbohydrates, known as Whipple's triad. To increase the sensitivity of the modified OGTT, it is recommended to combine it with symptoms-based questionnaires. Incorporating questionnaires, such as the Sigstad, Arts, or Mine, might enhance the accuracy or sensitivity of the OGTT for Dumping Syndrome (DS), although this hypothesis has not undergone evaluation. An alternative test for DS is the MMTT, which can be utilized to verify the diagnosis. In terms of late DS diagnosis, MMTT has a higher sensitivity than modified OGTT [4]. In the MMTT, carbohydrates, fats, and proteins are consumed, and glucose and insulin levels are measured every 30 minutes [57]. However, even healthy people might experience a fall in blood sugar levels after eating, so the test has a significant false positive rate [54].

Treatment

A variety of bariatric operations, cancer surgeries, and peptic ulcer disease all cause anatomical and functional alterations to the GI tract, which have a significant impact on an individual's dietary habits. Nutritional problems ranging from DS to reactive hypoglycemia may occur. As a result, a patient's lifestyle should always be tailored to contemporary gastric physiology. The first and most important step in treating DS is to establish dietary modifications postoperatively. A conservative approach is considered if no signs of impaired cognition, coma, or functional disability are present. In the case of dissatisfaction medical and surgical therapy should be considered. Additionally, the preoperative phase plays a crucial role in hypoglycemia prevention.

Nutritional Manipulation

Nutritional Assessment Preoperatively

Several studies have revealed that obesity causes a variety of micronutrient deficiencies due to the excessive caloric and fat content of patients' diets [58, 59, 60]. Preoper-

ative malnutrition can result in a variety of postoperative complications. Nutritional assessment of patients before bariatric surgery is vital in preoperative care for providing a favorable prognosis postoperatively. Indeed, it is crucial to precisely evaluate the preoperative nutritional status through various biochemical and physiological tests. The comprehensive evaluation aims to improve nutritional status, metabolism, the prevalence of surgical complications such as DS, quality of life, and survival. Lodewijks *et al*. [61] conducted a wide evaluation of the various preoperative programs for bariatric surgery candidates. Overall, the preoperative weight loss program benefited postoperative physical activity, and post-interventional mental health, and reduced the incidence of DS.

Nutritional Assessment Postoperatively

Post bariatric hypoglycemia (PBH) is associated with prompt absorption of dietary glucose. Consequently, dietary modifications are the cornerstone treatment for patients complaining of DS. The proper diet routine helps to keep symptoms from worsening. Clinicians should encourage patients to eat less with each meal. A practical approach to compensate for low food consumption is to increase and divide the daily meals into six smaller portions [42]. Furthermore, fluid consumption should be postponed by at least 30 minutes after a meal. The idea is that drinks accelerate gastric emptying, aggravating the symptoms of DS [5]. Limiting carbohydrates and choosing low-glycemic-index foods are crucial nutritional strategies for preventing hypoglycemia symptoms or the progression of diabetes. To offset the lower carbohydrate consumption, it is advisable to eat foods rich in fiber and protein rather than simple carbohydrates [4]. In nutritional therapy, it is often recommended to lie down for 30 minutes after eating. This can prolong the stomach emptying process and may help reduce symptoms associated with hypovolemia [5].

Furthermore, dietary supplements like glucomannan, guar gum, and pectin may be incorporated into an individual's diet [43]. These pills enhance the viscosity of food, which slows down its movement from the stomach to the small intestine [62]. This could decelerate the absorption of dietary glucose and reduce the fluctuations in postprandial hyperglycemia [47]. Bloating and gas formation are common and unpleasant side effects [43]. 3–6 mg/kg caffeine can be used to maintain glycemia and alleviate hypoglycemia symptoms by increasing endogenous glucose synthesis [63].

Adopting proper measures to address hypoglycemic episodes is another modern aspect of nutritional management. Current research and clinical practice endorse nutritional therapy to manage DS and alleviate its serious consequences. However, these practical solutions do present certain obstacles. Adhering to the present requirements necessitates a robust grasp of nutritional information, encompassing skills in carbohydrate counting and knowledge of the glycemic index [48]. Physical activity, the rate at which food passes through the intestines, and the rate of glucose absorption in the proximal intestines all play a role in determining an individual's daily glucose profile. Consequently, achieving these goals necessitates consistent monitoring of dietary and glycemic patterns. Presently, digital technologies offer a hopeful outlook for surmounting challenges and enhancing the widespread adoption of nutritional management in DS. Wearable gadgets, mobile apps, and artificial intelligence facilitate the systematic gathering of detailed health and nutrition data [48].

Pharmacological Intervention

Because DS has a substantial influence on an individual's quality of life, pharmacological therapy should be considered a second-line option for those who do not respond to dietary changes. Medications, such as acarbose and somatostatin analogs, may be administered. However, due to the high costs and adverse effects, patients' commitment to this type of therapy may be challenging. Flatulence in the case of acarbose and diarrhea in the case of octreotide are two main side effects. Additionally, numerous small studies and case reports cited the symptom-controlling abilities of medications including propranolol, tolbutamide, and verapamil. However, no indication of ongoing success was noted.

Acarbose

Acarbose, as an alpha-glycosidase inhibitor, diminishes the absorption of carbohydrates [47]. It reduces postprandial hyperglycemia and subsequent hypoglycemia by inhibiting the formation of monosaccharides from carbohydrates in the small intestine's epithelial brush border cells (α-glycosidase). The current data consistently indicate that acarbose, administered thrice daily in doses between 50 to 100 mg, enhances glucose tolerance, diminishes GI hormone secretion, and reduces the incidence of hypoglycemia, a crucial aspect of late Dumping Syndrome [5]. While there is no definitive proof of acarbose's impact on early dumping syndrome symptoms, limited research has pointed out the absence of a detailed distinction between early and late dumping syndrome symptoms. Consequently, the possibility that acarbose may affect the treatment of early dumping syndrome symptoms remains open [47]. The primary adverse effects of this medication include bloating and abdominal distention, which result from carbohydrate malabsorption. Patients should be informed and aware of the unavoidable pharmaceutical side effects, as they may interfere with treatment compliance.

Somatostatin Analogs

Somatostatin and its synthetic analogue octreotide are effective in the treatment of dumping. The list of analogs has demonstrated an appealing effect on disease pathogenesis. Octreotide inhibits the release of insulin and many gut hormones, including glucagon-like GLP-1, gastric inhibitory polypeptide (GIP), vasoactive intestinal peptide (VIP), and

pancreatic polypeptide (PP), via activating the somatostatin receptor. In turn, this would avoid late hypoglycemia by delaying the maximal rise in plasma glucose levels and lowering peak insulin concentration [47]. Additional advantages of somatostatin analogs encompass the slowing of gastric emptying and small intestine transit time, the diminishment of post-meal vasodilation and splanchnic blood flow constriction, as well as enhancement of the absorption of water and sodium in the intestines [64]. Both short-acting and long-acting octreotide formulations were found to be potentially beneficial for both stages of DS. Short-acting medications are administered subcutaneously three times a day, whereas long-acting medications are administered intramuscularly once every two to four weeks [5].

The most common side effects of somatostatin analogs include injection site pain, gallstone formation, nausea, and the development of moderate steatorrhea [5]. Despite the presence of steatorrhea, long-term usage of somatostatin analogs rarely results in weight gain. Furthermore, one major drawback of somatostatins is their high cost. Therefore, they are not recommended as the first-line treatment for DS patients.

Several investigations have shown that the long-term use of octreotide subcutaneously and intramuscularly is limited by efficacy loss, inconvenient administration, and noncompliance. Consequently, pasireotide, a multi-receptor ligand, and a second-generation somatostatin analog, has been introduced as an effective medical treatment for DS. It possesses a 39-fold greater affinity for the somatostatin receptor subtypes SST 1, 2, 3, and 5 [65]. Somatostatin receptor 2 (SSTR2) and somatostatin receptor 5 (SSTR5) both have a role in blood glucose regulation by blocking the release of glucagon (SSTR2) and insulin (SSTR2 and SSTR5). A case study indicated that pasireotide was more effective than octreotide in reducing GLP-1 and insulin production [66]. This results in improved control of postprandial hyperinsulinemic hypoglycemia after a gastric bypass. Another newly published phase 2 dose escalation study revealed that subcutaneous pasireotide effectively functions to suppress the increase in pulse rate and prevent postprandial hypoglycemic symptoms [67].

Over the last few decades, an enormous amount of research has improved our understanding of GLP-1 and glucagon-like peptide 2 (GLP-2). This is because their biological actions converge at multiple levels in the regulation of nutrient assimilation. Accordingly, due to their incretin effect, GLP-1 inhibitors, also known as analogs, have been developed and directed toward the treatment of endocrine abnormalities and T2DM. GLP-1 is an incretin hormone released by L cells in the small intestine distal part. The release of the hormone is stimulated by the presence of the ingested nutrients in the area [68]. As a result, GLP-1 analogs were discovered to be extremely effective in lowering hyperglycemia in individuals with T2DM. They also demonstrated favorable impacts on body reduction by boosting satiety [69]. In addition, GLP-1 analogs have a therapeutic impact on DS patients by inhibiting gastric emptying.

Liraglutide is a long-acting type of GLP-1. Previously published research showed that liraglutide successfully controlled glycemic control for 24 hours. Interestingly, its effect on reducing body weight was discovered to be dose-dependent [65]. It helps people with late DS by impairing insulin production both before and after meals. GI-related adverse effects, such as nausea and headache, were the most frequently reported adverse events in various reports [27, 65].

Beinaglutide is a fully homologous recombinant human GLP-1 polypeptide. This type of therapy had adequate efficacy on the glycemic fluctuation, which lasted for one month with no side effects [66]. It can be provided in a flexible and coordinated manner with meals for this purpose. Beinaglutide preliminary studies indicate that it is more effective and has fewer negative effects than long-acting glucagon-like peptide-1 receptor agonists (GLP-1Ras).

Recent research indicates that the sodium-glucose cotransporter-1 (SGLT-1) in the gastrointestinal tract plays a role in the pathophysiology of reactive hypoglycemia. Canagliflozin is an SGLT-2 inhibitor that has been approved for the treatment of T2DM. The most widely accepted technique for reducing blood glucose is to decrease renal SGLT-2, hence increasing urine glucose excretion [70]. An inhibitory effect of SGLT-1 was induced in patients by administering canagliflozin in increasing doses just before each meal. Along with the postprandial urinary glucose excretion, it resulted in a further decrease in postprandial plasma glucose and insulin concentrations. A case described by Katayama *et al.* [71] furthered the data on the function of SGLT2 inhibitors. SGLT2 inhibitors were effective at suppressing the symptoms of DS. It blocks glucose reabsorption in the proximal renal tubules, leading to the excretion of excess glucose in the urine and the regulation of plasma glucose levels, which reduces symptoms of hypoglycemia. Additionally, it helps decrease hypoglycemic episodes by activating SGLT-1.

Other Pharmaceutical Treatments

Diazoxide is another treatment option for DS. It is a non-diuretic benzothiadiazine with both antihypertensive and hyperglycemic characteristics. The hyperglycemic activity results from an interaction with ATP-sensitive potassium channels on the pancreatic β-cell membrane. This interaction promotes continuous potassium efflux, thereby inhibiting the stimulation of the insulin release pathway [47]. This drug has long been recognized as an effective treatment option for pediatric patients suffering from congenital hyperinsulinemic hypoglycemia [72]. Nonetheless, the use of diazoxide for the management of late DS symptoms has always been reported anecdotally in the literature, such as in case reports. For example, one of many case studies demonstrated that diazoxide, when taken at low therapeutic levels,

can be a significantly effective and safe alternative for individuals with hypoglycemia symptoms who are refractory to dietary modifications or acarbose treatment [72]. However, due to its mechanism of action, diazoxide is not predicted to have any effect on the initial symptoms of DS [5].

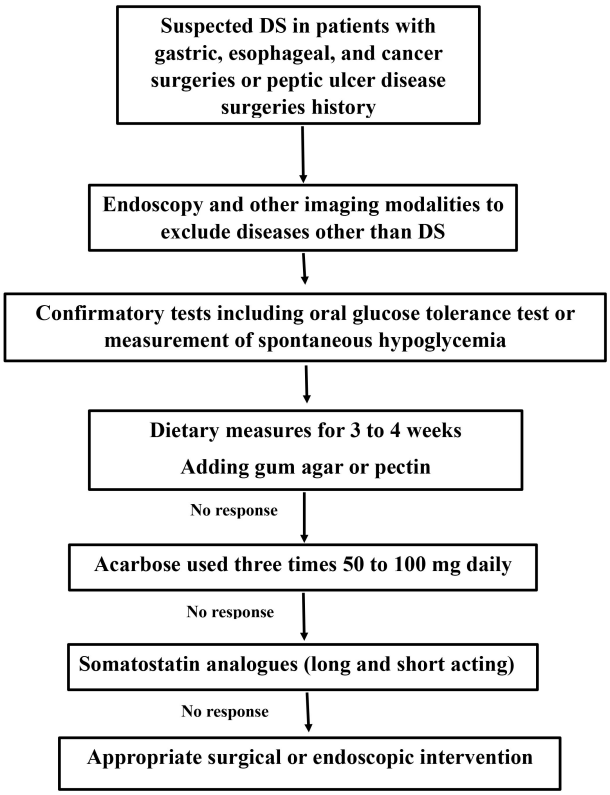

Fig. 1. Management of dumping syndrome (DS) algorithm (Microsoft ward 365, version 2022, Microsoft IT corporation, Redmond, WA, USA).

Surgical Intervention

Conservative management is the preferred treatment for patients primarily complaining of DS symptoms. Medical treatment options, including nutrition, behavioral, and pharmacological therapy, are always recommended as a first line of treatment for at least one year before considering corrective surgery. Most individuals with postprandial hypoglycemia induced by Roux-en-Y gastric bypass (RYGB) respond well to dietary and pharmacological treatments [73]. Nevertheless, for those suffering from severe post-RYGB hypoglycemia, surgical reintervention may be considered a viable option [46]. Surgical or endoscopic interventions for dumping syndrome can involve pylorus reconstruction or the reversal of gastric bypass surgery, i.e., the goal is to restore normal anatomy and function as closely as possible. Several surgical treatments have been developed to alleviate dumping symptoms by slowing gastric emptying. Because surgical reintervention methods are largely ineffective and have high morbidity, selecting the optimal surgical intervention is critical. Several procedures have been proposed, including anastomosis narrowing, Billroth type II to Billroth type I gastroenterostomy conversion, conversion to a Roux-en-Y construction, pylorus reconstruction, and interposition of a 10 cm antiperistaltic jejunal loop. For those who develop DS following vagotomy with pyloroplasty, the primary surgical treatment is pyloric reconstruction [5]. Surgical repair of the pylorus alleviates symptoms and decreases the rate of stomach emptying [74]. Roux-en-Y reconstruction enhanced gastric emptying in individuals who had Billroth I or Billroth II gastrectomy [5, 67].

An alternative method for managing refractory DS involves administering a consistent flow of nutrients via a feeding jejunostomy. While continuous enteral feeding can be successful in preventing dumping symptoms resulting from meal intake, this invasive procedure may diminish the quality of life for some individuals [5].

Despite continual breakthroughs in medication, the management of DS remains a difficult task. A comprehensive management strategy based on the severity of the DS is provided based on the wide variety of treatments listed [4]. In mild cases resistant to dietary manipulations, the utilization of thickening agents and the appropriate pharmacological elixir should be recommended. Surgical interventions ought to be considered for patients who have not benefited from conservative or minimally invasive treatments [74]. Nonetheless, given the growing number of patients undergoing bariatric surgery, novel therapeutic alternatives for patients with DS who do not respond to early therapies are critical. Further prospective clinical trials are necessary to ascertain the prevalence of DS and to evaluate how early detection and treatment of clinical symptoms impact weight loss and quality of life. Additionally, while digital solutions for nutritional control in DS patients are still in their early phases, there is enormous potential for future development and improvement. Integrating digital support systems into the daily routines of DS patients necessitates extensive collaboration between technology experts, doctors, and device manufacturers [4]. Finally, efficient care of DS requires close collaboration among experts in gastroenterology, endocrinology, surgery, and nutrition. Fig. 1 depicts an algorithm for managing DS.

Endoscopic Interventions

Endoscopic therapy can assist in decreasing the size of a dilated or incompetent gastrojejunal anastomosis, known as transoral outlet reduction (TORe) [75], or endoscopic gastrojejunostomy revision (EGJR), or revision of the gastrojejunal anastomosis (GJA). Endoscopic GJA revision can be accomplished with a variety of devices with varied methods. The Apollo OverStitch suturing device (Apollo Endosurgery, Austin, TX, USA) is the most thoroughly studied. Other study investigated the process using the USGI EndoSurgical Operative System (EOS) [USGI Medical, San

Clemente, CA, USA] and the StomaphyX device (Endogastric Solutions, Redmond, WA, USA) [76]. Considering that different devices were employed for revision of the gastrojejunal anastomosis, technical and clinical success was reported in 98% and 89% of patients, respectively, with a re-intervention rate of 11 [76].

The adoption of endoscopic procedures has resulted in outstanding success rates in individuals who were previously therapy-refractory. These techniques are far from ready for application in regular clinical practice since they are technically challenging, and extensive practice is necessary to develop expertise [4].

Conclusions

Dumping syndrome is categorized into early and late types. The early type results from the swift movement of hyperosmolar food into the small intestine, which can be managed by reducing the size of the gastrointestinal anastomosis and altering the diet to increase its water content, thereby lowering the osmolarity. The anastomosis site may be corrected surgically or endoscopically. Late dumping typically stems from heightened insulin sensitivity following weight loss and is addressed through dietary adjustments or medications to prevent hypoglycemia or hyperglycemia.

Prospects may explore whether hypoglycemia is a result of insulin action on pre-existing hyperglycemia or if it occurs independently from the outset. More research is needed to determine the link between the increased GLP-1 response and the subsequent hypoglycemia. Longer-term clinical trials are needed to confirm the efficacy and safety of treatments, particularly GLP-1 receptor antagonists, which could be used to treat post-prandial hypoglycemia.

While numerous medical and surgical treatment options exist, evidence supporting high-quality treatments remains limited, and their routine use is not advised in clinical practice due to the limited evidence and the uncertainty regarding outcomes. Finally, it is concluded that future clinical practice ought to be multidisciplinary from the outset, accompanied by a clear, sequential treatment plan.

Abbreviations

DS, dumping syndrome; DGB1, distal gastrectomy with Billroth I reconstruction; DGRY, distal gastrectomy with Roux-en Y reconstruction; RYGB, Roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy; GI, gastrointestinal; HRLQ, health-related quality of life; HADS, hospital anxiety and depression scale; PBH, post bariatric hypoglycemia; SGLT2, sodium-glucose cotransporter-2; VIP, vasoactive intestinal peptide; GLP-1, glucagon-like peptide-1; PYY, peptide YY; GIP, gastric inhibitory polypeptide; GPBAR-1, G protein-coupled bile acid receptor; FGF-19, fibroblast growth factor 19; FXR, Farnesoid-X receptor; CGM, continuous glucose monitoring; GV, glucose variability; T2DM, type 2 diabetes mellitus; MMTT, mixed meal tolerance test; OGTT, oral glucose tolerance test; PG, proximal gastrectomy; PP, pancreatic polypeptide; PPG, pylorus preserving gastrectomy; SSTR2, somatostatin receptor 2; SSTR5, somatostatin receptor 5; GLP-2, glucagon-like peptide 2; GLP-1Ras, glucagon-like peptide-1 receptor agonists; SGLT1, sodium-glucose cotransporter-1; TG, total gastrectomy.

Availability of Data and Materials

Not applicable.

Author Contributions

MN: conceptualization, data analysis, and reference collection; AY: writing and editing the manuscript, collected references, and analyzed data; IA: writing manuscript, data collection and analysis; MAJ: references collection; SZ: references collection; SZE: references collection. All authors contributed substantially to this article and agreed on its final manuscript with no objection to copyright transfer upon publication. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

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Conflict of Interest

The authors declare no conflict of interest.

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