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## Functional exocrine pancreatic insufficiency as target of pharmaceutical and surgical approaches in treatment of overweight

### Funkcjonalna zewnątrzwydzielnicza niewydolność trzustki jako efektywna droga farmaceutycznego i chirurgicznego leczenia nadwagi

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#### S u m m a r y

Overweight and obesity are major health problem in today's society, where the western diet and a sedentary lifestyle has been suggested as primary causes. Lifestyle changes, such as the introduction of a healthier diet and increased physical activity, should be considered a first step in the management of obesity. However, many patients struggle to lose weight with these types of interventions. For these patients, pharmaceutical and surgical treatments may be an option. The most commonly used pharmaceutical and surgical approaches for the management of obesity aim to induce weight loss by creating functional exocrine pancreatic insufficiency. Pancreatic enzymes are crucial for the digestion of macronutrients. Thus, by targeting these enzymes, digestion and absorption of nutrients will be reduced. Although these treatment strategies usually show good results in terms of weight loss, they are associated with nutritional and metabolic complications. It is therefore of great importance that both medical doctors and patient are well informed about the risks that come with various therapies.

#### S t r e s z c z e n i e

Nadwaga i otyłość są poważnym problemem zdrowotnym w dzisiejszym społeczeństwie. Za pierwotne przyczyny tego zjawiska uważa się „zachodnią” dietę i siedzący tryb życia. Zmiany stylu życia, takie jak wprowadzenie zdrowszej diety oraz zwiększony wysiłek fizyczny, należy rozważyć jako pierwszy etap w leczeniu otyłości. Jednakże dla wielu pacjentów powyższe sposoby walki z otyłością są nierealne ze względów psychologicznych. Dla tych pacjentów jedyną alternatywą są zabiegi chirurgiczne lub odchudzanie farmakologiczne. Wydaje się, że najbardziej skuteczne leczenie farmakologiczne czy chirurgiczne otyłości sprowadza się do wytworzenia funkcjonalnej niewydolności trzustki zewnątrzwydzielniczej. Enzymy trzustkowe są niezbędne do trawienia pokarmów i w konsekwencji do wchłaniania ich elementów składkowych. W wyniku autokatalizy enzymów trzustkowych (operacje bariatryczne) lub ich blokowania (leczenie farmakologiczne) trawienie i absorpcja składników zostają zmniejszone. Mimo że te sposoby leczenia dają na ogół dobre rezultaty, w postaci utraty wagi, to wiążą się z nimi powikłania odżywcze i metaboliczne. Jest więc bardzo ważne dla lekarzy, a przede wszystkim dla pacjentów, posiadanie wiedzy o ryzyku, z którym związane są poszczególne postępowania terapeutyczne.

Abbreviations: AGB – adjustable gastric binding; BMI – body mass index; ESRD – end-stage renal disease; EMA – European Medicines Agency; EPI – exocrine pancreatic insufficiency; GLP-1 – glucagon-like

peptide-1; GLUT2 – glucose transporter-2; PYY – peptide YY; RYGB – Roux-en-Y gastric bypass; SG – sleeve gastrectomy; SGLT2 – sodium-dependent glucose co-transporter-2; WHO – World Health Organization

## INTRODUCTION

Overweight and obesity are major health problems in today's society, especially in the westernized countries. The western diet, together with a sedentary lifestyle with a lack of physical activity, is suggested to be the main reasons for the epidemic of these conditions (1). Overweight is defined by the World Health Organization (WHO) as a body mass index (BMI)  $> 25 \text{ kg/m}^2$  and obesity as a BMI  $> 30 \text{ kg/m}^2$ . In 2008, around 35% of the global adult population was overweight and 11% obese. Huge differences can however be seen between westernized and non-westernized countries. Overweight and obesity are associated with comorbid conditions such as type 2 diabetes, cardiovascular diseases, and cancer. This might explain why overweight and obesity are linked to more deaths worldwide than underweight (2).

Lifestyle changes such as the introduction of a healthier diet and increased physical activity should be considered a first step in the management of overweight and obesity (3). However, for many overweight and obese patients it is difficult to lose weight and maintain this weight loss over a long period of time (4). For patients who have failed to achieve weight loss through lifestyle interventions, pharmacological or surgical treatments may be an option (3).

The most commonly used pharmaceutical and surgical approaches to treat obesity are based on the creation of functional exocrine pancreatic insufficiency (EPI) (1, 5). Orlistat, an inhibitor of pancreatic lipase, is currently the only drug approved by the European Medicines Agency (EMA) for treatment of obesity (1). However, several plant-derived phytochemicals have been identified as potent inhibitors of both pancreatic lipase and pancreatic  $\alpha$ -amylase, and the clinical potential of these agents are widely investigated (6). In addition, Roux-en-Y gastric bypass (RYGB), the most commonly performed bariatric surgery worldwide (7), is designed to induce weight loss through a combination of malabsorption and gastric restriction (5). Nevertheless, one should remember that these types of interventions usually are associated with nutritional (4) and metabolic (8) complications. It is therefore of great importance that both medical doctors and patient are well informed about the risks that come with various therapies.

## PHARMACEUTICAL APPROACHES AFFECTING THE EXOCRINE PANCREAS

### Pancreatic lipase inhibitors

Pancreatic lipase is an important enzyme in the digestion of dietary fat. It is produced and secreted from acinar cells of the exocrine pancreas, and enters the duodenum via the common bile duct. In the intestinal lumen, pancreatic lipase act on triglycerides to generate free fatty acids and monoglycerides. These digestive products are then absorbed by the enterocytes lining the small intestine (9). By inhibiting the action of pancreatic lipase, the digestion of triglycerides in the

intestinal lumen will be reduced. This will in turn result in a decreased absorption of free fatty acids and monoglycerides and, thus, a reduced caloric uptake (1).

The pharmaceutical and nutraceutical industry has proposed various inhibitors of pancreatic lipase for the management of weight loss. A few of these agents have after successful clinical trials been able to reach the market, however, the majority are still under investigation (6).

Orlistat is a potent, specific and irreversible inhibitor of pancreatic lipase (10) that is approved by the EMA for long-term use in two forms: as a prescriptive drug in 120 mg capsules under the trade name Xenical, and as a non-prescriptive drug in 60 mg capsules under the trade name Alli (1). Orlistat acts by forming a covalent bond to the active site of pancreatic lipase, thus preventing catabolism of luminal triglycerides into absorbable free fatty acids and monoglycerides (10). Studies have shown that the action of orlistat is not only associated with weight loss, but also reduced blood pressure and lowered plasma levels of low-density lipoprotein cholesterol (11). However, numerous adverse effects have been reported following treatment with orlistat, such as intestinal cramps, oily rectal spotting, flatus with discharge, and fecal incontinence. These are usually detected during the first week of treatment, but are reduced once the patients learn how to avoid high-fat diets. In addition, treatment with orlistat is associated with decreased absorption of fat-soluble vitamins, such as vitamin D, vitamin E, and  $\beta$ -carotene. Therefore, multivitamin supplementation should be recommended to patients treated with this agent (12).

Cetilistat is a pancreatic lipase inhibitor that recently was approved in Japan for the treatment of obese patients with comorbid conditions (13). Its mechanism of action is similar to that of orlistat (14). However, due to structural differences, it has been suggested that the safety profile of cetilistat is superior to that of orlistat (15).

A novel approach for the treatment of obesity is the use of plant-derived phytochemicals (6). These agents are hybrids between nutrients and pharmaceuticals, and are therefore referred to as nutraceuticals (16). It has been shown that several phytochemicals that belong to the chemical classes saponins, polyphenols, and terpenes are able to inhibit the activity of pancreatic lipase. For some of these, the inhibitory activity can reach as high as 70%. However, more research is needed to further evaluate the clinical potential of these agents (6).

### Pancreatic amylase inhibitors

Carbohydrates are the main energy source of the human diet, accounting for about 40-80% of the total caloric intake. These are either digestible or non-digestible. The most frequently consumed digestible carbohydrates are disaccharides, such as sucrose and lactose, and larger polysaccharides, such as starch. These are comprised of monosaccharides, which are

joined together by glycoside bonds. The digestion of carbohydrates is initiated in the mouth, where salivary  $\alpha$ -amylase hydrolyzes the  $\alpha$ -1,4 bonds in starch. The products of this process include maltose, maltotriose and dextrins. The digestion of starch is continued in the small intestine by the action of pancreatic  $\alpha$ -amylase, and completed by enzymes located at the brush border membrane. The action of these enzymes yields the monosaccharides glucose, fructose, and galactose, which are absorbed by the enterocytes lining the small intestine. Non-digestible carbohydrates, such as fibers and cellulose, as well as digestible carbohydrates that manage to escape the action of the digestive enzymes in the small intestine, enter the colon where they are fermented by the colonic microbiota. Fermentation yields short chain fatty acids, which can be absorbed in the colon, used as bacterial substrate, or excreted in the feces (6).

Since a high amount of consumed calories are ascribed to carbohydrates, it is of great interest to limit the uptake of these nutrients in the management of obesity. Inhibitors of pancreatic  $\alpha$ -amylase have been suggested as potential anti-obesity agents, and numerous  $\alpha$ -amylase inhibitors have been isolated from a number of different plant sources (6). These include *Phaseolus vulgaris* (17), *Cinnamomum cassia* (18), *Rosmarinus officinalis* (19), and black, green, and mulberry teas (20). Administration of  $\alpha$ -amylase inhibitors causes reduced luminal activity of pancreatic  $\alpha$ -amylase, resulting in limited absorption of carbohydrates. This in turn leads to decrease postprandial plasma glucose and insulin levels, and increased activity of the colonic microbiota (6).

### **SURGICAL APPROACHES AFFECTING THE EXOCRINE PANCREAS**

Bariatric surgery, or weight loss surgery, is a possible treatment for obese patients who do not manage to lose weight and maintain this weight loss with lifestyle interventions such as increased exercise and diet modifications (5). In 2011, a total number of 340 768 bariatric surgeries worldwide were reported. This is more than twice as many compared to 2003 (7).

To be considered a candidate for bariatric surgery, the patient must meet the criteria of a BMI  $> 40$  kg/m<sup>2</sup> or a BMI  $> 35$  kg/m<sup>2</sup> with an obesity-related comorbid condition (5). Different surgical procedures can be performed on these patients, where the most common include RYGB, sleeve gastrectomy (SG), and adjustable gastric banding (AGB) (7). RYGB is designed to induce weight loss through a combination of gastric restriction, creating early satiety, and malabsorption. On the contrary, SG and AGB are solely restrictive procedures and, because they do not aim to induce weight loss by affecting the function of exocrine pancreatic enzymes, they will not be further discussed (5).

#### **Roux-en-Y gastric bypass**

RYGB is the most commonly performed bariatric surgery worldwide (7). As mentioned earlier, the in-

duced weight loss that results from this surgical procedure is suggested to be due to a combination of gastric restriction and malabsorption (5). In addition, altered secretion of hormones involved in appetite control has been implicated as an important factor contributing to weight loss following RYGB (21).

Gastric restriction is achieved by partitioning the stomach into two sections by the use of a stapler-cutting device, creating a small gastric pouch and a larger gastric remnant (22). The gastric pouch ranges from 15 to 30 ml in size and is the only section that will receive food and liquid due to its connection to the esophagus. At this stage, the gastric pouch is not attached to the intestine. To achieve this, the jejunum is divided into two sections creating a long distal limb known as the Roux limb and a shorter proximal limb known as the biliopancreatic limb. The Roux limb is attached to the gastric pouch, making it possible for ingested food and liquid to enter the intestine. In a final step, the biliopancreatic limb is reattached further down the Roux limb, creating a common channel that continues into the ileum. Due to that the common bile duct is connected to the biliopancreatic limb, digestive enzymes secreted from the gastric remnant, gallbladder, and pancreas are allowed to enter the reconstructed intestine. However, because ingested food and liquid bypasses the duodenum and the first part of the jejunum, a smaller amount of nutrients is absorbed than usual, contributing to the induced weight loss (5).

During physiological conditions, the exocrine pancreas secretes digestive enzymes including proteases, lipases, and amylase. These enzymes enter the duodenum, via the common bile duct, where they play a crucial role in the digestion of proteins, lipids, and carbohydrates, respectively. Digestion of the macronutrients is necessary for absorption, a process that is carried out by the enterocytes lining the lumen of the small intestine (9). Following RYGB, the pancreatic enzymes need to pass through the biliopancreatic limb before they can reach the common channel and exert their action on the macronutrients (5). This delays the interaction between the enzymes and the macronutrients, resulting in decreased digestion and subsequent malabsorption of digestive products (23). Malabsorption of both fats (24, 25) and proteins (23) has been reported following RYGB. In addition to the delayed effect of lipases, destruction of pancreatic lipase in the biliopancreatic limb has been suggested as a mechanism contributing to the reduced absorption of fats. However, altered carbohydrate absorption does not seem to be associated with this type of procedure (24, 26). This might be explained by several factors. Digestion of starch starts in the mouth and continues in the gastric pouch by the action of salivary amylase. Thus, when the digestive products enter the Roux limb, they can be absorbed by the enterocytes. In addition, pancreatic amylase is a relatively indestructible enzyme that to some extent can survive the journey through the biliopancreatic limb, hence, further contributing to

carbohydrate digestion in the common channel (24). It has also been shown that the expression of the two primary glucose transporters, sodium-dependent glucose co-transporter 1 (SGLT1) and glucose transporter-2 (GLUT2), is markedly increased in the intestine following RYGB, suggesting a molecular adaptation to prevent malabsorption of carbohydrates (27).

Although RYGB is referred to as a combined restrictive and malabsorptive procedure, it has been proposed that altered secretion of hormones involved in appetite control is the main cause of the reduced body weight after this type of intervention. Patients who have undergone RYGB often report a reduced feeling of hunger and faster satiation, contributing to weight loss. This might be associated with the increased levels of the gut hormones peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) that has been observed after RYGB. These hormones are secreted from L cells in the small intestine, mainly in the distal region, in response to nutrients in the lumen. They act on neurons in the hypothalamus and brainstem, resulting in reduced food intake and the feeling of satiety. The reason for the increased levels of PYY and GLP-1 following RYGB are not completely understood, but a suggested mechanism is the rapid delivery of nutrients to the common channel via the Roux limb (21).

### Nutritional complications after Roux-en-Y gastric bypass

Nutritional deficiencies are serious complications that may develop after bariatric surgery (23). After RYGB, the ingested food will bypass a large part of the stomach, as well as the duodenum and the first part of the jejunum (5). As a result, the absorption of nutrients will be reduced and subsequent nutrient deficiencies often develop (tab. 1) (23).

### MACRONUTRIENTS

Protein malnutrition due to changes in protein intake and metabolism has been reported following malab-

sorptive procedures such as RYGB. Early clinical symptoms usually manifest three to six month after surgery. Hair loss is often the first sign of potential protein malnutrition, whereas severe cases are indicated by the presence of edema. Furthermore, studies have shown that malabsorptive procedure may lead to the development of lactase deficiency and decreased function of sucrase (28). These enzymes are important for the degradation of lactose and sucrose, respectively (9).

### MICRONUTRIENTS

Nutrients that in humans are required in quantities of microgram or milligram are called micronutrients. These include water-soluble vitamins, such as thiamine and vitamin B<sub>12</sub>, fat-soluble vitamins, such as vitamin A and vitamin D, essential minerals, and trace elements (4).

Thiamine, or vitamin B<sub>1</sub>, plays an important role in the metabolism of carbohydrates, lipids, and branched-chain amino acids (28). Thiamin deficiency commonly develops after RYGB as a result of persistent vomiting, reduced food intake, or lack of supplement intake (23). Symptoms can be of neuropsychiatric, neurological, cardiovascular, or gastroenterological character and can be resolved with oral thiamin supplementation (28). However, in some patients, malabsorption of thiamin is caused by small intestine bacterial overgrowth following RYGB. In these cases, thiamin supplementation is not enough to treat the condition. Instead, antibiotics may be required to restore thiamin homeostasis (4).

Another well-described nutritional complication that often develops in patients after RYGB is vitamin B<sub>12</sub> deficiency. As been described previously, a large part of the stomach is excluded during RYGB. Consequently, the parietal cells lose their ability to produce and secrete hydrochloric acid and gastric intrinsic factor. An acidic environment favors the bioavailability of vitamin B<sub>12</sub> in the ingested food, whereas gastric intrinsic factor is important for absorption of vitamin B<sub>12</sub>. Loss of function of the parietal cells will therefor results in

**Table 1.** Nutrient deficiency following bariatric surgery. The table shows the most commonly reported nutrient deficiencies following bariatric surgery as well as their clinical signs and symptoms.

Nutrient	Risk factors	Signs and symptoms
Macronutrients		
Protein Fat Carbohydrates	Malabsorption after RYGB Malabsorption after RYGB Malabsorption after RYGB?	Hair loss, oedema Await to be described Not predicted
Micronutrients		
Thiamine (vitamin B <sub>1</sub> )	Recurrent vomiting and reduced food intake after RYGB, SG and AGB, small intestine bacterial overgrowth after RYGB	Neuropsychiatric: aggression, hallucination, confusion, ataxia, nystagmus, paralysis of the motor nerves of the eye Neurologic: convulsion, numbness, muscle weakness and/or pain of lower and upper extremities, brisk tendon reflexes Cardiovascular: tachycardia or bradycardia, lactic acidosis, dyspnoea, leg oedema, right ventricular dilatation Gastroenterological: slow gastric emptying, nausea, vomiting, jejunal dilatation, mega colon, constipation
Vitamin B <sub>12</sub>	Malabsorption after RYGB	Pernicious anaemia, depression, paraesthesia, ataxia
Vitamin D	Malabsorption after RYGB and SG	Osteomalacia, osteoporosis, arthralgia, depression, myalgia, fasciculation
Iron	Malabsorption after RYGB and SG	Iron-deficiency anaemia, fatigue, shortness of breath, chest pain

impaired bioavailability and reduced uptake of the vitamin. Usually, clinical manifestation of vitamin B<sub>12</sub> deficiency occurs several years after surgery. This is due to that the storage of vitamin B<sub>12</sub> in the liver and kidneys can compensate for the reduced uptake during a period of up to three years (4). Lack of vitamin B<sub>12</sub> is one of the leading causes of anemia after RYGB. In addition, vitamin B<sub>12</sub> deficiency may cause neurological and psychiatric symptoms if not treated. Nutritional supplementation is normally administered orally, intramuscular, or subcutaneously. Oral administration is recommended in patients who are not diagnosed with vitamin B<sub>12</sub> deficiency before surgery, whereas intramuscular or subcutaneous supplementation is preferred in cases of pre-operative existing vitamin B<sub>12</sub> deficiency (28).

Deficiency of fat-soluble vitamins, including vitamin A and vitamin D, has also been reported following RYGB. The absorption of vitamin A is dependent on the formation of micelles, a process that is mediated by bile acids. However, relative bile acids deficiency has been observed in patients with a short common channel after extended RYGB, resulting in reduced micelle formation and subsequent vitamin A deficiency. This may lead to nyctalopia, xerophthalmia, pruritus, and dry hair (28). On the contrary, vitamin D is crucial for the intestinal absorption of calcium and stimulation of bone formation. Lack of vitamin D and subsequent reduction of calcium absorption stimulates the secretion of parathyroid hormone from the parathyroid glands. As a result, calcium is reabsorbed from the bones, subsequently leading to osteoporosis and osteomalacia. This explains the increasing incidence of bone fractures that has been reported following RYGB. It is therefore important that patients that have undergone this surgical procedure are closely monitored regarding abnormal bone metabolism (4).

As mentioned earlier, anemia may develop after RYGB due to vitamin B<sub>12</sub> deficiency. Another common cause of post-operative anemia is iron deficiency (28). During normal physiological conditions, iron is absorbed in the duodenum. However, following RYGB, this part of the intestine is bypassed by the ingested food, resulting in reduced iron absorption. In addition, the decreased production of hydrochloric acid by parietal cells after RYGB may further contribute to the reduced absorption of iron (4).

### Metabolic complications after Roux-en-Y gastric bypass

The malabsorptive mechanisms of RYGB may not only cause nutritional deficiency, but also metabolic complications such as hyperoxaluria, nephrolithiasis and oxalate nephropathy (29-31). Hyperoxaluria, a condition that might be related to fat malabsorption (30), has been observed not only in patients with nephrolithiasis, but also in patients without nephrolithiasis, following RYGB (29). Furthermore, oxalate

nephropathy as a result of RYGB may lead to renal failure (29, 32) as well as the development of end-stage renal disease (ESRD), a condition that will require patients to undergo dialysis or even renal transplantation (33). Also, functional EPI, which is reached with RYGB as well as pharmaceutical agents approved for the treatment of obesity, can lead to marked neurological deficits due to impaired absorption of long-chain polyunsaturated fatty acids (34). However, with this in mind, it is important to remember that obesity by per se is a risk factor for the development of metabolic diseases such as ESRD. Moreover, morbid obesity may cause nephrotic syndrome, and it has been reported that proteinuria and segmental glomerulosclerosis can be present in obese patients even in the absence of diabetes (8).

### CONCLUSIONS

Pharmaceutical and surgical approaches that aim to create functional EPI are the most commonly used treatments for overweight and obese patients in Europe. Not only do these treatment strategies show good results in terms of weight loss, but they may also improve associated comorbid conditions, such as cardiovascular diseases and type 2 diabetes. However, regardless of which of these approaches that are chosen, life style changes such as a healthier diet and increased physical activity should always be included as a part of the treatment.

Orlistat is currently the only anti-obesity drug approved in Europe. Even though this drug usually shows good result in terms of weight loss, it is associated with numerous gastrointestinal adverse effects, as well as fat-soluble vitamin deficiency. Therefore, it is of great importance to continue the investigation of novel pharmaceutical interventions. It has been proposed that cetilistat, which was recently approved in Japan for the treatment of obesity, has a better safety profile compared to orlistat. In addition, several plant-derived phytochemicals are able to inhibit the action of pancreatic enzymes. However, the clinical potential of these agents are yet to be evaluated.

It has been suggested that bariatric surgery is the most effective treatment for obesity and related comorbid conditions. Although this type of treatment has a very low mortality rate (0.3%) and is regarded as safe, it is important to acknowledge that it is associated with postoperative complications of different nature and severity. Common complications often seen after malabsorptive procedures, such as RYGB, include nutritional and metabolic disturbances. Functional EPI, as a consequence of RYGB, can also lead to deterioration of cognitive function as well as depressive symptoms. Continuous medical follow-ups and regular education might be a way to get patients more aware of the im-

portance of long-term adherence to the recommendations regarding life changes and nutrient supplementation that are given following surgery.

Finally, professional help with lifestyle changes should be provided to patients as a supplement

to pharmaceutical and surgical treatment of overweight and obesity. Because food addiction may be the underlying cause of these conditions, talking groups may also be a good way to support patients in their weight loss process.

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