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Obesity and diabetes

Otyłość a cukrzyca

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S u m m a r y

Obesity epidemic is one of the major global health problem and generates dramatic rise of diabetes incidence. Obesity is the major determinant of type 2 diabetes presumably through its effect on insulin resistance – the condition in which normal amount of insulin is inadequate to produce a normal insulin response from fat, muscle and liver cells. These functional defects may result from impaired insulin signaling in all three target tissues. Impaired insulin signaling may be produced by lipid accumulation in skeletal muscle and liver cells or by adipocytes dysfunction and local inflammation. Physicians should consider weight issues at every stage of treatment type 2 diabetes through the use of appropriate therapy and take care to choose anti-diabetic medication that is weight neutral or produces weight loss.

Key words: diabetes, obesity, insulin resistance, inflammation, diabetes therapy

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

Epidemia otyłości, będąca jednym z poważniejszych globalnych problemów zdrowotnych, nie pozostaje bez wpływu na równie gwałtowny wzrost zachorowań na cukrzycę typu 2. Otyłość jest czynnikiem indukującym rozwój cukrzycy typu 2 głównie poprzez wpływ na insulinooporność – stan, w którym insulina w prawidłowym stężeniu nie jest w stanie wywołać właściwej odpowiedzi ze strony tkanki tłuszczowej, mięśni i wątroby. Patologia ta może być wynikiem zaburzeń w przekazywaniu sygnału insulinowego w tkankach docelowych. Zaburzenia insulinowego szlaku przekaźnictwa sygnału mogą być wywołane akumulacją lipidów w mięśniach szkieletowych i wątrobie lub dysfunkcją adipocytów i rozwojem miejscowego stanu zapalnego. Lekarze powinni uwzględniać kwestię masy ciała na każdym etapie leczenia cukrzycy typu 2, wybierając odpowiednią strategię postępowania oraz stosując doustne leki hipoglikemizujące o neutralnym wpływie na masę ciała lub powodujące jej redukcję.

Słowa kluczowe: cukrzyca, otyłość, insulinooporność, zapalenie, leczenie cukrzycy

INTRODUCTION

Health care on obese people is one of the biggest challenge of current medicine. The new IASO/IOTF (International Association for the Study of Obesity/International Obesity Task Force) analysis (2010) estimates that approximately 1.0 billion adults in the world are currently overweight (BMI 25-29.9 kg/m²), and a further 475 million are obese (1) which means that around 1.5 billion adults are too heavy. The survey performed In Poland during 2003-2007 found that: 40.3 percent of men (aged 20+) were overweight, 20.8 percent of men (aged 20+) were obese, 28.4 percent of women (aged 20+) were overweight, 23.8 percent of women (aged 20+) were obese (2). In the future that will be even a greater problem because the incidence of obesity rises. Between 1980 and 2008, mean BMI worldwide increased by 0.4 kg/m² per decade for men and 0.5 kg/m² per decade for women (3). The epidemiological data point also at a systematic rise of diabetes incidence. The IDF (International Diabetes Federation) analysis shows that in 2012 more than 371 million people in the world have diabetes, and by 2030 this will have risen to 552 million (4). This dramatic rise of diabetes incidence is not surprising because BMI is thought to be responsible for about 60% the risk of developing type 2 diabetes. A stronger association with developing a type 2 diabetes than BMI has visceral fat, particularly in the abdominal region (5). Around 80-90% of patients with type 2 diabetes are overweight or obese (6).

OBESITY AND INSULIN RESISTANCE

Obesity is the major determinant of type 2 diabetes, presumably through its effect on insulin resistance.

Insulin resistance is the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Each standard deviation (SD) increase in visceral adipose tissue mass increases the odds of insulin resistance by 80% (7).

There are two hypotheses which explain the insulin resistance cause. In the first, lipid accumulation in skeletal muscle and liver cells play the central role. In the second, the most important is lipid accumulation in adipocytes and local inflammation.

Skeletal muscles play a crucial role in maintaining systemic glucose metabolism, accounting for 85% of whole body insulin-stimulated glucose uptake (7). In skeletal muscles, insulin stimulates glucose uptake by increasing the translocation of glucose transport molecules, mainly GLUT4, from intracellular vesicles to the cell surface (8). Insulin resistance in muscles is manifested as a decrease in glucose transport and a storage reduction of glucose as glycogen and triglycerides in response to circulating insulin. Glucose disposal in skeletal muscles is not entirely independent from the metabolic effects of insulin on other peripheral tissues, such as adipose tissue. It seems that insulin resistance of skeletal muscles might be also secondarily induced to adipose tissue (8).

Adipose tissue is a major site of energy storage and increased mobilization of stored lipids in adipocytes elevates free fatty acids in the blood plasma. Many studies have shown that intra-abdominal adipocytes are more lipolytically active than subcutaneous adipocytes. Evidence suggests that fatty acids might play a role in the development of skeletal muscle insulin resistance (9) via inflammatory signaling after binding Toll-like receptors at the cell membrane of muscle cells or after accumulating as intramyocellular lipid metabolites (10). Accumulation of excess lipids or their metabolic derivatives cause decreased insulin signaling in skeletal muscle. Muscle insulin resistance in obese diabetic humans has also been correlated with decreased transcapillary insulin transport (11).

Insulin resistance in the liver results in reduced glycogen synthesis and storage, failure to suppress glucose production (gluconeogenesis) and stimulation of fatty acid synthesis. Visceral fat released proteins are directly transported to the liver by the portal vein and the anatomical feature of this fat depot may explain the harmful metabolic effects of visceral adiposity (12). Thse fat released proteins may decrease the cellular response to insulin. Very important in hepatic insulin resistance may be also lipid accumulation in the liver. Weight gain of 10% by overfeeding of fast food and sedentary lifestyle in 18 young healthy subjects has been shown to increase hepatic triglyceride content by 2.5-fold in 4 week (13). Excess lipid accumulation in the liver may result in impaired insulin signaling through cell autonomous mechanisms, or through the induction of inflammation and the subsequent production of inflammatory cytokines by macrophages, which impair insulin action (11).

Insulin resistance in fat cells reduces the normal insulin effects on lipids. It results in reduced uptake of circulating lipids and increased hydrolysis of stored triglycerides. Insulin resistant adipose tissue no longer fulfills its role of fat storage – other tissues will be exposed to excess levels of plasma glucose and free faty acids, and store these fuel molecules in the form of triglycerides in order to compensate for the dysfunction in adipose tissue (14). As in skeletal muscle or in the liver, obesity may produce adipocyte insulin resistance through cell autonomous mechanisms, or through the interactions between the adipocyte and mediators of inflammation.

Genetic predisposition to obesity contributes to increased insulin resistance and to its compensation through increased β-cell function, and weakly increases the type 2 diabetes risk (15). The progression from insulin resistance alone to impaired glucose tolerance (IGT)/impaired fasting glucose (IFG) to overt type 2 diabetes mellitus is regulated by the relationship between insulin resistance and insulin secretion. Hyperglycemia develops when β-cell secretion is insufficient for the level of insulin resistance. Insulin secretion is dependent on β-cell mass and secretory capacity, which are governed by genetic and environmental factors. Insulin resistance-induced hyperglycemia itself may cause further β-cell apoptosis. Insulin resistance adults reportedly lose an average of 7% of their β-cells per year (16).

ADIPOKINES, INFLAMMATION AND TYPE 2 DIABETES

Adipose tissue plays a critical role in maintenance of energy homeostasis through secretion of a large number of adipokines that interact with central as well as peripheral organs such as brain, liver, pancreas and skeletal muscle to control diverse processes, such as food intake, energy expenditure, carbohydrate and lipid metabolism, blood pressure, blood coagulation, and inflammation. While many of these adipokines are adipocyte-derived and have a variety of endocrine functions, others are produced by resident macrophages and interact in a paracrine way to control adipocyte metabolism. It is also abundantly clear that the disregulation of adipokine secretion and action that occurs in obesity, plays a fundamental role in the development of a variety of cardiometabolic disorders, including the metabolic syndrome and type 2 diabetes (17).

Adipocytes secrete increasing levels of monocyte chemotactic protein (MCP-1) which is known to attract blood monocytes into adipose tissue where they transform into macrophages (18). Obesity is associated with a chronic low-grade inflammatory state by increased numbers of macrophages in adipose tissue witch are able to secret a huge array of pro-inflammatory cytokines such as TNFα and IL-6 (19).

TNFα induces insulin resistance in skeletal muscle and liver by decreasing insulin signaling. In adipocytes, TNFα inhibits insulin signaling as well, and down-regulates PPARγ activity that eventually leads to

a decreased adiponectin secretion (hypoadiponectinemia is associated with insulin resistance and T2DM). TNF can alter insulin sensitivity also by decreasing glucose transporter-4 in adipocytes (20, 21).

IL-6 is secreted by adipose tissue and enters the circulation (adipose tissue contributes to up to 35% of circulating IL-6 (22). IL6 reduces adiponectin secretion, increases lipolysis, and in experimental animals IL6 administration increases free fatty acids levels. In both adipocytes and hepatocytes, IL6 inhibits the insulin signaling pathway by up-regulating suppressor of cytokine signaling 3 (SOCS3) expression, which leads to an impairment of insulin receptor (23). The role of IL6 in obesity and insulin resistance remains however controversial because IL6 is also a myokine produced and released from skeletal muscle during exercise. In mice endogenous IL-6 contributes to the exercise-induced increase in insulin sensitivity (24).

Adiponectin is secreted exclusively by adipocytes but it was found to be decreased in obesity (this downregulation has not been fully explained). Adiponectin increases insulin sensitivity by inhibiting hepatic glucose production and by increasing fatty acid oxidation in both the liver and skeletal muscle as a result of increased AMP-activated protein kinase (AMPK) activity. Adiponectin also induces glucose lowering by decreased hepatic glucose output and suppression of gluconeogenic genes. It reduces the production of cytokines by macrophages and directly inhibits the action of TNFα (23).

Leptin is adipose-derived hormone present in serum in direct proportion to the amount of adipose tissue. Its primary role is to provide the central nervous system with a signal of energy (adipose) stores in the body. Leptin regulates appetite and affects energy expenditure. Obese people have very high plasma leptin concentrations but this endogenous hyperleptinemia does not reduce appetite or increase energy expenditure. This state has been termed "leptin resistance" (circulating leptin fails to reach its targets in the brain or there is a failure of components of the intracellular leptin receptors signaling cascade) (25).

Leptin has a key function in the regulation of glucose homeostasis. Although leptin acts through central and peripheral mechanisms to modulate glucose metabolism, its receptors are present in the β-cell, and their activation directly inhibits insulin secretion. This hormone inhibits insulin gene expression as well. Additionally, β-cell mass can be affected by leptin through changes in proliferation, apoptosis, or cell size. It has been proposed that alterations in this level of β-cell regulation could contribute to the impairment of β-cell function in obesity states (26).

TREATING THE PATIENT WITH OBESITY AND TYPE 2 DIABETES

As mentioned above, obesity induces insulin resistance and pancreatic β-cell dysfunction. These obesity-related defects tend to progress following weight gain and can eventually lead to worsening hyperglycaemia

over time. Thus, effective weight management is crucial for glycaemic control in overweight and obese patients with type 2 diabetes. In patients who have already been diagnosed with type 2 diabetes, weight loss may help to slow the natural history of the disease and delay the need for intensification of insulin therapy. Even a modest sustained reduction of the initial body weight (5-10%) can significantly mitigate diabetes-related complications by improving glycaemic control, lipid profiles and blood pressure (27).

Lifestyle modification should be the first step in every weight loss program and must always be included as part of diabetes management. Randomized controlled trials of comprehensive lifestyle-modification programs (dietary interventions, physical activity, behavioral therapy) have shown weight losses of 7% to 10% of initial body weight within 4 to 6 months after treatment. These programs also reduce the likelihood of developing T2DM by 58% for individuals with impaired glucose tolerance (28). The positive effect of lifestyle on body weight seems somewhat transient, whereas the effect on type 2 diabetes is sustained for longer periods. Furthermore, lifestyle modification appears to have an effect on diabetes risk independently of body weight and even of weight loss (29). Long-term adherence remains a major limitation of diet and exercise, as seen by the high rate of weight regain among overweight patients.

The benefits from lifestyle modification may have less impact on patients with extreme obesity or more significant health problems. For these individuals, bariatric surgery may be a more appropriate treatment. Bariatric surgical procedures induce mean weight losses of 15 to 30% of initial body weight (depending on the procedure) within 2 years after surgery, as well as a 45 to 95% rate of diabetes remission (28).

Over the long term, weight loss may not prevent the eventual development of diabetes mellitus in at-risk patients presumably due to progression of pancreatic β-cell dysfunction. Then, antidiabetic treatment of the patient is required. Weight gain is a side effect of several commonly used diabetes medication so when selecting drug to treat diabetes, physician should choose drugs that are weight neutral or produce weight loss. Table 1 shows categorization of antidiabetic drugs by their effects on body weight.

Table 1. Categorization of antidiabetic drugs by their effects on body weight.

Weight loss	Weight neutral	Weight gain
Metformin	Dipeptidyl peptidase-4 inhibitors (DPP-4)	Insulin
Glucagon-like peptide-1 (GLP-1) receptor agonists	Acarbose	Sulfonylureas
		Glitinides
		Thiazolidynediones

Metformin reduces hepatic glucose production, decreases intestinal glucose absorption from the gastrointestinal tract, and enhances insulin sensitivity. The effect of metformin on body weight in randomized, controlled trials in patients suboptimally controlled by diet was variable, with about half of studies demonstrating significant reductions in body weight (30). In Diabetes Prevention Program the metformin-treated group (IGT) lost 2.1 kg of their body weight during 2.8 years versus 0.1 kg in the placebo group. The degree of weight loss was related to the adherence to metformin (31). The study published this year, examined the effectiveness of metformin (up to a dosage of 2 500 mg per day) in weight reduction in obese and overweight patients (BMI $\geq$ 27 kg/m^2) with regard to their degree of insulin resistance, found that metformin is effective drug to reduce weight. The mean weight loss in the metformin treated group was 5.8 $\pm$ 7.0 kg over 6 months (untreated controls gained 0.8 $\pm$ 3.5 kg). Patients with severe insulin resistance lost significantly more weight as compared to insulin sensitive subjects (32).

Incretin based therapies were introduced into the treatment of type 2 diabetes a few years ago. These therapies are classified as GLP-1 receptor agonists or dipeptidylpeptidase IV (DPP-4) inhibitors. The use of incretin based therapies in Poland is problematic because this treatment is very expensive and not refunded by National Health Fund.

Glucagon-like peptide-1 receptor agonists (GLP-1) are glucose-lowering drugs for the treatment of type 2 diabetes. GLP-1 is a gastrointestinal hormone, produced mainly in the postprandial phase, which stimulates insulin secretion and inhibits glucagon release. In this way GLP-1 reduces hyperglycemia without inducing hypoglycemia in patients with type 2 diabetes. It has also been shown to reduce body weight. The effects of GLP-1 and its agonists on body weight appears to be due to a reduction in food intake, mainly determined by a direct central (hypothalamic) effect of the hormone. The stimulation of GLP-1 receptor also retards gastric emptying (33). In Poland we have two GLP-1 agonists on the market: exenatide and liraglutide. Exenatide has 53% homology with GLP-1. It is administered via subcutaneous injection twice a day. The drug is associated with significant reductions from baseline in body weight – mean -1.94 kg (34). Liraglutide has a 97% homology to GLP-1. It is administered via subcutaneous injection once a day and produces weight loss of -1.66 kg (34). In head-to-head comparison, liraglutide and exenatide produced similar amounts of weight loss (-3.24 kg with liraglutide versus -2.87 with exenatide) (35).

As mentioned above, another class of drugs that are based on incretin effect are dipeptidylpeptidase IV (DPP-4) inhibitors. In Poland there are four DPP-4 inhibitors approved to the diabetes type 2 treatment: vildaglitin, sitaglitin, saxaglitin and linagliptin. The findings from the meta-analysis suggest potential differences between the GLP-1 agonists and the DPP-4 inhibitors in terms of weight. DPP-4 inhibitors were associated only with a trend toward weight loss. Mean changes in weight observed in meta-analysis were: for saxagliptin -0.64 kg, for sitagliptin -0.29 kg and for vildagliptin -0.21 kg (34).

Linagliptin is a novel DPP-4 inhibitor with a distinct pharmacological profile (it is eliminated by a hepatic/biliary route rather than a renal route). In 1-year double-blind study investigating the efficacy and safety of linagliptin in type 2 diabetes mellitus patients for whom metformin was inappropriate, no weight gain (mean change from baseline of -0.2 kg) during the 34-week was observed (36).

Alpha-glucosidases in the brush-border of the small intestine are competitively inhibited by the pseudo-carbohydrate acarbose. This inhibition delays digestion of complex carbohydrates in the upper small bowel and subsequently retards absorption of glucose and 'blunts' postprandial hyperglycaemia. Systematic review and meta-analyses have shown that acarbose is weight-neutral. Results from 16 randomized controlled trials showed a weighted mean absolute difference in body weight between acarbose and placebo of -0.1 kg. Similarly, a meta-analysis of 41 randomized controlled trials of α-glucosidase inhibitors confirmed that these agents had no statistically significant effect on body weight (37). For patients who do not reach glycemic goals on oral anti-diabetic agents, there is a need to start insulin therapy. Numerous studies have documented that improvements in glycemic control wrought by insulin are frequently accompanied by increases in body weight, so in people with type 2 diabetes who are overweight or obese, insulins that effectively control blood glucose but with lesser weight gain should be considered. Of the insulin preparations, insulin detemir provides the most favorable weight profile, especially in patients with high baseline BMI (37).

CONCLUSIONS

Weight and diabetes go hand in hand – around 80-90% of patients with type 2 diabetes are overweight or obese. Obesity induces insulin resistance and pancreatic β-cell dysfunction, so optimizing weight should be a priority in type 2 diabetes. Physicians should consider weight issues at every stage of the disease through the use of appropriate therapy. Diabetes therapies such as insulin and sulfonylureas are associated with weight gain, but some drugs such DPP-4 inhibitors or acarbose are weight neutral and metfromin or GLP-1 agonists produce weight loss. Despite the pharmacological therapy lifestyle changes are essential in each step of diabetes and obesity treatment.

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