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REVIEW / PRACA POGLĄDOWA

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INSULIN RESISTANCE AS A DISEASE OF CIVILIZATION

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Summary

Civilization - related diseases can be defined as those caused by the effects of harmful factors resulting from the development of civilization, the progressive industrialization and changes in lifestyle that derive from the use of achievements of modern civilization. Abdominal obesity and diabetes are the most typical examples of such ailments.

Insulin resistance underpins the obesity and type 2 diabetes' twin epidemics and explains many of the metabolic problems that, linked together, are called a metabolic syndrome. It is defined as a glucose homeostasis disorder, in terms of reduced sensitivity of muscle, fat, liver and other body tissues to insulin. There are three possible mechanisms of insulin resistance: pre-receptor, receptor and post-receptor.

Insulin resistance may not be the only and the basic problem of the patient directly leading to impaired glucose metabolism in the form of diabetes. It may be an additional issue, related to another disease the patient is suffering from, and leading to serious complications, including diabetes. This is due to a variety of hormonal disorders occurring in various diseases and leading to the emergence of resistance to insulin.

Most of the hormones diminish the effect of insulin in the body in the mechanism of action of the liver and the peripheral tissues. The hormones that in excess most often cause carbohydrate metabolism disorders include growth hormone, thyroxine, glucocorticoids, catecholamine, parathyroid hormone, aldosterone, glucagon and somatostatin. The effect of their activity is hyperinsulinemia resulting from the compensatory rise in insulin secretion in response to increasing insulin resistance.

The awareness of insulin resistance prevalence in different globally widely spread disease entities and the understanding of the mechanisms leading to it should contribute to taking better care of patients originally being treated because of other reasons.

Streszczenie

Choroby cywilizacyjne można zdefiniować jako choroby spowodowane oddziaływaniem na ludzki organizm szkodliwych czynników, będących skutkiem rozwoju cywilizacji, postępującym uprzemysłowieniem oraz zmianą stylu życia wynikającą z wykorzystania zdobyczy współczesnej cywilizacji. Typowymi przykładami takich schorzeń są otyłość brzuszna i cukrzyca.

Insulinooporność stanowi podstawę bliźniaczej epidemii otyłości oraz cukrzycy typu 2, jak również tłumaczy wiele problemów metabolicznych zdefiniowanych jako zespół metaboliczny. Definiowana jest jako zaburzenie homeostazy glukozy, polegające na zmniejszeniu wrażliwości mięśni, tkanki tłuszczowej, wątroby oraz innych tkanek organizmu na insulinę. Wyróżniamy trzy mechanizmy insulinooporności: przedreceptorowy, receptorowy i postreceptorowy.

Insulinooporność może nie być tylko jedynym, podstawowym problemem chorego, bezpośrednio wiodącym do zaburzenia metabolizmu glukozy pod postacią cukrzycy. Może ona stanowić dodatkowy problem, towarzyszący innej, pierwotnie u danego pacjenta występującej jednostce chorobowej, a prowadzący do poważnych powikłań, w tym cukrzycy. Dzieje się to na skutek rozmaitych zaburzeń hormonalnych występujących w różnych chorobach a prowadzących do pojawienia się oporności na insulinę.

Większość hormonów zmniejsza działanie insuliny w organizmie w mechanizmie działania na poziomie wątroby oraz tkanek obwodowych. Do hormonów, które w nadmiarze najczęściej powodują zaburzenia gospodarki węglowodanowej należą: hormon wzrostu, tyroksyna, glikokortykosteroidy, katecholaminy, parathormon, aldosteron oraz glukagon i somatostatyna. Skutkiem ich działania jest hiperinsulinemia będąca wynikiem

kompensacyjnego wzrostu wydzielania insuliny w odpowiedzi na narastającą insulinooporność.

Świadomość tak powszechnego występowania insulinooporności w różnych, globalnie szeroko rozpowszechnionych jednostkach chorobowych oraz zrozumienie mechanizmów do niej prowadzących, powinny przyczynić się do lepszej opieki nad chorymi pierwotnie leczącymi się z innych powodów.

Key words: insulin resistance, obesity, carbohydrate metabolism disorders
Słowa kluczowe: insulinooporność, otyłość, zaburzenia gospodarki węglowodanowej

Civilization - related diseases can be defined as those caused by the effects of harmful factors resulting from the development of civilization, the progressive industrialization and changes in lifestyle that derive from the use of achievements of modern civilization. Abdominal obesity and diabetes are the most typical examples of such ailments.

Insulin resistance underpins the obesity and type 2 diabetes' twin epidemics and explains many of the metabolic problems that, linked together, are called a metabolic syndrome [1]. In the original description of the syndrome by Raeven, the major etiological role has been attributed to insulin resistance. This assumption has still remained the metabolic syndrome's dominant paradigm [2]. Since the announcement of this hypothesis, several epidemiological and clinical researches have confirmed an increased risk of diabetes and cardiovascular diseases in people with insulin resistance [3].

Insulin resistance is defined as a glucose homeostasis disorder, in terms of reduced sensitivity of muscle, fat, liver and other body tissues to insulin. There are three possible mechanisms of insulin resistance: pre-receptor, receptor and post-receptor (Table1).

Table 1. *The mechanisms of insulin resistance*

Pre-receptor	Receptor	Post-receptor
-incorrect structure of insulin's molecules (mutant insulin syndrome) -increased degradation of insulin - presence in the blood of antibodies binding molecules of insulin -presence in the blood of substances or hormones antagonistic to insulin: cortisol, glucagon, growth hormone, thyroid hormones, androgens	-decreased number of insulin receptors -decreased affinity of insulin receptors to insulin (mutations)-insulin has it maximum effect in peripheral tissues after saturating 10% of receptors	-disturbances in the process signaling the connection of insulin to insulin receptor (disturbances in the intracellular signal transmission) -anomalies in the structure and the activity of glucose transporters to the cell - intense lipolysis – the number of free fatty acids increases, and their over-oxidation is responsible for the inhibition of glycolysis

There are many ways of investigating insulin resistance (Table 2.). However, the gold standard in the evaluation of sensitivity to insulin is the tissue glucose consumption calculation by the euglycemic hyperinsulinemic clamp. Its principle is to determine the amount of glucose that must be administered to a patient to maintain a constant blood glucose value during the 120-minute infusion of insulin. The amount of glucose given, reflects its tissue consumption, therefore indirectly, the tissue sensitivity to insulin. The lower dose of glucose is needed to maintain euglycemia, the greater the insulin resistance. This study allows identification insulin resistance that plays an important role in the development of metabolic syndrome. It is also used to assess the contribution of insulin resistance in the pathogenesis of diabetes

Unfortunately, due to the complicated and time-consuming procedure and high cost, this method is rather used in clinical trials than in the population studies. Therefore, the insulin resistance in epidemiological studies is estimated using the approximate ratios calculated from glycaemia and fasting insulin or the oral glucose tolerance test [3]. Due to the unquestionable connection between the insulin resistance and the metabolic syndrome and also the difficulties of accurate assessment of insulin resistance, numerous studies have sought indicators of insulin resistance, which could override the method of metabolic clamp in practice [3]. Szurkowska et al., comparing indices: HOMA-IR, QUICKI, Matsuda found out that they have a similar predictive value in diagnosing the metabolic syndrome in patients with normal glucose tolerance. However, in patients with impaired glucose tolerance, the Matsuda index seems to have the greatest value.

Insulin resistance is one of the causes of type 2 diabetes and gestational diabetes. It also usually arises in the course of type 1 diabetes. According to etiologic classification of diabetes mellitus (WHO and ADA), there are four basic types of this disease: type 1 diabetes, type 2, other specific types of diabetes and gestational diabetes.

Table 2. *Methods of studying insulin resistance*

Direct methods	Indirect methods
1.The metabolic clamp method- ‘ the golden standard’ 2.The insulin tolerance test 3.The endogenous insulin suppression test	1.The insulinaemia/glycaemia index 2.The HOMA-IR index 3.The Quicki index 4.The Matsuda index 5.The intravenous glucose tolerance test 6.The double intravenous glucose tolerance test 7. The Bergman’s method.

Insulin resistance may not be the only and the basic problem of a patient leading directly to impaired glucose metabolism in the form of diabetes. It may be an additional issue, related to another disease the patient is suffering from, and leading to serious complications, including diabetes. This is due to a variety of hormonal disorders occurring in various diseases and leading to the emergence of resistance to insulin.

Most of the hormones diminish the effect of insulin in the body in the mechanism of action of the liver (an increase in glucose production) and the peripheral tissues (a reduction in use of glucose) [4]. The hormones that in excess most often cause carbohydrate metabolism disorders include growth hormone, thyroxine, glucocorticoids, catecholamine, parathyroid hormone, aldosterone, glucagon and somatostatin. The effect of their activity is hyperinsulinemia resulting from the compensatory rise in insulin secretion in response to increasing insulin resistance, as well as direct stimulation of pancreatic β cells by antagonistic hormones [4].

There are certain endocrinopathies that as a result of progressive insulin resistance predispose to the development of diabetes. These are: acromegaly, hypercortisolism, hyperthyroidism, hypothyroidism hyperparathyroidism, polycystic ovary syndrome, hyperprolactinemia, pheochromocytoma, VIPoma and glucagonoma. The effect of hormones on insulin secretion and carbohydrate metabolism are shown in Table 3.

Glucagon’s action is extremely antagonistic to insulin. In the pancreatic endocrine tumor deriving from alpha cells of islets of Langerhans, there is a significant hypersecretion of this hormone, which results in the fact that the carbohydrate metabolism disorders are, in addition to thromboembolic complications and skin lesions, one of the basic symptoms of glucagonoma.

Table 3. *The effect of hormones on insulin secretion and carbohydrate metabolism*

Hormones	**Insulin secretion**	**Glucose liver production**
Growth hormone	+	+
Cortyzol	+	+
Thyroxine	?	+
Catecholamines	-	+
Aldosterone	-	+
Glukagon	+	+
Somatostatin	-	**?**
Parathyroid hormone	-	+
Prolactine	+	**?**

+ stimulation, - inhibition, unacknowledged influence

In the polycystic ovary syndrome (PCOS), insulin resistance is relatively common and it can be provoked by the moderate increase in serum prolactin levels [5], which occurs in this disease. On the other hand, insulin resistance and elevated insulin levels may be significant in the pathogenesis of the syndrome due to the fact that this condition favors the activity of the hypothalamic - pituitary - adrenal axis resulting in the increment of adrenal androgens, particularly in obese women [6].

From the group of patients with hyperthyroidism, 50% have impaired glucose tolerance and 2-3% diabetes. In this case there are several mechanisms leading to impaired glucose tolerance. In thyreotoxicosis it comes to an accessed absorption of glucose in the gastrointestinal tract due to faster gastric emptying and increased blood flow in the portal vein, which leads to the postprandial hyperglycemia- the characteristic of hyperthyroidism [7]. Moreover, thyroid hormones also escalate the glucose liver production, have lipolytic action and accelerate the degradation of insulin.

Hypothyroidism is not the only cause of obesity, dyslipidemia and increased cardiovascular risk; it is also associated with insulin resistance [8]. The resistance to insulin in patients with hypothyroidism can result from accessed free fatty acids levels, leading to reduced glucose uptake and its oxidation [9]. It turns out that insulin resistance affects the relationship between thyroid function and lipids; what is more, the impact of elevated TSH levels on LDL- cholesterol is different depending on the level of insulin sensitivity [8].

What contributes to the formation of carbohydrate metabolism disorders in primary hyperparathyroidism are hypercalcaemia and hypophosphatemia, leading to

insulin resistance, hyperinsulinemia and reduction of the insulin receptors number [6].

In the pheochromocytoma, the resistance to insulin is caused by an excess of antagonistic to insulin catecholamine hormones. The main effect here can be ascribed to the adrenaline, which inhibits the secretion of insulin and intensifies that of glucagon. Therefore, pheochromocytoma may lead to impaired glucose tolerance or diabetes, although they seem to disappear after successful treatment [4].

A similar situation appears in the hypercortisolism, where a resection of incidentaloma may improve the sensitivity of peripheral tissues to insulin [10].

Growth hormone secreted in excess in acromegaly may contribute to insulin resistance directly by reducing the inhibition of hepatic glucose production and depleting the glucose uptake by peripheral tissues, as well as indirectly through its lipolytic action. More specifically, an access in non-esterified fatty acids level leads to increased hepatic glucose production and inhibition of glucose utilization by the striated muscles.

The glucose tolerance disorders stemming from endocrinopathies are placed within the third category of the previously mentioned classification of diabetes mellitus and are known under the name of secondary diabetes [11]. This occurs most likely due to post-receptor mechanism of insulin resistance. Secondary diabetes is characterized by reversibility of glucose intolerance, which means it is usually equalized after application of effective treatment of the underlying disease [4]. In addition to pancreatic diseases, endocrinopathies are the leading cause of other specific types of diabetes [4].

Insulin resistance also occurs in cancer. The determinants of impaired carbohydrate metabolism in patients with advanced cancer are: chronic hypercortisolemia, chronic hipercatecholaminemia and the relative dominance of glucagon over insulin, which results in the acceleration of lipolysis and glycogenolysis. In addition, all of the mentioned mechanisms also lead to a significant acceleration of gluconeogenesis in the liver with accompanying insulin resistance and impaired insulin secretion [12].

Obesity, next to type 2 diabetes, is a disease that first comes to mind when talking about diseases of civilization. This condition, resulting from the excessive accumulation of adipose tissue in the body, results in many serious consequences [13], among others, through effects on insulin action and hepatic glucose production [14]. Obesity is associated with chronic inflammation of a minor intensification, which can lead to insulin resistance, type 2 diabetes and dyslipidemia [15], which in conjunction with elevated blood pressure in these patients, inevitably lead to atherosclerosis [14]. The deteriorating effect of abdominal obesity, described by waist circumference (WC), on the risk of coronary heart disease, has been repeatedly confirmed in numerous clinical trials [16], and C-reactive protein, a marker of inflammation, and a reliably factor of cardiovascular risk, is elevated in obese individuals [15]. The importance of abdominal obesity underlines the fact that, since 2005, a waist circumference has been a basic criterion in the metabolic syndrome definition by the International Diabetology Federation (IDF) [16].

Insulin resistance is associated with obesity through a number of bioactive peptides produced in adipocytes, called adipocytokines [14]. These include leptin, adiponectin, and resistin. Their physiological function is to maintain homeostasis by affecting insulin sensitivity, glucose, lipid metabolism and inflammation. In obese patients, they have an impact on the final course of the metabolic syndrome. The amount of adiponectin in the circulation is reduced in obese people with type 2 diabetes and insulin resistance [14], and proportional to the level of obesity and insulin resistance decline in plasma adiponectin in obese people may have a proinflammatory and prothrombotic effect [13]. The amount of leptin, in turn, increases in direct proportion to the access of body adipose tissue [14]. It has been proven that an access in plasma leptin and the decrease in the blood concentration of adiponectin exaggerate insulin resistance in obese patients [14]. Lastly, the still going on research reveals that resistin may be linked directly to the inflammation phenomenon and indirectly to insulin resistance [14].

Not only do the peptide hormones produced in the adipocytes affect inflammation and insulin resistance in obese patients. Both, fat cells and immune cells contained in adipose tissue, produce proinflammatory cytokines such as IL-6, what eventually leads to inflammation, clinically manifested by an increase in serum levels of CRP, WBC and fibrinogen [15]. It subsequently potentially results in insulin resistance as well as any other complications of obesity. It should be noted that, like weight gain leads to an increase in the previously mentioned parameters, its loss results in a significant decrease in their concentrations [15]. In obese subjects there is a positive correlation between

CRP and leptin, which confirms the pro-inflammatory actions of this hormone [13]. An inverse correlation between adiponectin and the concentration of proinflammatory cytokines, on the other hand, confirms its anti-inflammatory nature [13].

Whatever the mechanism leading to insulin resistance, it is a significant independent risk factor for a coronary heart disease [17]. What is found in people with insulin resistance and metabolic syndrome is a typical picture of aterogenic dyslipidemia characterized by low levels of HDL-C, high TG and small particles of VLDL [18]. Because of the serious consequences resulting from the condition of insulin resistance, the need for a rapid diagnosis does not appear to raise any doubt. Taking into account that abdominal obesity is often the first noticeable feature of the metabolic syndrome, the identification of insulin resistance in subjects with BMI $\geq$ 30 kg/m2 seems needless to be emphasized the necessity. It should be, however, taken into consideration that even patients with weight within normal limits, but an increased amount of abdominal adipose tissue, may have metabolic obesity in the form of insulin resistance and dyslipidemia [14].

The awareness of insulin resistance prevalence in different globally and widely spread disease entities and the understanding of the mechanisms leading to it, should contribute to taking better care of patients originally being treated because of other reasons. The ability to eject early suspicion of the disorder, the possibility to objectively establish its presence and to try the treatment, can effectively prevent serious complications. Nevertheless, what should be remembered is the most basic method of therapy in patients suffering from metabolic syndrome, which is the attempt to reduce body weight. Even a slight loss of body weight achieved by diet change and regular physical activity improves the lipid profile, increases insulin sensitivity and reduces markers of inflammation [15]. It all, in turn, leads to a reduced risk of complications, what is of great importance, especially given the fact of increased risk of cardiovascular disease in people with insulin resistance [19].

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