Insulin resistance and thyroid disorders

Insulinooporność a choroby tarczycy

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Abstract

Insulin resistance is defined as a glucose homeostasis disorder involving a decreased sensitivity of muscles, adipose tissue, liver and other body tissues to insulin, despite its normal or increased concentration in blood.

Insulin resistance may be asymptomatic or occur presenting a variety of disorders, such as: glucose tolerance impairment, type 2 diabetes, as well as hypercholesterolaemia, hypertriglyceridaemia, obesity, and arterial hypertension.

Insulin acts via specific receptors present on the surface of most cells of the body. The greatest number of these receptors is found on adipocytes, hepatocytes and striated muscle cells.

There are three mechanisms of insulin resistance: pre-receptor, receptor and post-receptor.

Multiple methods of assessing insulin resistance are based on the concurrent measurements of glucose and insulin levels in blood serum. The glucose and insulin measurements are conducted in baseline conditions or after intravenous administration of a specific quantity of glucose or insulin. The methods of assessing insulin resistance are divided into direct and indirect.

The current 'gold standard' in the assessment of insulin sensitivity is the determination of tissue glucose utilisation using the metabolic clamp technique.

The presence of disorders of carbohydrate metabolism has been demonstrated in thyroid disease involving either overt hyperthyroidism or overt hypothyroidism. The severity of the disease is proportional to the severity of these disorders. The possible influence of subclinical forms of both hyperthyroidism and hypothyroidism on carbohydrate disorders is still under discussion.

Thyroid hormones have a significant effect on glucose metabolism and the development of insulin resistance. In hyperthyroidism, impaired glucose tolerance may be the result of mainly hepatic insulin resistance, whereas in hypothyroidism the available data suggests that the insulin resistance of peripheral tissues prevails. **(Endokrynol Pol 2014; 65 (1): 70–76)**

Key words: *insulin resistance; thyroid disorders; hyperthyroidism; hypothyroidism*

Streszczenie

Insulinooporność definiuje się jako zaburzenie homeostazy glukozy polegające na zmniejszonej wrażliwości mięśni, tkanki tłuszczowej, wątroby oraz innych tkanek na insulinę pomimo jej prawidłowego lub podwyższonego stężenia we krwi. Insulinooporność może przebiegać bezobjawowo lub towarzyszyć różnorodnym chorobom i zaburzeniom, takim jak upośledzona tolerancja glukozy, cukrzyca typu 2, hipercholesterolemia, hipertriglicerydemia, otyłość i nadciśnienie tętnicze.

Insulina działa za pośrednictwem swoistych receptorów obecnych na powierzchni większości komórek organizmu. Najwięcej tych receptorów stwierdza się na komórkach tłuszczowych, hepatocytach i komórkach mięśni poprzecznie prążkowanych.

Wyróżnia się trzy rodzaje insulinooporności: przedreceptorową, receptorową i poreceptorową.

Metody rozpoznawania insulinooporności oparte są na jednoczesnym oznaczaniu stężenia glukozy i insuliny w surowicy krwi. Pomiary stężenia glukozy i insuliny wykonywane są albo w warunkach podstawowych, albo po dożylnym podaniu określonej ilości glukozy lub insuliny. Metody oceny insulinooporności można podzielić na bezpośrednie i pośrednie.

Obecnie za „złoty standard" w ocenie insulinowrażliwości uważa się pomiar zużycia glukozy przez tkanki metodą euglikemicznej klamry metabolicznej.

Występowanie zaburzeń gospodarki węglowodanowej wykazano w chorobach tarczycy przebiegających z jawną nadczynnością lub jawną niedoczynnością. Nasilenie zaburzeń gospodarki węglowodanowej jest proporcjonalne do nasilenia zaburzeń czynności tarczycy. Nadal toczą się dyskusje na temat ewentualnego wpływu podklinicznych postaci nadczynności i niedoczynności tarczycy na zaburzenia gospodarki węglowodanowej.

Hormony tarczycy wywierają istotny wpływ na metabolizm glukozy i rozwój insulinooporności. W nadczynności tarczycy upośledzona tolerancja glukozy może być konsekwencją przede wszystkim insulinooporności wątrobowej, natomiast w przypadku niedoczynności tarczycy z dostępnych danych wynika, że dominującą komponentą insulinooporności jest insulinooporność tkanek obwodowych. **(Endokrynol Pol 2014; 65 (1): 70–76)**

Słowa kluczowe: *insulinooporność, choroby tarczycy, nadczynność tarczycy, niedoczynność tarczycy*

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Abbreviations

VLDL — very low density lipoprotein
GLUT — glucose transporter
HO — hypothyroidism
SHO — subclinical hypothyroidism
HR — hyperthyroidism
SHR — subclinical hyperthyroidism
fT_3 — free triiodotyronine
fT_4 — free tetraiodotyronine
TSH — tyreothropin
BMI — Body Mass Index
HOMA-IR — Homeostatic Model Assessment-Index
OGTT — oral glucose tolerance test
QUICKI — Quantitative Insulin Sensitivity Check Index
IgG — immunoglobulin G
PEPCK — phosphoenolpyruvate carboxykinase
TNF — tumour necrosis factor

Introduction

Insulin resistance is defined as a glucose homeostasis disorder involving a decreased sensitivity of muscles, adipose tissue, liver and other body tissues to insulin, despite its normal or increased concentration in blood [1, 2].

Insulin resistance may be asymptomatic or occur presenting a variety of disorders, such as: glucose tolerance impairment, type 2 diabetes, as well as hypercholesterolaemia, hypertriglyceridaemia, obesity, and arterial hypertension.

Mechanisms of insulin resistance

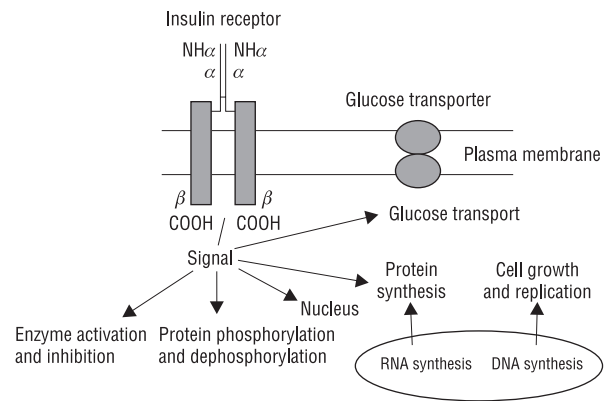Insulin acts via specific receptors present on the surface of most cells of the body (Fig. 1). The greatest number

Figure 1. *Structure and function of insulin receptor (following [1])*
Figure 1. *Struktura i funkcja receptora insuliny (wg [1])*

of these receptors is found on adipocytes, hepatocytes and striated muscle cells.

An insulin receptor is a heterodimer composed of two alpha-subunits, located extracellularly, and two beta-subunits, transmembrane proteins. The cytoplasmic part of the beta-subunit is endowed with tyrosine kinase activity and contains a region with autophosphorylation capability. Once insulin binds to the alpha-subunit, autophosphorylation of the beta-subunit occurs, which leads to the release of one or several signals triggering a pathway of cellular response to the hormone and internalisation of the receptor (its translocation into the cell interior).

There are three mechanisms of insulin resistance: pre-receptor, receptor and post-receptor, all of which are presented in Table I [1, 2].

Insulin resistance is distinguished into peripheral and hepatic. The peripheral type of insulin resistance develops in skeletal muscles and adipose tissue, and is

Table I. *Insulin resistance mechanisms*
Tabela I. *Mechanizmy oporności na insulinę*

| Pre-receptor	Receptor	Post-receptor
Genetic abnormalities in the structure of insulin molecules (the so-called 'mutant insulin syndrome')	Decreased number of insulin receptors	Abnormalities in the processes signalling the binding of insulin to the insulin receptor (intracellular signal transduction disorders)
Increased degradation of insulin	Lower affinity of insulin receptors to insulin (due to mutations)	Abnormalities in the structure and function of glucose transporters carrying glucose into the cell
Presence of antibodies (IgG) binding normal insulin molecules in blood		Increased lipolysis leading to higher quantity of free fatty acids, whose excessive oxidation is responsible for inhibiting glycolysis
Presence of substances or hormones acting as insulin antagonists in blood: cortisol, glucagon, growth hormone, thyroid hormone, androgens		
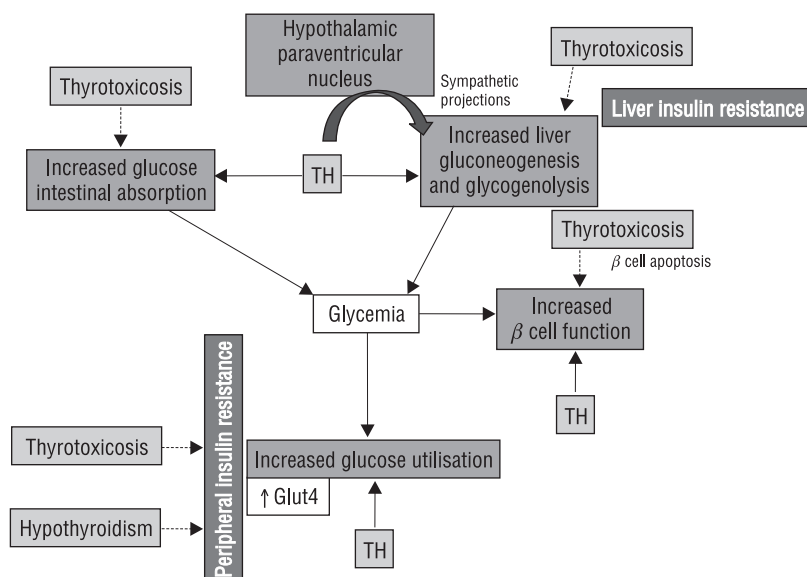
Figure 2. *Effect of thyroid hormones on glucose metabolism in patients with euthyreosis, hyperthyroidism and hypothyroidism*
Rycina 2. *Wpływ hormonów tarczycy na metabolizm glukozy u pacjentów z eutyreozą, nadczynnością tarczycy i niedoczynnością tarczycy*

characterised by abnormalities in glucose uptake and utilisation by muscle tissue, as well as increased lipolysis in adipose tissue followed by an increased release of free fatty acids. The hepatic type of insulin resistance involves increased glycogenolysis and gluconeogenesis, as well as production of the VLDL fraction of cholesterol and triglycerides by hepatocytes.

Insulin resistance in thyroid disease

Normal glucose metabolism may be disrupted by either a deficit or an excess of thyroid hormones, leading to carbohydrate disorders (Fig. 2).

Insulin receptors on monocytes quickly respond to changes in blood serum glucose levels and rapidly increase the glucose elimination rate in the presence of glucose [3–5]; therefore the cells may constitute a readily available and reliable model for metabolic studies.

Moreover, monocytes exhibit the expression of all isoforms of glucose transporter (GLUT) on their plasma membrane, found either in muscle or adipose tissues; increased glucose transport in response to the higher glucose levels in those cells correlates with that observed in tissues that are quantitatively significant for glucose elimination [3, 4].

In the study by Maratou et al., patients with overt hypothyroidism (HO) and subclinical hypothyroidism (SHO) presented a decreased level of insulin-stimulated glucose transport in monocytes due to disrupted translocation of the GLUT4 — glucose transporter in the plasma membrane [6].

Patients with overt hyperthyroidism (HR) and subclinical hyperthyroidism (SHR) in the study by Maratou et al. [4] also presented an increased level of baseline density of the GLUT4 and GLUT3 receptors. This is in line with the results of earlier studies in patients with HR [5, 7]. The increased expression of the GLUT3 and GLUT4 glucose transporters at the baseline insulin levels reflects the ability of monocytes to 'cope' with the increased rate of metabolism associated with this condition [4].

Another potential pathogenetic mechanism of the development of insulin resistance in hypothyroidism is associated with a decreased blood flow in peripheral tissues [8].

Assessing insulin resistance
Multiple methods of assessing insulin resistance (Table II) are based on the concurrent measurements of glucose and insulin levels in blood serum [1]. The glucose and insulin measurements are conducted in baseline conditions or after intravenous administration of a specific quantity of glucose or insulin. The methods of assessing insulin resistance are divided into direct and indirect.

The current 'gold standard' in the assessment of insulin sensitivity is the determination of tissue glucose utilisation using the metabolic clamp technique. The method involves quantification of glucose that needs to be administered to the patient to maintain a constant glycaemia during a 120-minute insulin infusion. The administered quantity of glucose corresponds to its utilisation in tissues and therefore, indirectly, their

Table II. *Methods of assessing insulin resistance*
Tabela II. *Metody oceny insulinooporności*

Direct methods	Indirect methods
1. Metabolic clamp technique — the 'gold standard'	1. Insulinaemia/glycaemia index
	2. HOMA-IR index
2. Insulin tolerance test	3. Quicki index
3. Endogenous insulin suppression test	4. Matsuda index
	5. Intravenous glucose tolerance test
	6. Double intravenous glucose challenge test
	7. Bergman method

insulin sensitivity. Lower doses of glucose necessary to maintain a constant glycaemia indicate greater insulin resistance. Unfortunately, due to the complex and time-consuming procedure employed, the method is used in clinical studies rather than population studies.

Another direct method is the insulin tolerance test. This involves administration of a single insulin dose of 0.1 U/kg body weight followed by the measurement of blood serum glucose levels. In subjects with insulin resistance, the decrease in blood glucose levels is insignificant, while in insulin-sensitive subjects, blood glucose levels decrease to 50% of the baseline glycaemia value.

The endogenous insulin suppression test involves inhibition of the secretion of endogenous insulin by administering adrenalin and propranolol. In insulin-sensitive subjects, the glucose levels obtained in the test are within the normal range, while in subjects with insulin resistance, higher glycaemia values are observed.

In epidemiological studies, insulin resistance is assessed using estimates determined from fasting glycaemia and insulinaemia values or using the oral glucose challenge test [9].

The most straightforward method is the determination of the quotient of insulin and glucose levels in blood serum. Values above 0.3 are indicative of insulin resistance.

Currently, a mathematical model of assessing insulin resistance (HOMA, Homeostatic Model Assessment) is widely used. The insulin resistance index is determined from glucose and insulin levels in blood in baseline conditions, according to the following formula:

HOMA-IR (mmol/L × μU/mL) = fasting glucose levels × fasting insulin levels/22.5. The physiological value of the index is 1.0. Higher values are indicative of insulin resistance.

QUICKI (Quantitative Insulin Sensitivity Check Index) is determined according to the following formula: 1/(log fasting insulinaemia (μU/mL) + log fasting glycaemia (mmol/L). Values < 0.34 are indicative of insulin resistance.

Matsuda index is determined using the following formula: 100,000/fasting insulinaemia (μU/mL) × fasting glycaemia (mg/dL) × mean glycaemia value in the Oral Glucose Tolerance Test (OGTT) × mean insulinaemia value in OGTT. Values < 7.3 are indicative of insulin resistance [2,9].

The **intravenous glucose tolerance test** involves administration of glucose at the dose of 0.33 g/kg b.w. in a fast intravenous infusion with concurrent measurements of blood serum glucose levels (immediately before the test starts and every ten minutes in the first hour of the test). In this way, the tissue glucose assimilation index (K) may be determined, which indicates the percentage of glucose that will be depleted from the extracellular space in one minute. Normal values of the K index are within the range 1.5–2.5. Values < 1.5 combined with increased or normal plasma insulin levels are indicative of insulin resistance.

The double intravenous glucose challenge test involves i.v. administration of glucose at the dose of 0.33 g/kg b.w. in a fast intravenous infusion with concurrent measurements of blood serum glucose levels (immediately before the test starts and every ten minutes in the first hour of the test), and then repeating this procedure with an additional infusion of insulin at the dose of 0.1 U/kg b.w. The difference between the tissue glucose assimilation indices K1 and K2 provides information on the function of endogenous insulin.

The Bergman method involves intravenous administration of glucose at the dose of 0.3 g/kg b.w. which, 20 minutes later, is followed by an i.v. administration of tolbutamide (dosage depends on body weight) that activates the secretion of endogenous insulin [2, 10]. The test duration is three hours. During that time, insulinaemia and glycaemia in venous blood are determined 26 times. The obtained results, along with the mathematical model proposed by Bergman, permit the determination of the tissue insulin sensitivity index.

By comparing the HOMA-IR, Quicki and Matsuda indices, Szurkowska et al. established that the indices had a similar predictive value in diagnosing metabolic syndrome in the group of subjects with normal glucose tolerance. However, in the group of subjects with impaired glucose tolerance, the Matsuda index presents the greatest value [9].

The clinical outcomes of insulin resistance primarily include: metabolic syndrome, type 2 diabetes, cardiovascular disease, nonalcoholic steatohepatitis, obstructive sleep apnoea, and polycystic ovary syndrome.

Insulin resistance and hormonal disorders

Most hormones decrease the effect of insulin in the organism at the level of the liver (increased glucose

Table III. *Effect of hormones on insulin secretion and carbohydrate metabolism*

Tabela III. *Wpływ na wydzielanie insuliny, hormonów i metabolizmu węglowodanów*

Hormone	Insulin secretion	Hepatic glucose production
Growth hormone	+	+
Cortisol	+	+
Tyroxine	?	+
Catecholamines	–	+
Aldosterone	–	+
Glucagon	+	+
Somatostatin	–	?
Parathormone	–	+
Prolactin	+	?

+ activation, – inhibition, ? effect unconfirmed

production) and peripheral tissues (decreased glucose utilisation) [11]. Among the hormones whose excess is the most common cause of carbohydrate disorders are: growth hormone, glucocorticosteroids, tyroxine, catecholamines, parathormone, aldosterone, as well as glucagon and somatostatin. Their activity induces hyperinsulinaemia as a result of a compensatory increase in insulin secretion in response to the higher insulin resistance and of a direct stimulation of pancreatic β-cells by antagonistic hormones [2, 11] (Table III).

Insulin resistance and thyroid disease

The presence of disorders of carbohydrate metabolism has been demonstrated in thyroid disease involving either overt hyperthyroidism or overt hypothyroidism [9]. The severity of the disease is proportional to the severity of these disorders. The possible influence of subclinical forms of both hyperthyroidism and hypothyroidism on carbohydrate disorders is still under discussion [9, 10, 12].

Hyperthyroidism

Hyperthyroidism is a condition characterised by an increase in the blood serum levels of thyroid hormones and their effect on tissues [9]. The condition involves a significant increase in the level of tissue metabolism. In order to adapt to the greater energy loss, both baseline and insulin-stimulated rate of cellular glucose depletion increases as a result of the more intense glucose oxidation and lactic acid formation, the latter of which is subsequently used by the liver to accelerate gluconeogenesis and the production of endogenous glucose [4, 13].

Clinical hyperthyroidism (HR) is often accompanied by abnormal glucose tolerance and insulin resistance [4, 13–15]. In approximately 50% of patients with hyperthyroidism, glucose tolerance disorders were observed, and 2–3% of patients had diabetes. In non-diabetic subjects, normal or increased fasting insulin, peptide C and proinsulin concentrations are observed, which is indicative of moderate peripheral insulin resistance [9]. This is associated with an increased insulin resistance in the liver, aggravation of general peripheral insulin resistance, and increased glucose uptake in muscles.

Overt hyperthyroidism increases the demand for insulin. It is associated with accelerated metabolism, tissue resistance to insulin and increased insulin degradation. In thyrotoxicosis, increased glucose absorption occurs in the digestive tract thanks to a higher rate of stomach emptying and increased blood flow in the portal vein, which leads to postprandial hyperglycaemia, characteristic of hyperthyroidism [16].

The effect of thyroid hormones on hepatocytes is antagonistic to insulin and stimulates glucose production in the liver (increases gluconeogenesis and glycogenolysis). In the conducted studies, it was demonstrated that thyrotoxicosis increases the production of endogenous glucose in the liver in baseline conditions (fasting state) and decreases the hepatic sensitivity to insulin. Observations indicate that thyroid hormones may have both a direct and an indirect effect on hepatic cells. The direct effect is achieved via alteration of transcription and translation of the genes responsible for gluconeogenesis and glycogen metabolism. Another mechanism by which thyroid hormones stimulate hepatic glucose production is based on the increased expression of the GLUT2 glucose transporter on hepatocyte plasma membranes. The indirect effect is achieved by increasing the activity of the parasympathetic nervous system, modulated by the hypothalamus, and its influence on hepatocytes [17].

Moreover, thyroid hormones promote lipolysis, thereby increasing the concentration of free fatty acids in blood and accelerating insulin degradation. In thyrotoxicosis, the high levels of triiodothyronine (fT$_3$) directly stimulate gluconeogenesis as a result of the increased activity of PEPCK (phosphoenolpyruvate carboxykinase).

In subjects with hyperthyroidism, lower peripheral tissue sensitivity to insulin and abnormal insulin secretion are also responsible for glucose metabolism disorders. Explaining the effect of hyperthyroidism on glucose utilisation in peripheral tissues is difficult due to the complexity of the problem. On the one hand, it was observed that the glucose uptake rate in peripheral tissues is increased by thyroid hormones, which suggests that glucose utilisation is considerably higher, especially

in skeletal muscles. This increased glucose utilisation is caused mainly by the higher level of glucose oxidation stimulated by insulin. On the other hand, it has also been observed that anaerobic glucose metabolism stimulated by insulin is inhibited, as glycogenogenesis decreases due to the 'redirection' of intracellular glucose to the process of glycolysis and generation of lactic acid. The lactic acid released from peripheral cells returns to the liver, where it becomes a substrate for the increased hepatic glucose production. The occurrence of glucose intolerance associated with hyperthyroidism may be explained simply by the hepatic type of insulin resistance. However, in some studies, impaired peripheral glucose uptake stimulated by insulin was demonstrated.

Alternatively, peripheral insulin resistance in hyperthyroidism may be explained by the increased secretion of bioactive mediators (adiponectins), such as interleukin-6 and TNF-alpha, by adipocytes. Higher levels of these adiponectins have been observed in women with hyperthyroidism [18].

It is observed that in hyperthyroidism, blood insulin levels may be lower, normal or even higher. Yet the results of different studies indicating an increased degradation of insulin in hyperthyroidism are quite consistent. It is also suggested that in long-term severe thyrotoxicosis, irreversible damage to the pancreas may occur.

Subclinical hyperthyroidism (SHR) is defined as decreased TSH levels accompanied by normal levels of fT_3 and fT_4. Among the studies conducted to date, those regarding insulin resistance in SHR are few and their results are controversial. Adamczyk et al. only observed a weak impairment of insulin sensitivity that was associated with the lower activity of plasma paraoxonase [9, 19]. Other authors, in their papers on iatrogenic SHR, describe a lower or unchanged level of insulin sensitivity. Endogenous subclinical hyperthyroidism, compared to the exogenous type, may have a greater effect on glucose metabolism as a result of the chronic nature of the disease and the observed higher T3 levels [20].

In their study, Maratou et al. [16] determined the presence of insulin resistance in both clinical and subclinical types of hyperthyroidism. The increased HOMA index and the decreased Matsuda and Belfiore indices in patients with HR and SHR, compared to euthyreoid patients, suggest that insulin resistance is present in either fasting or postprandial state. Similar results were presented in the papers by Yavuz et al. [19, 21], who observed a significantly lower insulin sensitivity in the SHR group. Similar results were presented by Roos et al. [22] who also determined that insignificantly (slightly) lower levels of thyroid hormones within the physiological range negatively correlate with the HOMA index.

This suggests that even small deviations from thyroid hormone balance may lead to insulin resistance [4, 22].

Hypothyroidism

Clinical hypothyroidism (HO) is considered to be an insulin resistance risk factor [6, 8, 23–26]. In hypothyroidism, a decrease in the intestinal glucose absorption rate occurs, along with a decrease in the adrenergic activity leading to a reduction in liver and muscle glycogenolysis, as well as a decrease in gluconeogenesis and baseline insulin secretion [6, 9]. However, a postprandial increase in insulin secretion against the background of generalised peripheral insulin resistance has been observed, associated with a higher concentration of free fatty acids, reduced glucose uptake and increased glucose oxidation [9].

There are fewer studies of the effect of hypothyroidism on glucose metabolism than those assessing insulin resistance in patients with hyperthyroidism.

Rochon et al. determined the sensitivity of all tissues to insulin in patients with hypothyroidism. The metabolic clamp technique was used in their study. They concluded that hypothyroidism causes a decrease in insulin-dependent glucose utilisation, which may be reversed via appropriate treatment [23]. Similar results were obtained by Stanicka et al. [27]. Handisurya et al. also confirmed the above results by assessing insulin resistance via the metabolic clamp technique, as well as assessing glucose tolerance and the activity of pancreatic beta-cells during an oral glucose tolerance test [10]. Dimitriadis et al. investigated glucose uptake by skeletal muscles and adipose tissue in subjects with hypothyroidism and a control group. Reduced ability of insulin to increase blood flow in tissues in hypothyroidism was observed. This may be an alternative mechanism explaining the effect of hypothyreosis on decreasing glucose utilisation by peripheral cells [8]. Brenta et al. observed that patients with hypothyroidism, compared to euthyreotic subjects, demonstrated a significantly lower glucose utilisation during a short intravenous insulin tolerance test [28].

However, there are studies that do not confirm the above observations. Owecki et al. did not demonstrate any correlation between hypothyroidism and insulin sensitivity in patients with overt hypothyroidism, based on the assessment of the HOMA-IR index [29].

Subclinical hypothyroidism (SHO) is defined as increased TSH levels in blood plasma accompanied by normal plasma levels of thyroid hormones (fT_3, fT_4) [9]. The data on the effect of insulin on glucose metabolism in this disease is ambiguous.

In their study, Maratou et al. suggested that insulin resistance not only affects patients with HO, but also

those with SHO. In both studied groups (HO and SHO) of overweight patients of average age 50 years (with average BMI of approximately 26 kg/m^2), compared to euthyreoid patients, increased HOMA index score and decreased Matsuda index score were detected [6].

These results are in line with other studies in patients with hypothyroidism [30–32]. Interestingly, a positive correlation between thyroid hormones and Matsuda index has been found, which suggests that lower levels of thyroid hormones lead to a lower sensitivity of tissues to insulin [6].

The lower fasting insulin sensitivity assessed using the HOMA index was also found lower in a number of other studies in patients with SHO [4, 10, 33]. Yet, the results of other studies indicate a normal insulin sensitivity in that group of patients [34, 35].

However, it should be noted that in some of these studies in which insulin resistance was not found in patients with SHO, fasting hyperinsulinaemia was reported [33, 36]. These observations may be interpreted as an early sign of impairment of glucose metabolism.

Conclusions

Thyroid hormones have a significant effect on glucose metabolism and the development of insulin resistance. In hyperthyroidism, impaired glucose tolerance may be the result of mainly hepatic insulin resistance, whereas in hypothyroidism, the available data suggests that the insulin resistance of peripheral tissues prevails.

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