

REVIEW PAPERS

PROBLEM OF THE INSULIN RESISTANCE IN SURGERY

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Insulin resistance is the reduced reactivity of peripheral tissues to insulin. Its measure is the ratio of the concentration of insulin acting on the cell to the volume of glucose assimilation, dependent of its concentration. In healthy subjects and normal insulinemia tissues consume 6.5-8 mg of glucose/ body weight/min (1-7). According to another definition, insulin resistance is considered as the condition of impaired biological tissue response to endo- and exogenous insulin, considering the metabolism of carbohydrates, lipids, and proteins (1-9). The reasons for the occurrence of clinical manifestations of insulin resistance have not yet been clearly defined.

The following factors are considered in the pathogenesis of insulin resistance:

- influence of genetic factors (2, 4, 6-12),
- influence of environmental factors (11-17),
- influence of inflammatory cytokines and adipokines (hormones secreted by adipose tissue) (7, 8, 9, 11-15),
- hypersecretion of hormones antagonistically affecting insulin (growth hormone, glucagons, glyccorticosteroids, catecholamines) (3, 6, 7, 8, 11-16, 18, 19, 20).

Considering pathophysiology the following types of insulin resistance are distinguished:

A. Receptor insulin resistance

The insulin receptor belongs to a group of growth factor receptors exhibiting tyrosine kinase activity. A molecule of the above-mentioned receptor is formed by two heterotetram-

ers consisting of two alpha and beta subunits. The connection of the insulin molecule and alpha subunit leads towards the phosphorylation of the beta subunit. This corresponds to the enzymatic cascade of the metabolic effect of insulin on a cell. In case of insulin resistance one may observe the reduced number of receptors. The above-mentioned is diagnosed in patients with type 2 diabetes mellitus where the number of receptors is reduced by 20-50%, as compared to healthy subjects (1-13, 15, 16, 17). Other factors in the pathophysiology of receptor insulin resistance are mentioned, considering the change of insulin affinity to the receptors and their mutations. However, the saturation of 10% of the total number of insulin receptors leads to the maximum shift of glucose into the cell (4-7, 11-14). Thus, the reduction in the number of receptors or receptor disturbances, are responsible for the decrease in glucose consumption.

B. Mechanisms connected with post-receptor insulin resistance

Insulin resistance leads to the modification of protein phosphorylation, and that of many genes, in particular, those maintaining the homeostasis of glucose, such as IRS proteins (IRS1, IRS2), as well as adapter Grb-2 and PI-3K proteins. This leads to diabetogenic changes in the metabolism of glucose, proteins and lipids (2-17). During the initial period reduced tissue insulin resistance is compensated by the hyperactivity of beta pancreatic cells and

hyperinsulinism (3-6, 13, 15, 17, 19). One must mention the post-receptor insulin signalization disturbances, which leads to impaired cellular GLUT translocation. This leads to decreased intracellular glucose transport. GLUT or glucose transporters are molecules, which are located inside the cell, and after receiving a signal-tyrosine kinase autophosphorylation move to take the role of cellular membrane glucose transport (7-10, 12-17). Available literature data mentioned GLUT translocation impairment. This problem is discussed particularly in regards to GLUT4. In case of type 2 diabetes mellitus, GLUT4 translocation stimulated by insulin is reduced by nearly 70%. Additionally, the insulin-stimulated intracellular GLUT translocation is impaired in patients exhibiting both normal glucose tolerance and type 2 diabetes mellitus (4-8, 9-16).

MECHANISMS RESPONSIBLE FOR THE DEVELOPMENT OF INSULIN RESISTANCE

1. Influence of genetic factors

In case of studies concerning insulin resistance numerous authors showed changes in the expression of hundreds of genes regulating the glucose and lipid metabolism. Recent publications demonstrated that the effect of the impact of genes is dependent on environmental factors and may be modified by them (10-17, 20). Additionally, monogenic forms of insulin resistance are relatively rare. They are mostly associated with mutations of the insulin receptor located on chromosome 19p13.2 (5-9, 10-14). In case of receptor dysfunction or intracellular signal disturbances, alpha or beta subunit mutations are most often observed. The change of Gln to Lys at position 460 of the alpha subunit, alpha chain mutations at position 15 (Lys to Asp), RECQL2 98p12-11.2 gene mutation, and many more lead towards insulin resistance (7, 10, 12, 18). The theory of polygenic predisposition to insulin resistance is being underlined more and more often. Previous studies concerning genes conditioning insulin resistance concerned the following: genes connected with insulin resistance mediators (PPAR- γ receptor, TNF- α , adiponectin, and Il-6 genes), genes encoding proteins involved in intracellular signal transduction (9 polymorphism of gene IRS- 1/2

(7-20), and FABP2, ABCG5 genes (3-7, 9-14).

2. Influence of environmental factors:

- age and gender: the frequency of glucose tolerance disturbances increases with age, as well as the male gender;
- physical activity: in the seventies of the twentieth century one already observed the beneficial effects of exercising on the improvement of tissue sensitivity to insulin. Physical exercise increases tissue sensitivity to insulin by 30%;
- diet: an important role is played by the caloric and qualitative composition of the diet. A high-protein diet leads to increased glucagon and insulin secretion in the pancreas, accelerates the turnover of glycogen, and stimulates gluconeogenesis. A high-fat diet leads to the accumulation of triglycerides and hyperinsulinism, due to entero-pancreatic axis stimulation. The excessive consumption of carbohydrates leads to post-prandial hyperglycemia and increased insulin secretion. Thus, hyperinsulinemia leads to the weakening of the activity of insulin on muscle tissue in particular (2, 4, 16);
- overweight and obesity: body weight influences the development of insulin resistance in case of patients with a BMI ≥ 26.8 kg/m² (4, 8, 9, 10, 11);
- the use of diabetogenic drugs: glycocorticosteroids, diuretics, HIV protease inhibitors, oral contraception;
- alcohol and smoking,
- pregnancy.

3. Metabolic disturbances:

- type 2 diabetes mellitus,
- impaired glucose tolerance,
- impaired fasting glycemia,
- dyslipidemia.

4. Disease entities: insulin resistance accompanies most known inflammatory and neoplastic disorders, as well as organ insufficiency (8-12).

5. Hypersecretion of hormones antagonistically affecting insulin: growth hormone, glucagon, glycocorticosteroids, catecholamines and cortisol (3, 6, 9).

6. Influence of insulin resistance mediators and pro-inflammatory cytokines during meta-

bolic stress: CRP protein, TNF- α , Il-1, Il-6, adiponectin, lectin, resistin, Tanis protein (1-7, 9-11).

METHODS USED IN THE DETERMINATION OF INSULIN RESISTANCE

Methods used in the determination of insulin resistance include the following:

1. Fasting insulin level

The simplest parameter that can indicate the occurrence of insulin resistance. The following rule applies: the higher the insulin level the higher the degree of insulin resistance (1-8).

2. Indirect indices of insulin resistance based on the assessment of insulin and glucose levels:

– Homeostasis Model Assessment- Insulin Resistance (Homa IR)

$$\text{Homa IR} = \text{glucose} \times \text{insulin} / 22.5 \quad (1-9).$$

– Quantitative Insulin Sensitivity Check Index (QUICKI)

$$\text{QUICKI} = 1 / (\log \{ \text{glucose} \} + \log \{ \text{insulin} \}) \quad (1-7, 10-18).$$

– Modified Homa IR index determined using the Homa2 calculator

3. Insulin tolerance test

4. Endogenous insulin suppression test

5. The hyperinsulinemic and normoglycemic „buckle”. It was introduced in 1979. It involves the measurement of the amount of glucose needed to maintain stable glucose levels (normoglycemia) in experimental hyperinsulinemia conditions. Due to technical difficulties this method is only used for research purposes (1-8).

PERIOPERATIVE INSULIN RESISTANCE

When discussing the reasons of perioperative insulin resistance one must go back nearly 100 years to the second half of the nineteenth century. In 1877, Claude Bernard presented the problem of glucose metabolism disturbances occurring in case of hemorrhage (20). To this day, the above-mentioned is one of the best known reasons for the increase of insulin resistance. Other conditions responsible for the increase include multi-organ injuries and sepsis, acute liver insufficiency (20-30), and burn wounds (20-30).

All these studies speak for the metabolic stress as the cause of insulin resistance. At the

end of the nineties of the twentieth century Thorell and co-authors (20-27) investigated patients subject to planned inguinal hernioplasty and laparoscopic cholecystectomies. In case of the above-mentioned minimally invasive procedures one observed significant post-operative increase in insulin resistance. Patients subject to classical cholecystectomy comprised yet another group. Significant increase in insulin resistance persisted for at least 10 days (maximum 20 days). Based on the above-mentioned investigations one may conclude that the degree of insulin resistance depends on the extent of surgery (20-27).

Preoperative fasting is yet another mentioned problem, including short-lasting fasting connected with anesthesia, and long-lasting fasting which is connected with the course of the neoplastic disease. The surgical procedure and the time thereafter are also considered as injury type fasting (20-30). Therefore, the following determinants of perioperative insulin resistance may be presented:

1. The surgical procedure as a controlled injury

During the operation one may observe an increased secretion of many pro-inflammatory cytokines (Il-1, Il-6, TNF- α , CRP protein and others). In case of Il-1 and Il-6 one may observe the increased secretion of glucagon and cortisol. TNF- α is an insulin receptor inhibitor, which inhibits the phosphorylation of the above-mentioned receptor.

2. Perioperative fasting

In connection with the preoperative fasting period during surgery, one may observe the conversion of the carbohydrate metabolism of exogenous glucose to the metabolism of glycogen stored inside the liver. This phenomenon is one of many determinants of insulin resistance. Glucagon is mainly responsible for the above-mentioned under the authorization of cortisol. One must distinguish three types of fasting connected with the characteristics of patients subject to surgery, due to digestive tract carcinomas.

A – simple fasting before surgery leads to the reduction of insulin secretion and increase of glucagon and catecholamine secretion, which increases glycolysis and proteolysis;

B – stress fasting is a phenomenon where in addition to fasting one may observe the body's metabolic response to trauma. Increased liver gluconeogenesis is observed. Substrates include amino acids derived mainly from muscular proteolysis, lactates and pyruvates, as well as glycerol derived from lipolysis. The process is so strong that the supply of intravenous glucose does not suppress gluconeogenesis, and only enhances the effect of insulin resistance;

C – prolonged fasting- associated with the debilitating course of the neoplastic disease, due to catabolism.

Different factors that stimulate one another are required in case of perioperative insulin resistance. During the surgical procedure one may observe endocrine changes associated with increased secretion of catabolic hormones (cortisol, catecholamines, glucagon), and insulin activity weakening. These processes are further intensified by the action of pro-inflammatory cytokines. Glycogenolysis and increased liver gluconeogenesis provide glucose supply to gluco-dependent tissues.

In case of skeletal muscles insulin resistance both inhibits glucose uptake and transport. Paradoxically, it provides continuous *de novo* production and storage under the form of glycogen. Increased lipolysis provides free fatty acids and glycerol for gluconeogenesis.

The increased level of free fatty acids additionally intensifies insulin resistance. This is connected with the smaller response of liver cells to the hormone (20-30).

The problem of perioperative insulin resistance and its consequences is still being marginalized in everyday clinical practice. Investigations which were carried out to date have been mainly focused on the confirmation of its occurrence. As for attempts to prevent insulin resistance they only concerned patients undergoing minor surgical procedures. This might be connected with the determination of insulin resistance, due to the absence of an easy and reliable method. Another reason might be connected with the absence of large prospective studies demonstrating the problem and associated clinical implications. Based on the meta-analyses, glucose control and insulin resistance prevention might reduce patient mortality by 4-8%, as well as shorten the hospitalization period (30-35).

However, available studies have examined different patient groups, both treated surgically and those after myocardial infarction or trauma. The same situation was observed in regards to target blood glucose levels, which ranged between 90-180 mg/dl. The only conclusions drawn concern the issue of maintaining the glucose level below 150 mg/dl, as well as rational insulin therapy (30-35).

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Received: 20.10.2010 r.

Adress correspondence: 15-276 Białystok, ul. M. Skłodowskiej-Curie 24a