

Diabetes: Insulin Resistance

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Abstract

In the years prior to the onset of DM2 symptoms, despite insulin resistance being observed, there is an increase in insulin secretion, that is, compensatory hyperinsulinemia, maintaining normal glycemic concentrations until dysfunctions occur in beta cells and inability to control glycemia thus leading diagnosis of DM2 (CEFALU, 2001).

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Introduction

Different researchers have observed that subjects with insulin resistance show changes in energy metabolism. [1] Showed that in overweight women the insulin resistant group oxidized less carbohydrates than the control group [2]. Observed in type 2 diabetics, obese, a reduction in the oxidation of plasma fatty acids, but without differences in the total oxidation of fats and carbohydrates, when compared to the control group. In another study [3] studied non-obese type 2 diabetic patients. In this study, no changes were found in the oxidation of fats or carbohydrates. It should be noted in the last two studies cited that the subjects were type 2 diabetic, therefore, hyperglycemic. A characteristic common to almost all studies that measured the substrate balance in subjects with insulin resistance, diabetes and obesity was the use of fixed percentages of VO₂ max to control the intensity. However studies have shown great inter-individual differences in the use of fats during exercise [4]. Observed that bottom cyclists reached the maximum fat oxidation rate (Fat max) at intensities that ranged from 42 to 84% (64 ± 4%) of VO₂ max [5] also measured the fat max of triathletes and cyclists and related it to plasma lactate. Fat max was found at an intensity of 63 ± 9% and the lactate threshold at 61 ± 5%, with no significant differences between the two. Although the Fat max variation was not reported in the study, it was probably greater than that observed in the previous study due to the high standard deviation, once again highlighting the inter-individual differences in this variable. Given these results it can be speculated that it is possible that the maximum rate of oxidation of fats occurs at different intensities in people resistant to insulin, but the absolute oxidation of fats and carbohydrates is not different from that of people sensitive to insulin, when the intensity of exercise is controlled by the maximum fat oxidation rate or by the anaerobic threshold. The study by [6] supports this hypothesis. In this study, it was observed that the crossover point (point where the relative contribution of carbohydrate metabolism exceeds that of fat in energy production) occurred at significantly lower intensities in overweight subjects when compared to subjects with normal weight and the maximum rate of Fat oxidation also occurred at significantly lower intensities. However, to date, there are no studies showing whether it occurs

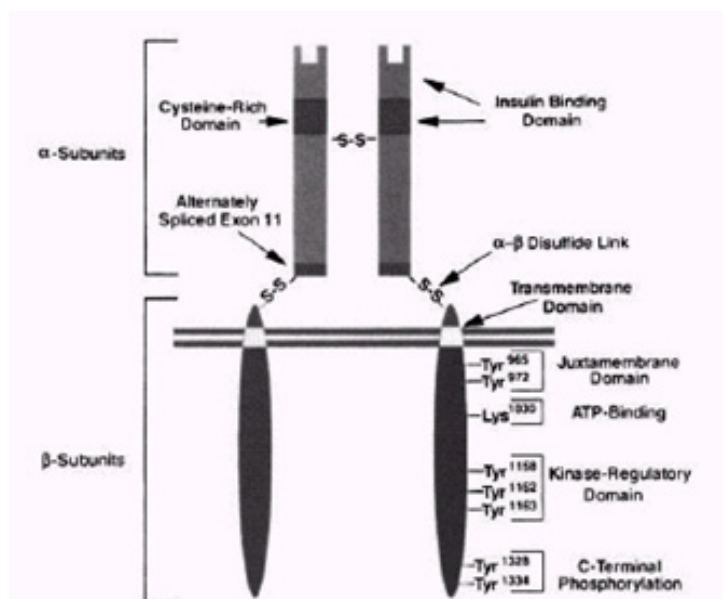
Insulin Resistance

[7] Insulin resistance is defined as a medical condition in which normal or elevated insulin concentration produces an attenuated

biological response. Such abnormality occurs mainly due to the defective action of insulin in peripheral tissues sensitive to insulin such as: adipose, muscular and hepatic tissue [8].

Insulin Signaling Mechanisms

Insulin triggers several metabolic processes in cells by binding to receptors on the cell surface. Such receptors are found in tissues classically sensitive to insulin such as muscle, liver and adipocytes and also in tissues that are traditionally seen as non-insulin sensitive such as the brain, erythrocytes and gonads. [9]. The insulin receptor is a heterotetrameric protein with kinase activity, composed of two subunits α and two β , linked by disulfide bridges forming a $\alpha_2\beta_2$ (Figure 2.1). The α subunit contains the insulin binding domain, while the β subunit has insulin-stimulated tyrosine kinase activity [10].



Source: Cheatham E Kahn (1995)

Figure 1: Structure of the insulin receptor

When insulin binds to the sub subunit of the receptor, it causes conformational changes in the receptor, leading to stimulation of the kinase activity of the unidate subunit. Once the sub subunit is activated, it auto phosphorylates in at least six tyrosine sites. Following activation, the insulin receptor stimulates the transfer of phosphate groups to tyrosine on intracellular substrates of the receptor [9]. The first substrate to be characterized was called the insulin receptor substrate 1 (IRS-1). Currently, ten insulin receptor substrates have been identified [11], among them IRS-1, IRS-2, IRS-3, Gab-1 and SHC. Spread by the IRS are several tyrosine phosphorylation sites activated by insulin stimulation. This phosphorylation of the IRS allows it to bind to certain proteins, among which stands out an enzyme called phosphatidylinositol 3-kinase (PI 3-kinase) which is considered the major link between IRS1 and the metabolic effects of insulin [9] and the only intracellular molecule considered essential for the transport of glucose [12]. PI 3-kinase consists of two subunits: a regulatory one (p85) that allows its connection to the IRS and a catalytic one (p110). The activation of PI 3-kinase is associated with the triggering of several metabolic processes such as increased GLUT-4 translocation for glucose uptake, glycogen synthesis and protein synthesis.

Glucose uptake by cells

One of the processes triggered in the cell by the action of insulin is the uptake of blood glucose. To enter cells, glucose must be carried by specific transporters. These transporters are called GLUT (glucose transporter) and consist of a group of 5 transmembrane proteins: GLUT 1, 2, 3, 4 and 5 that are found in different tissues [13]:

- GLUT 1 - Widely expressed; high concentrations in the brain, erythrocytes and endothelial cells. It is the constitutive glucose transporter.
- GLUT 2 - Found in the kidneys, small intestine, epithelium, liver and β -pancreatic cells. It has low glucose affinity and plays a role in modulating pancreatic islets to glucose concentration.
- GLUT 3 - Found in neurons and placenta. It has a high affinity for glucose.
- GLUT 4 - Found in skeletal muscle, cardiac muscle and adipose tissue. It is the insulin-responsive glucose transporter.
- GLUT 5 - Found in the small intestine, sperm, kidneys, brain, and fat and muscle tissue. It is the fructose transporter and has a low affinity for glucose.

The only insulin-dependent glucose transporter to perform its action is GLUT 4. As seen, this transporter is found mainly in muscles and adipose tissue, and as muscle is the main tissue responsible for the uptake of blood glucose the action of insulin becomes of great importance for the maintenance of blood glucose. In the absence of a stimulus such as insulin (or exercise), approximately 90% of GLUT 4 is stored within specific intracellular vesicles. In the presence of a stimulus, GLUT 4 moves out of these vesicles, Trans locating to the cell surface and connecting to the membrane to capture glucose [12, 13]. In the case of glucose uptake stimulated by insulin, GLUT 4 translocation occurs due to the activation of PI 3-kinase, however studies have shown that exercise has a stimulating effect on LUT 4 translocation even in the absence of insulin. [14] Observed, for the first time, in muscles isolated from rats submitted to electro stimulation that glucose uptake increased by up to 5 times, regardless of the presence of insulin, contrary to what was believed until then, that a minimum of insulin would be needed for the increase in glucose uptake observed during muscle contraction. In another study [15] also using muscles of rats, it was demonstrated that both insulin and muscle contraction stimulated glucose uptake via GLUT 4. In the same study, the authors raised the hypothesis that there are two “pools” different from GLUT 4, one sensitive to insulin and the other sensitive to contraction. In a study with humans, [16] studied the translocation of GLUT 4 after a session of 45 to 60 minutes of exercise on a cycle ergometer at 60 to 70% of VO₂max in normal subjects with DM2. The content of GLUT 4 present in the membrane increased by $74 \pm 20\%$ in patients with DM2 and $71 \pm 18\%$ in normal subjects. These results showed that despite defects in the mechanisms responsible for glucose uptake via insulin, DM2 patients are responsive to exercise-induced GLUT 4 translocation. Since the translocation of GLUT 4 into skeletal muscle, via the insulin-dependent mechanism, is mediated by the activation of PI-3 kinase, this pathway is

Mechanisms Involved in Insulin Resistance

Insulin resistance occurs when circulating insulin concentrations are not sufficient to properly regulate its processes, resulting from a defect in signal transduction [17]. Although the specific cause of insulin resistance is unknown, it is known that problems in lipid metabolism, and in particular an increase in the availability of lipids, are strongly related, suggesting that the increase in the availability of lipids may upset the interaction between fat metabolism and carbohydrates [18].

It is known that in addition to hyperglycemia, the individual with DM2 almost invariably presents disturbances in fat metabolism, often reflected by high concentrations of circulating FFA and TAG, in addition to excessive fat deposition in various tissues, including muscle [19]. An example of this are several studies that have shown a strong correlation between intramiocellular triglycerides and insulin resistance [20]. Studied young adults with normal weight, using Proton Magnetic Resonance Spectroscopy (1H-ERM) for the determination of intramiocellular triglycerides and the euglycemic-hyperinsulinemic clamp for the determination of insulin sensitivity. The authors found a correlation of $r = -0.692$ between the two parameters (Figure 2).

In another study [21] using the same techniques as the previous study showed that children of DM2 patients had significantly higher concentrations of intramiocellular triglycerides and insulin resistance than subjects without a family history of DM2. This increase in intramiocellular triglyceride content seems to be associated with a reduction in insulin receptor phosphorylation and in Pi 3-kinase activity associated with IRS-1 [22].

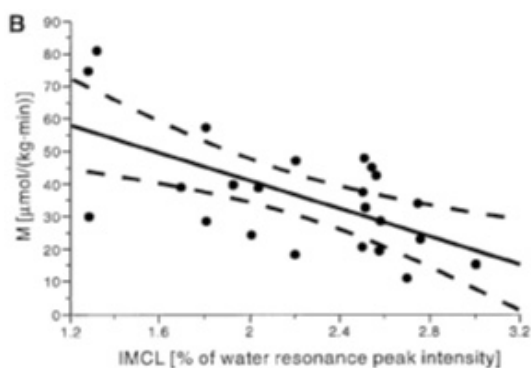


Figure 2: Correlation between insulin sensitivity and the content of intramyocellular triacylglycerides

Several hypotheses have been raised to explain the mechanism by which high concentrations of lipids could cause insulin resistance, the best known being the glucose-fatty acid cycle proposed by Randle in 1963 (Figure 3). According to this hypothesis, an increase in fatty acid concentrations results in an increase in the intramitochondrial proportions of acetyl CoA / CoA and NADH / NAD + leading to a deactivation of the enzyme pyruvate dehydrogenase, an increase in citrate concentrations and inhibiting phosphofrutokinase, a key enzyme in the control glucose. Increases in glucose-6-phosphate concentrations would inhibit the activity of the hexokinase II enzyme, resulting in an increase in intracellular glucose concentrations and thus decreasing glucose uptake [23].

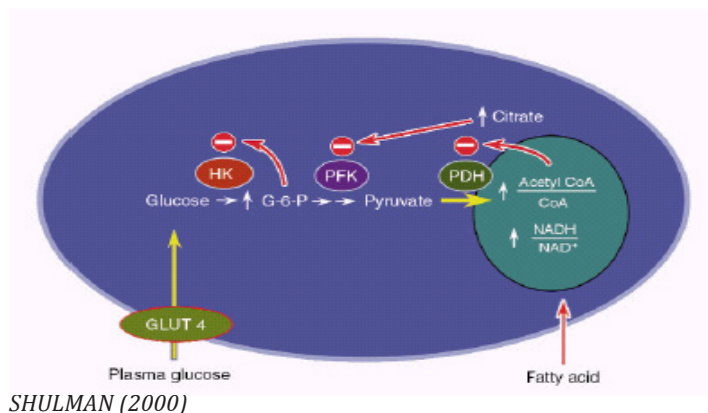


Figure 3: The fatty acid glucose cycle

Recent studies using Magnetic Resonance Spectroscopy (ERM) have proposed an alternative hypothesis to the fatty acid glucose cycle. [24] Observed with a lipid infusion, in contrast to the Randle cycle, a drop in glucose-6-phosphate concentrations accompanied by a ~ 40% reduction in glucose oxidation. In another study [25] measured, using 13C ERM (carbon magnetic resonance spectroscopy), intracellular glucose concentrations after lipid infusion. The authors found a significant reduction in intracellular glucose concentrations after lipid infusion, showing that hexokinase II activity was not reduced, which again goes against the Randle mechanism. The authors argue that such findings suggest that the infusion of lipids caused insulin resistance through an inhibition of glucose transport activity, since in the same study, a reduction in the activity of IRS-1 associated with PI 3-kinase was observed.

From these studies, the following mechanism was proposed (Figure 4), by which the increased availability of fatty acids could induce insulin resistance [23].

An increase in the availability of fatty acids to the cell or a reduction in the intracellular metabolism of fatty acids leads to an

increase in their quantity and their metabolites (diacylglycerol, fatty acyl CoA and ceramides). These metabolites activate a cascade of phosphorylation in serine and threonine of the insulin receptor substrates (IRS1, IRS2), probably triggered by the protein kinase theta. The phosphorylation of insulin receptor substrates in serine and threonine reduces its activation action of PI 3-kinase, thus reducing the effects of insulin such as glucose transport [23].

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