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Diabetes & its Complications

Insulin Resistance - Pathogenesis of Prevention and Treatment

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Diabetes, Insulin resistance, Exercise, Pyruvate.

Introduction
Diabetes is another major global health problem. For example, this is the case for the death of 1 million deaths per year. In 2013, the International Diabetes Federation (IDF) reported that 382 million, by 2035 [1,2]. It will be estimated that it will be approximately 250 million people affected by type 2 diabetes mellitus worldwide [3].

Insulin resistance (IR) is manifested by reducing the ability of insulin to activate the insulin signaling pathway [4,5]. At the molecular level, IR is characterized by diverse alterations in various intracellular signaling pathways. In fact, it has been shown that insulin signaling is impaired in the liver, muscle, adipose tissue, hypothalamus, and others tissues, in IR states [6]. While there are several biological events that can lead to the impairment of the insulin signaling pathway, chronic inflammation is perhaps the best described. Several factors have been proposed to explain the mechanisms of insulin resistance. These include: (a) obesity; (b) inflammation; (c) mitochondrial dysfunction; (d) hyperinsulinemia; (e) lipotoxicity/hyperlipidemia; (f) genetic background; (g) endoplasmic reticulum stress; (h) aging; (i) oxidative stress; (j) fatty liver; (k) hypoxia; (l) lipodystrophy; (m) pregnancy. Although the primary factors causing this disease are unknown, it is clear that insulin resistance plays a major role in its development.

Since the last century, all recommendations for diabetics have been based on indications of limiting carbohydrate intake (diet) and an increase in their utilization (exercise). It would seem that everything is simple, but a person is a weak creature and he wants to eat and lie down on the couch and therefore the number of people with diabetes increases from year to year. Diabetics do not understand why some people can do everything - eat as much as you like and lie on the sofa and have normal blood sugar levels, and they have to limit themselves in everything that often contributes to the development of a stressful state and increased glycemia.

Diabetes is a metabolic disease associated with impaired metabolism of proteins, fats and carbohydrates. However, most authors believe that diabetes is primarily a violation of carbohydrate metabolism (glucose). Glucose is the main source of energy, since the brain and blood cells use only glucose as an energy source, and only glucose can supply ATP energy under anaerobic conditions. Therefore, all regulatory systems, all types of metabolism (Figure 1) are involved in maintaining glucose homeostasis.

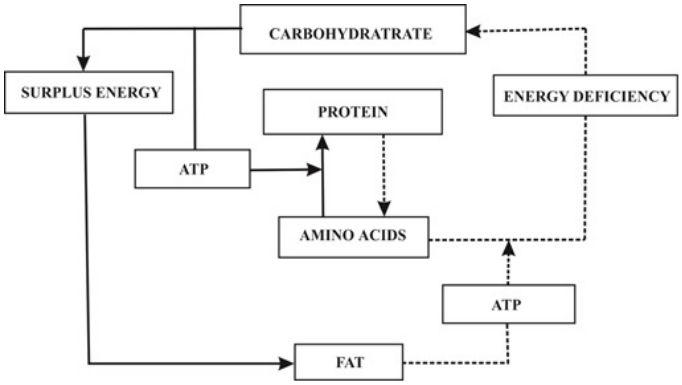

Figure 1: Model of the relationship between the metabolism of proteins, fats and carbohydrates with excess (→) and insufficient (···>) provision in glucose.

Figure 1 presents a conceptual model of the relationship between the metabolism of proteins, fats and carbohydrates, depending on the carbon skeleton transport pathways and the stages of the relationship between the processes of formation and utilization of ATP energy at different levels of the body's supply of glucose. After

a meal (surplus energy), a state of excess energy (glucose) occurs. Informational signals of the magnitude of excess glucose is the hormone insulin, the purpose of which is to activate the metabolic pathways to eliminate this excess. It is known that it is essential for the use of whole-body glucose homeostasis. This is a hormone is secreted by the cells of the pancreatic islets. Insulin regulates glucose homeostasis at many sites, contributes to the deposition of glucose (muscle glycogen), reducing the amount of glucose uptake, primarily striated muscle and adipose tissue.

With low physical activity decreases the use of muscle glycogen and, consequently, reduces the need for its recovery. Therefore, in patients with diabetes, the glycogenesis value is reduced [7]. The most expedient way is to use the extra energy flow to the processes of rehabilitation or restoration of worn protein and cellular structures through the activation of the protein synthesis process. According to the proposed relationship model, a correlation is noted between the processes of energy production and protein synthesis. It lies in the fact that if the diet contains an excess of carbohydrates, then the amount of their flow is higher than the possibility of using their energy in the process of protein synthesis, therefore, the "discharge" of the carbon skeleton of glucose into fats or lipogenesis is activated. On the contrary, with insufficient content in the diet of carbohydrates, the amount of ATP energy production decreases and the possibility of including amino acids in proteins decreases, which leads to their accumulation or hyperamino acidemia develops. These aspects need to be considered when developing a diet for people with diabetes.

When glucose is in excess, alternative pathways of its metabolism are activated, in particular, its conversion to fructose and sorbitol is enhanced. However, the accumulation of poorly digestible sugars in the cell leads to the formation of conglomerates and cell deterioration, especially in tissues with low metabolic activity, as in the pupil this leads to the formation of cataracts, and in the nervous tissue the development of polyneuritis. Therefore, the cell must protect itself from excessive glucose intake through the development of IR, which will be an adaptive response against the negative effects of an excess glucose flux.

Excessive glucose flow and activation of alternative ways of its utilization also occurs when the amount of glucose oxidation decreases. Special attention should be paid to this aspect of glucose metabolism. The first stage of glucose oxidation is anaerobic glycolysis, therefore, this stage is under the regulation of many factors, in particular, under the influence of insulin [8].

Glycolysis proceeds with the expenditure of two ATP molecules for the phosphorylation of glucose and fructose-6-phosphate [9]. The cell will not be wasting energy, i.e. these are important steps in glucose metabolism and must be tightly controlled in the cell. Therefore, to pass glucose into the cell, appropriate "block posts" are put, which control the cell's need for glucose. Hexokinase is involved in glucose phosphorylation, so the first control is at the level of its activity and, on the contrary, the accumulation of its reaction product (glucose-6-phosphate) on the basis of feedback inhibits the activity of the enzyme [10]. The second post block is the regulation of glycolysis at the second stage of phosphorylation [11]. In this article we will not dwell on the final product of glycolysis of pyruvic acid (pyruvate).

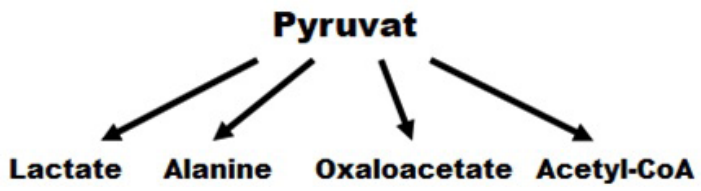

Figure 2: Ways to make pyruvate.

- With the participation of Lactate dehydrogenase, pyruvate is converted into lactic acid (lactate);
- With the participation of Alanine aminotransferase, pyruvate is converted to the amino acid alanine;
- With the participation of Pyruvate carboxylase, pyruvate is converted to oxaloacetate;
- With the participation of Pyruvate dehydrogenase, pyruvate is converted to Acetyl-CoA.

Therefore, a violation of the metabolism of pyruvate leads to the development of a number of diseases [12]. It is known that all compounds lying at the crossroads of metabolic pathways in the body should be maintained at the homeostatic level, therefore the process of its formation is inhibited by the feedback principle, i.e. glycolysis ("pyruvate block") is inhibited and, accordingly, glucose utilization decreases or IR develops.

In the body at the same time work all the ways of turning pyruvate. When recovering pyruvate to lactate, the recovered equivalents formed during glycolysis are used. This is not a very economical way of glucose oxidation, since it only releases 7% of the energy of chemical bonds of glucose, but this is an important stage of life preservation, as the NAD/NAD.H2 factor is maintained (an important aspect of life preservation), but this leads to a decrease in the substrate (pyruvate) for other metabolic processes.

Under anaerobic conditions, pyruvate can also turn into alanine during transamination. Branched chain amino acids (leucine, valine, isoleucine) act as substrates for the supplier of amino groups for transamination; therefore, the intake of these amino acids leads to an increase in the utilization of pyruvate and is the prevention of diabetes [13]. In these cases, branched-chain amino acids, and especially leucine, will act as an informational molecule to enhance protein synthesis during the transcription and translation stages [14].

Under aerobic conditions, pyruvate can add carbon (carboxylate to oxaloacetate) or release carbon (decarboxylate to acetyl CoA). Vitamin B1, magnesium, lipoic acid are involved as cofactors in carboxylase and pyruvate dehydrogenase activities; therefore, their deficiency impairs the activity of these enzymes, decreases the amount of pyruvate utilization, and develops a pyruvate block; therefore, there are many data on the deficiency of these

compounds in people with diabetes and obesity [15-18].

If oxaloacetate and acetyl-CoA can enter the mitochondria, but the structural and functional activity of mitochondria is impaired or the possibility of including oxaloacetate and acetyl-CoA is reduced in the tricarboxylic acid cycle (TCA), the principle of feedback again turns on and the process of pyruvate conversion is automatically broken in oxaloacetate and acetyl CoA. Indeed, in patients with diabetes, structural changes in mitochondria are detected [19]. Reducing the inclusion of pyruvate in oxaloacetate and acetyl-CoA will lead to the restoration of pyruvate in lactate, so the level of lactate in patients with diabetes and obesity is increased [20]. From this point of view, when the process of glucose oxidation is disturbed, the accumulation of its exchange intermediators occurs, which, by the principle of feedback, inhibit the entry of glucose into the cell or manifestations of IR are detected.

At the level of acetyl-CoA formation, there can be competition for its formation between proteins, fats and carbohydrates (Figure 3).

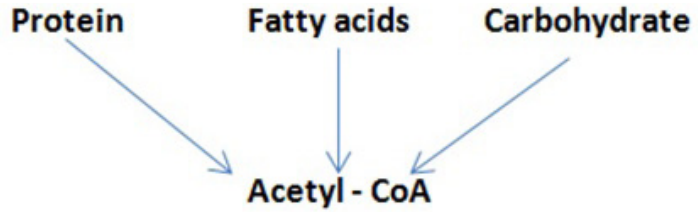

Figure 3: Scheme of the competitive influence of macronutrients on the level of acetyl-CoA formation.

In biochemistry, the ability to form one substrate from different compounds is usually considered as the principle of interchangeability of nutrients, but in fact one macronutrient will compete for the formation of a substrate with others. The most widely considered in this plan is the competition between carbohydrates and fats or the so-called cycle Rendla (glucose - fatty acids). The cheapest and most significant source of acetyl-CoA formation is fats, therefore, when carbohydrates and fats are supplied with food, the body will preferably choose fats and therefore decrease the amount of glucose utilization by tissues, i.e. manifestations of IR are detected [21].

In relation to competition between carbohydrates and proteins, a double situation may arise. Carbohydrates supply energy to protein synthesis. In this case, there is a direct correlation between them and proteins (amino acids), or proteins will increase the need for glucose energy and reduce IR. This is well manifested in the example of giving branched amino acids, especially leucine, which exhibits anabolic characteristics and thereby increases the need for glucose energy. But, in cases of a decrease in the rate of protein synthesis, leucine will not be able to increase protein synthesis and, accordingly, facilitate glucose utilization. In these cases, it will act as a competitor for the formation of acetyl CoA and lead to a competitive decrease in glucose utilization, i.e. promote the development of hyperglycemia and IR [22]. The level of branched amino acids in the protein is the highest, so they are an informational signal about the substrate capability of the protein synthesis process, which is usually accomplished by insulin secretion. But, if there is no substrate (low protein nutrition or deficiency of essential amino acids), then an information error occurs when taking branched amino acids or leucine, i.e. in reality, there are simply not enough amino acids to build a protein. The same picture is observed at a high rate of protein breakdown. In these cases, an increase in the concentration of branched amino acids is detected in the blood, but the rate of protein synthesis is reduced, which is noted with an increase in the level of inflammatory cytokines, under various catabolic states. Therefore, in these cases, the giving of branched amino acids will lead to competition for the possibility to form acetyl-CoA and a decrease in the use of glucose for these purposes, which leads to an increase in blood glucose and manifestations of IR are noted [23].

Since according to the proposed interconnection model, the need for glucose largely depends on the magnitude of the energy requirement of the protein synthesis process, the magnitude of protein synthesis will correlate with the cell's need for glucose energy and, accordingly, correlate back to IR.

Energy balance is an important component of life, so it must be under the dynamic control of all regulatory systems. In recent years, the cytokine system has been of particular interest in terms of energy balance regulation. All insulin-dependent tissues provide information about their energy balance through the secretion of cytokines: muscle tissue secretes myokins, liver tissue - hepatokins, adipose tissue - adipokines, which allow you to cooperate to maintain energy balance. Since muscles define 70–80% of insulin-stimulated glucose uptake [24], they act as a conductor in the general chorus of insulin-dependent tissues in the regulation of energy homeostasis. During exercise, the muscle's need for energy is increased; the signal is the release of myokin IL-10, which is an information signal for glucose supply from the liver (gluconeogenesis is activated) and fatty acids from adipose tissue (lipolysis is activated).

With a decrease in physical activity (hypokinesia), the muscle's need for energy substrates decreases and it secretes IL-6 myokin, which inhibits gluconeogenesis and lipolysis. In these cases, the excess flow of energetic material is transferred to the fatty tissue. An increase in the number and size of adipocytes leads to a deterioration in their blood supply or the development of hypoxia, which contributes to the activation of HIF (hypoxia inducing factor). To improve the nutrition of adipocytes, activation of the vascular factor (VEGF) takes place, and to reduce the negative effect of excessive lipid accumulation, lipogenesis is adaptively inhibited due to the development of IR for adipose tissue.

Suppression of gluconeogenesis in the liver will contribute to the development of hypoglycemia and the deterioration of the energy supply of brain activity. Therefore, IR for the liver in a certain way can also be considered as an adaptive response to maintain the energy supply of the brain, so strong hypoglycemia leads to brain cell death and death.

Conclusion

Thus, all principles of competitive interaction between substrates, all regulatory systems are involved in the mechanism of regulation of glucose homeostasis and the development of IR. These aspects need to be considered when developing preventive and curative measures.

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