Causes of insulin resistance - beware of gray literature!

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The gray literature suggests that insulin resistance is caused by a high-fat diet rather than excessive carbohydrate consumption. Obviously, this statement is wrong, or caused by the vegan beliefs of some nutritionists. Next, we will discuss for everyone's understanding, roughly, the mechanism that leads to the development of insulin resistance, as well as that of increasing insulin sensitivity in the healthy individual.

Excessive consumption of carbohydrates, especially consumption of refined carbohydrates, glucose or sucrose, leads to an abundant discharge of insulin into the blood. Insulin will facilitate the entry of glucose into the muscle and liver cells, together with the amino acids necessary for protein synthesis. This process is possible due to the existence of insulin receptors on the surface of muscle and liver cells (Figure 1). Continuing this process for a reasonable amount of time will lead to the complete filling of the muscles with glycogen and muscle anabolism (muscle growth). Continuing this process for a longer period of time can lead to somewhat reversed effects, namely insulin resistance. Why? The human body has incredible self-regulatory capabilities. Once the muscles have completely filled their glycogen stores, but the glucose level is still high in the blood, the body will try to limit the entry of glucose into the muscle and liver cells by limiting the abundance of insulin receptors on the cell surface. Thus, although high blood sugar discharges equally large amounts of insulin into the blood, the rarefied receptors will internalize the insulin signal with increasing difficulty. The glucose level will rise more and the pancreas will release more insulin into the blood. In parallel, cells will refuse glucose by drastically reducing the number of insulin receptors (Yaribeygi et al 2019). Anti-insulin receptor antibodies have been detected in the blood of some diabetics (Ashraf et al 2021). These antibodies have the role of numerically reducing the insulin receptors on the cell surface. Thus, excess glucose and fats absorbed into the blood will be directed to adipocytes (ie, stored as abdominal fat, visceral fat, etc). Basically, no matter how much an individual with insulin resistance eats, his muscle and liver cells refuse to assimilate any more glucose. Thus, it goes from muscle anabolism to muscle catabolism, caused by insulin resistance.

Insulin resistance can occur in healthy individuals, but it can present gradual forms of severity, leading to pathological forms in the case of diabetics. Assuming that the individual with insulin resistance is relatively healthy and will limit the consumption of high glycemic index carbohydrates, preferentially consuming fat as an energy source, then blood glucose levels will drop considerably. This drop in blood sugar will lead to a significant drop in insulin in the blood, because in the absence of high blood sugar, insulin is no longer needed. Decreased insulin production will deplete muscle and liver glycogen and starve muscle cells. The shortage of glycogen will send alarm signals throughout the

body, which will trigger the increase in the number of insulin receptors on the surface of the muscle cells in order to internalize the insulin signal as best as possible. Basically, the muscles will absorb even that little glucose from the blood, even at a low insulin level in the blood. Thus, a high insulin sensitivity and muscle anabolism are established in conditions of glucose deficiency (Luukkonen et al 2020). The body will switch to gluconeogenesis, making glucose from lipids and amino acids. This insulin sensitivity will not be lost as soon as the body again receives an abundance of carbohydrates, but only after this abundance persists even after the full restoration of glycogen stores.

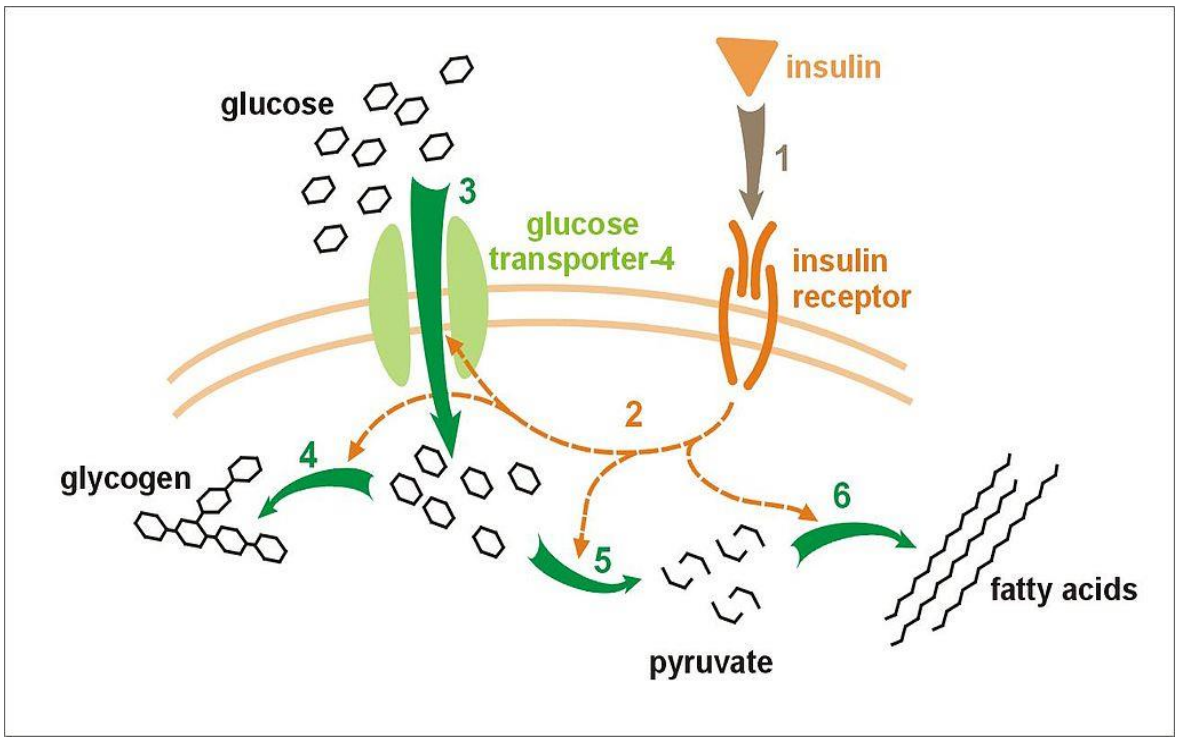

Figure1. Effect of insulin on glucose uptake and metabolism. Insulin is binding to the receptor (1), thus starting a cascade of protein activation (2). These include: translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5), and fatty acid synthesis (6) (source: User Meiquer, CC BY-SA 3.0 <http://creativecommons.org/licenses/by-sa/3.0/>, via Wikimedia Commons).

As a conclusion, high-fat, low-carbohydrate diet cannot generate insulin resistance, but on the contrary, it generates insulin sensitivity (Jani et al 2022; O'Neill 2020). Yes, it's true, obesity can facilitate insulin resistance (Wu & Ballantyne 2020). But it is important to distinguish between high-fat diet and obesity. An individual following a low carb or ketogenic diet is not necessarily an obese individual.

As good news for those of the vegan persuasion, with a diet based on vegetables, fruits and greens, these foods have little potential to raise blood sugar to dangerous levels (they are generally low in calories), so they are unlikely to develop insulin resistance if we are referring to healthy individuals.

Conflict of interest. Authors declare that there is no conflict of interest.

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