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# INSULIN RESISTANCE AND METABOLIC DISEASES - A REVIEW

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## ABSTRACT

**Introduction:** This review paper aims to discuss the effects of insulin resistance, and its association with various metabolic diseases. Insulin resistance (IR), characterized by diminished tissue responsiveness to physiological insulin levels, is a key component in various metabolic diseases, including type 2 diabetes, cardiovascular disorders (CVDs), obesity, and non-alcoholic fatty liver disease (NAFLD).

**State of knowledge** The consequences of IR are profound; in type 2 diabetes, it hinders glucose utilization by muscle cells, leading to hyperglycemia, muscle damage, and loss of mass and strength. IR also plays a central role in NAFLD, promoting lipid accumulation, hepatic inflammation, fibrosis, and cell death.

**Materials and methods:** A review of chosen literature in the PubMed and Google Scholar databases was conducted, using the following key words: „Insulin resistane", „Insulin resistance in obesity", „Obesity", „Insulin resistance NAFLD", „Diebetes", „Insulin resistance CVD"

**Summary:** The consequences of insulin resistance are far-reaching. In the context of type 2 diabetes, it impedes glucose utilization by muscle cells, resulting in hyperglycemia and subsequent muscle cell damage, contributing to loss of mass and strength. Insulin resistance is also a central player in the pathogenesis of non-alcoholic fatty liver disease (NAFLD), fostering lipid accumulation, hepatic inflammation, and, ultimately, fibrosis and cell death.

**Conclusions:** In conclusion, understanding insulin resistance is paramount in addressing the rising prevalence of metabolic diseases globally Controlling insulin resistance emerges as a

crucial aspect of managing these metabolic disorders and their complications. Further research into the mechanisms of IR formation and effective intervention strategies is imperative for improving public health outcomes.

Keywords: insuline resistance, obesity, diabetes, NAFLD, CVD

## INTRODUCTION

The insulin is a hormone that contains 55 amino-acids. It was initially isolated by Dr. Frederick Banting during the years 1921-192.[1] Discovery of insulin led to discovery od other hormones, such as glucagon..[2] Insulin's role in the body is much greater than just the regulation of blood glucose. Insulin is involved in the metabolic processes not only of glucose, but also of fats and proteins, and enables cells to use them in their own metabolic pathways.

There are about 2 million pancreatic islets in the pancreas,[3,4] containing various hormonally active cells, including insulin-producing β-cells, glucagon-producing α-cells, and somatostatin-source δ-cells.[5] After food intake, plasma glucose reaches a level that stimulates pancreatic β-cells to secrete insulin through a process called glucose-stimulated insulin secretion (GSIS).[3,6,7] Subsequently, insulin transports glucose to insulin-dependent tissues - skeletal muscle, adipose tissue, and the liver - while lowering blood glucose levels.[8,9] Additionally, it inhibits glucagon secretion from pancreatic α-cells.[3,10] Thus, insulin is involved in the metabolism of virtually the entire body.

Recent publications suggest that insulin also plays an important physiological role in many major organs, including the brain, kidneys, bones, and skin and hair follicles.[3] Insulin promotes bone formation and weakens inflammation associated with osteoporosis.[11] Clinical studies have also revealed its presence at low concentrations in some neurons of the central nervous system.[12]

The pancreas secretes insulin by pulses directly into the portal vein, causing the liver to receive about 2-3 times more insulin than into the bloodstream. [13] Insulin bonds to the receptors on the cell membrane of hepatocytes. Then it is drawn into the cells where it is degraded; this is called hepatic insulin clearance. It determines the amount of insulin that reaches the rest of the tissues and thus regulates insulin action throughout the body.[14]

In the liver, insulin activates the synthesis of all major metabolic macromolecules-glycogen, lipids and proteins. It also reduces hepatic glucose production by inhibiting the expression of genes responsible for gluconeogenesis and lipolysis in adipose tissue. [15]

In skeletal muscle and adipose tissue, insulin induces the incorporation of the GLUT4 transporter into the cell membrane of myocytes and adipose cells, respectively.[16] Through this transporter, glucose enters cells. Insulin also affects free fatty acids (FFA), amino acids and potassium levels in these tissues,[17] and regulates glycogen synthesis in skeletal muscle.[18]

Insulin resistance (IR) is defined as reduced sensitivity of insulin-dependent tissues to physiological insulin levels. It is an essential component of a number of metabolic diseases, including type 2 diabetes, cardiovascular diseases, obesity and non-alcoholic steatohepatitis. [8,19,20] Insulin resistance is also associated with metabolic syndrome, which includes hypertension, dyslipidemia and obesity. [7] Depending on the studied demographic, the prevalence of insulin resistance is estimated to be between 17-61.2%.[21]

In clinical trials described in 2011, diabetic patients were given glucose and insulin simultaneously. Two results could be observed: some of the subjects showed stable or reduced glucose levels - they were defined as insulin-sensitive. In the latter part, hyperglycemia was observed-those were called insulin resistant.[22]

Insulin resistance is characterized by a lessened response of the aforementioned tissues to insulin stimulation, or reduced insulin sensitivity-it takes a higher concentration of insulin to get half of the full cellular response. [7] As a result, serum glucose is not properly utilized. This is followed by a lack of inhibition of lipolysis, stimulation of gluconeogenesis, and secretion of the subsequent glucose into the system. Consequently, hyperinsulinemia occurs as the hormone is secreted in compensatory mechanizm as a response to the resulting hyperglycemia. [23] When subjected to a long-term caloric surplus, an endless cycle of hyperinsulinemia and increasing insulin resistance can result in pancreatic β-cell failure, likely due to the toxic effects of glucose and lipids accumulating not only in postcutaneous tissue, but also in visceral organs, where their metabolism is disrupted.[15]

Research is still underway to understand the exact mechanism of insulin resistance. At this point, there are several very plausible theories.

**OBESITY**

Obesity has become an epidemic of modern times. According to the WHO, nearly 60% of adults in Europe in 2022 were overweight or obese. [24] In children, as well, we are seeing an alarming increase in the prevalence of obesity-about 8% of children under the age of 5 are higher in weight than the norm would recommend. [25] Compared to normal-weight children, obese children's risk of obesity in adulthood increases by as much as 5 fold.[26]

It is diagnosed on the basis of Body Mass Index ( BMI)-overweight is diagnosed when BMI>25, obesity- BMI>30.[27]

Obesity is a condition in in which there is a pathological increase in body fat. It is led to by a long-term excess of energy consumed over the energy expended during day-to-day life. [28] To store excess energy, fat cells that are already present in the body multiply, and undergo hypertrophy. [29] If excessive caloric supply is maintained, hypertrophic adipocytes signal the need for the formation of the new adipocytes. During the process of proliferation and differentiation of new fat cells, the adipogenesis pathway may be disrupted. [30] Dysregulated metabolic activity of compromised adipocytes may lead to metabolic diseases.[31] They decrease the secretion of adiponectin, which is responsible for insulin sensitivity, and increase the waste products of their metabolism, including free fatty acids, which also lead to changes in insulin secretion.[32]

Chronic caloric excess is also accompanied by consistently elevated serum glucose levels, which is associated with a decreased β-cell response to incretins, which results in reduced insulin sensitivity. [28] Lack of incretin sensitivity and the reduction in β-cell mass due to the glucose toxicity may also be factors that can lead to non-alcoholic hepatosteatosis..[33]

We can distinguish two types of obesity- android obesity, which occurs predominantly in men, and genoid obesity- which is found mainly in women. In android-type obesity, the adipose tissue is located in the central area of the body, which is why it is also called abdominal obesity. Accumulation of visceral fat also occurs in this type of obesity, which accumulates around the internal organs. In genoid- type obesity, on the other hand, fat cells concentrate mailny around the hips region and on the lower extremities.[34] Abdominal obesity

particularly leads to the development of insulin resistance and type 2 diabetes.[35] It is often accompanied by hypertension and dyslipidemia- signs of metabolic syndrome.

## TYPE 2 DIEBETES MELLITUS

According to the World Health Organization, about 422 million people worldwide suffer from diabetes, and every year 1.5 million of them succumb from complications caused by the disease.[36] Furthermore, the population of diabetics is expected to rise to 700 million the year 2045.[37] With the rising prevalence of diabetes, the weight of the population is also increasing. Hyperglycemia is present in 7-14% of the population in most highly developed countries.[38] Type 2 diabetes mellitus accounts for the majority of cases worldwide and is mostly found in adults.[36]

The core mechanism of type 2 diabetes is impaired insulin secretion by the β cells of the pancreas.[37] The insulin resistance compromises the ability of skeletal muscle cells, adipose tissue and the liver to utilize glucose for their own benefit, resulting in plasma hyperglycemia.[28] Hyperglycemia damages muscle cells, potentially leading to loss of the muscle mass and strength. Loss of muscle mass is an important determinant of loss of function with the progression of the disease in diabetic patients.[39] The consequence of inuslinoresistance in adipose tissue is a lack of inhibition of lipolysis, resulting in the release of free fatty acids into the system, which then reach hepatocytes. As a result of insulin resistance, and supplying the liver with substrates for gluconeogenesis, the glucose is produced, regardless of the hyperinsulinemia present.[40]

Since the lack of correct insulin response is also affecting other organs, including the kidneys, vasculature[41] and the brain,[42] type 2 diabetes is associated with an increased likelihood of developing disability and premature death as a consequence of it.[43]

## NONALCOHOLIC FATTY LIVER DISEASE

The steatohepatic diseases are an ever increasing problem in the present society, as well as being closely intertwined with the obesity and the diabetes mellitus.[44]

Nonalcoholic fatty liver disease ( NAFLD) is diagnosed when there is an accumulation of fat cells in hepatocytes in patients, who are not consuming the excessive amounts of alcohol. It is identified when >5% of the liver volume or weight accounts for intrahepatic triglycerides (IHTG)[45], or in microscopic examination of a liver sample that was

taken during a fine-needle biopsy, there is evidence of lipid droplets present in at least 5% of the hepatocytes. [46]

Clinical studies have shown that the percentage of fat in the liver is directly correlated with insulin resistance in liver, skeletal muscle and adipose tissue. [47] Liver steatosis is an important marker of insulin resistance in a number of organs.[48]

It has been proven that hyperinsulinism accompanying the insulin resistance and the excess of free fatty acids (FFA) are both essential contributors to NAFLD. The excess of free fatty acids is mainly caused by the consumption of excess calories and obesity, and the resistance of adipocytes to insulin, leading to lipolysis and hyperinsulinemia. Free fatty acids that are released into the bloodstream from overdeveloped adipose tissue are transported to the liver and skeletal muscle. In tandem with free fatty acids (FFA) go intrahepatic triglycerides (IHTGs)-thus resulting in insulin resistance in these tissues.[49] The fatty acids in the cytoplasm of hepatocytes have a negative effect on the cell's response to insulin. Hyperinsulinemia enhances IHTG accumulation by stimulating the liver to synthesize triglycerides.[33]

Ultimately, lipotoxicity in the fatty liver leads to hepatocyte apoptosis, increasing inflammation due to oxidative stress, and dysregulation of the microbiome. Subsequently, fibrosis and liver cell death occur. [19,50]

## CARDIO-VASCULAR DISEASES

In the year of 2021, 20.5 million people in the world lost their lives due to cardiovascular diseases- this accounts for almost 1/3 of all global deaths. [51] This number is expected to rise to >22.2 million in the year 2030, thereby making it the number one cause of deaths worldwide.[52]

There are numerous risk factors that increase the likelihood of occurrence of cardiovascular disease, including insulin resistance, obesity, and type 2 diabetes.[53,54]

Insulin resistance, through the disruption of lipid metabolism, contributes to the lipid triad: 1) high levels of TG, 2) low levels of HDL, and 3) the formation of sd-LDL, all of which contribute to the formation of atheriosclerotic plaque. [53] The study results seem to indicate an atherogenic effect of TG and sd-LDL. The described dyslipidemia and the free

fatty acids liberated by lipolysis have a lipotoxic effect on the vascular epithelium. [55] The epithelium is also affected by insulin resistance-it increases prothrombotic and proinflammatory factors.[53] It also affects changes in the balance between vasoconstrictors and vasodilators-insulin stimulates the release of vasodilator NO. Thus, insulin resistance makes vasoconstriction predominant, contributing to increased cardiovascular risk.[56]

The heart has the ability to adapt, so under the conditions of this disturbed metabolism, it adjusts itself to use FFA as a substrate for its metabolism.. This is achieved at the expense of impairing its function-it can lead to left ventricular hypertrophy, hypertension and ischemic heart disease..[57] High FFA levels also contribute to impaired pancreatic β-cell function, which in a vicious cycle contributes to increased insulin resistance. Insulin resistance is directly related to hypertriglyceridemia and FFA- which increases the risk of CVDs.[58]

## SUMMARY AND CONCLUSIONS

The article outlines the role of insulin in the body, and the consequences that occur when its function is disrupted. It focuses on the relationship between insulin resistance and metabolic diseases, such as obesity, type 2 diabetes mellitus, non-alcoholic liver disease and cardio-vascular diseases.

Insulin regulates blood glucose levels and plays a complex role in fat and protein metabolism. It is responsible for transporting glucose to the muscles, adipose tissue and liver, affecting their metabolic processes. Studies indicate that insulin also affects other organs in the body, such as the kidneys, bones, brain and hair follicles. Insulin resistance is a key component of many metabolic diseases. Sedentary lifestyles and caloric excess are the reason why an increasing proportion of the population suffers from IR and related syndromes. Since insulin virtually regulates the metabolism of the entire body, disorders in its functioning have serious health consequences, resulting in increasing rate of metabolic syndormes prevalance. It is worth noting that controlling insulin resistance may be an important aspect of managing these metabolic diseases and their complications. Further research into the mechanisms of insulin resistance and effective intervention strategies is important for improving public health.

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