

Insulin Resistance Related to Metabolic Syndrome

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Abstract

Insulin resistance and metabolic syndrome are one of the major factors associated with higher risks of developing cardiovascular diseases and Type II Diabetes (T2D). Insulin resistance is believed to be one of the underlying causes of the development of T2D. There are numerous environmental and genetic factors influencing the development of these conditions, and while there have been many studies conducted on the topic, there are still many gaps in the scholarly literature on the topic. The interplay between genetic and environmental factors is quite complex, considering that there are many genes involved in the regulation of energy consumption as well as in the protective functions of an organism. Currently, the prevalence of insulin resistance among different populations ranges from 20% to 40%. Still, while the studies conducted before 2016 have found 88 loci associated with the development of T2D most of them are associated with secretion of insulin and function of β -cell, and far fewer studies have identified loci associated with insulin resistance. This means that the vast majority of studies are either focused on the insulin response pathway or on the immune response to inflammatory processes caused by metabolic disorders.

It can be concluded that biological and genetic mechanisms underlying the development of insulin resistance in metabolic syndrome are complex. For now, it is known that insulin resistance in metabolic syndrome develops due to malfunctioning insulin response pathway, or malfunctioning chronic inflammation response system, and other problems associated with energy and fatty acid metabolism.

Considering that the rates of obesity and T2D in developing countries are alarming, it is highly important to develop effective evidence-based interventions targeting this problem.

Key words; Insulin resistance, genetic factors, Metabolic Syndrome, environmental factors, fatty acid metabolism.

Insulin Resistance Related to Metabolic Syndrome

Insulin resistance and metabolic syndrome are one of the major factors associated with higher risks of developing cardiovascular diseases and Type II Diabetes (T2D) (Brown & Walker, 2016). Insulin resistance is believed to be one of the underlying causes of the development of the metabolic syndrome and T2D (Roberts et al., 2013). There are numerous environmental and genetic factors influencing the development of these conditions, and while there have been many studies conducted on the topic, there are still many gaps in the scholarly literature on the topic. Previously studies have identified several important biological factors associated with insulin resistance in metabolic syndrome, such as insulin-like growth factors IGF1 and IGF2 (Hakuno & Takahashi, 2018). Chronic inflammation and macrophages were also identified as crucial factors contributing to metabolic syndrome and insulin resistance (Rung et al., 2009; Paniagua, 2016; Rosen et al., 1989). The interplay between genetic and environmental factors is quite complex, considering that there are many genes involved in the regulation of energy consumption as well as in the protective functions of an organism (Brown & Walker, 2016).

Insulin resistance refers to the inability of an individual's body to stimulate glucose disposal, and when an individual's body is unable to produce sufficient insulin, it leads to T2D development (Brown & Walker, 2016). In other words, insulin resistance occurs when the body is unable to optimally transport glucose to body cells (Roberts et al., 2013). Insulin resistance may develop independently, because of biological factors, or may be caused by environmental factors, such as consumption of unhealthy food, poor diet, and physical activity. Currently, the prevalence of insulin resistance among different populations ranges from 20% to 40% (Brown & Walker, 2016; Guallar-Castillon et al., 2014; Prasad et al., 2012). Still, while the studies conducted before 2016 have found 88 loci associated with the development of T2D most of them are associated with secretion of insulin and function of β -cell, and far fewer studies have identified loci associated with insulin resistance (Brown & Walker, 2016). This means that the vast majority of studies are either focused on the insulin response pathway or on the immune response to inflammatory processes caused by metabolic disorders.

NAT2 is one of the loci directly associated with insulin resistance, however, it did not reach genome-wide significance (Brown & Walker, 2016). NAT2 is involved in the acetylation process and is also associated with resistance to certain drugs (Sim et al., 2014). The studies have also identified loci near GCKR as well as loci near IGF1 associated with insulin resistance. Previous studies have also found that risk loci associated with insulin resistance can be subdivided into 5 major clusters, and one cluster is associated with four loci PPAR γ , KLF14, IRS1, and GCKR (Dimas et al., 2014). Additional loci, such as IRS1, COBLL1-

GRB14, PPP1R3B, PDGFC, UHRF1BP1, and LYPLAL1 were also found to be associated with insulin resistance. The researchers have also found loci associated with fasting insulin levels, that could also be related to insulin resistance, including TCF7L2, PPARG, FTO, RSPO3, ANKRD55-MAP3K1, ARL15, HIP1, TET2, YSK4, PEPD, and FAM13A (Brown & Walker, 2016). It should be noted that IGT as well as impaired fasting glucose are the most commonly used clinical measures for insulin resistance (Roberts et al., 2013). Loci associated with lower HDL and higher triglycerides are also likely to be associated with insulin resistance. These loci are: IRS1, GRB14, ARL15, PPARG, PEPD, ANKRD55-MAP3K1, PDGFC, LYPLAL1, RSPO3, and FAM13A1 (Scott et al., 2012; Mahajan et al., 2014; Altshuler et al., 2000). Additionally, the study by Walker et al., (2016) has found that 2 loci near r TMEM163 (transmembrane protein 163) are associated with lower plasma insulin and the homeostasis model assessment (HOMA-IR).

One of the first genetic variants identified that is associated with insulin resistance is the peroxisome proliferator-activated receptor gamma (PPAR γ) variant Pro12Ala (Deeb et al., 1998; Altshuler et al., 2000). Studies have found that PPAR γ is a nuclear receptor that is directly involved in energy metabolism and fatty acid metabolism, and therefore agonists of this receptor are commonly used for treating T2D nowadays (Brown & Walker, 2016). Another important component associated with insulin resistance is IRS1 (insulin receptor substrate 1) and IRS2, which are actively involved in the pathway initiating the activation of PI3K as the response to insulin (Roberts et al., 2013). In fact, the C allele at rs2943641 adjacent to IRS1 is directly associated with insulin resistance (Rung et al., 2009). The insulin-stimulated tyrosine phosphorylation, which takes an active part in response to insulin can be reduced by mutations and various genetic factors, which in turn leads to the development of insulin resistance (Roberts et al., 2013). IRS1, as well as IRS2, are directly involved in the transportation of glucose, and mutations in these proteins were found to be related to both T2D and insulin resistance (Araki et al., 1994; Tamemoto et al., 1994). IRS2 is expressed in all the primary glucoregulatory tissues, and mutations in IRS2 can result in the malfunctioning of the liver, pancreas, skeletal muscles, and adipose (Roberts et al., 2013; Figure. 2).

Figure 1. Mechanisms underlying the development of dysfunctional adipose tissue (Paniagua, 2016)

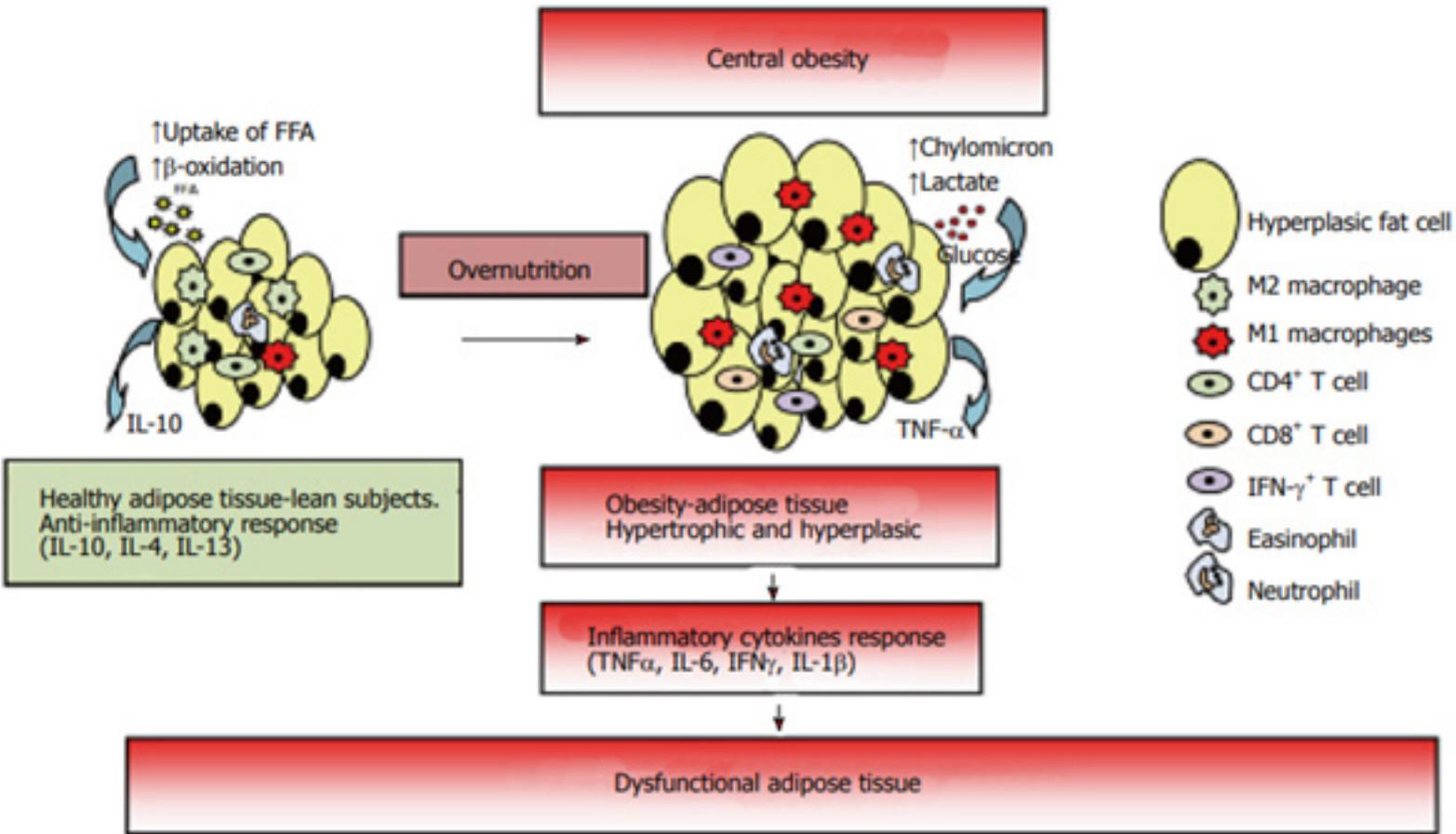
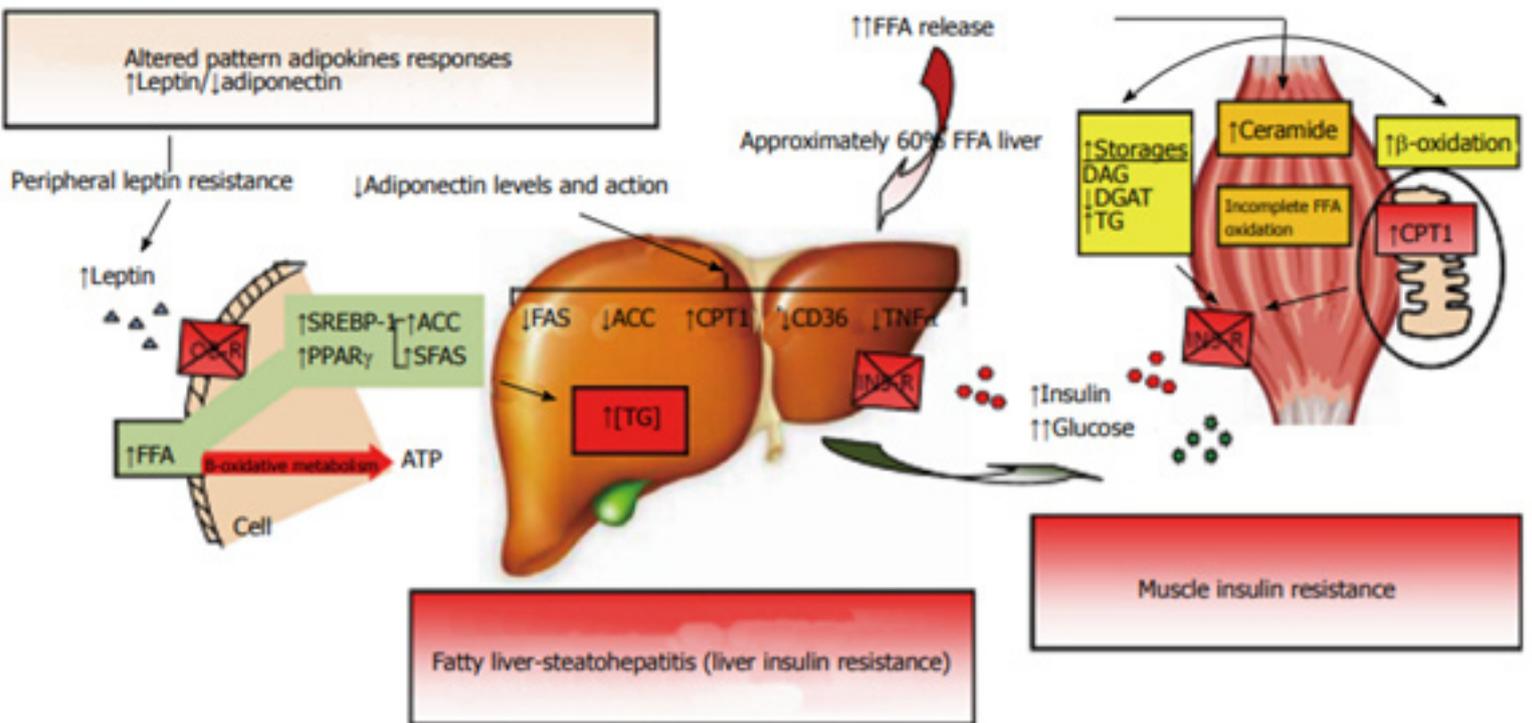


Figure 2: Dysfunctional Adipose Tissue (Paniagua, 2016)



Discussion

Early obesity results in the development of chronic inflammation in the body, and the influence of chronic inflammation puts excessive stress on protecting mechanisms of the organism (Weisberg et al., 2003; Xu et al., 2003). This chronic inflammation is associated with slow infiltration of macrophages which are the important source of inflammation of adipose tissue (Paniagua, 2016). Immune cells, such as T-cells, as well as macrophages and adipocytes, participate in the creation of cytokines (Paniagua, 2016). There are two different types of macrophages, which are M1 and M2. M1 macrophages are the major source of inflammatory cytokines such as TNF- α , while M2 macrophages are activated by type 2 (Th2) cytokines such as IL-4 and IL-13 (Rung et al., 2009; Paniagua, 2016; Rosen et al., 1989). M2 macrophages are abundant in adipose tissue of lean subjects (Paniagua, 2016; Fig. 1). Hence, while lean subjects provide a normal healthy response to the inflammatory process, people suffering from obesity have problems associated with inflammatory response, resulting in damage to the liver and other body organs. The inflammation response caused by M1 macrophages eventually leads to the development of insulin resistance because the liver is unable to function properly any more, as well as other organs with adipose tissue. This condition is also often referred to as fatty liver and is associated with various metabolic disorders and other health-related issues. Inflammatory cytokines TNF- α produced by M1 macrophages result in inhibition of differentiation to mature adipocyte, which leads to insulin resistance (Prieur et al., 2011; Chadli et al., 2012; Paniagua, 2016). IL-6 cytokines associated with the chronic inflammatory process were also found to be associated with both T2D and insulin resistance. It should be noted that resistin and leptin cytokines were also found to be associated with insulin resistance (Steppan et al., 2001). While leptin is supposed to decrease FFA, its effects can be blocked by the anabolic effects of hyperinsulinemia (Panuagua et al., 2014). Hence, cytokines that are produced by an improperly functioning immune system, that experiences enormous stress due to chronic inflammation, is one of the main explanations of why insulin resistance develops. The metabolic syndrome exhausts the protective resources of the body.

The problems caused by insulin resistance in adipose tissue result in chronic inflammation in the above mentioned organs, which contributes to lipotoxicity and the malfunctioning of different processes in the body (Paniagua, 2016). Chronic inflammation in the liver results in an increase in the total release of TNF- α and IL-6 (Vidal-Puig & Unger, 2010).

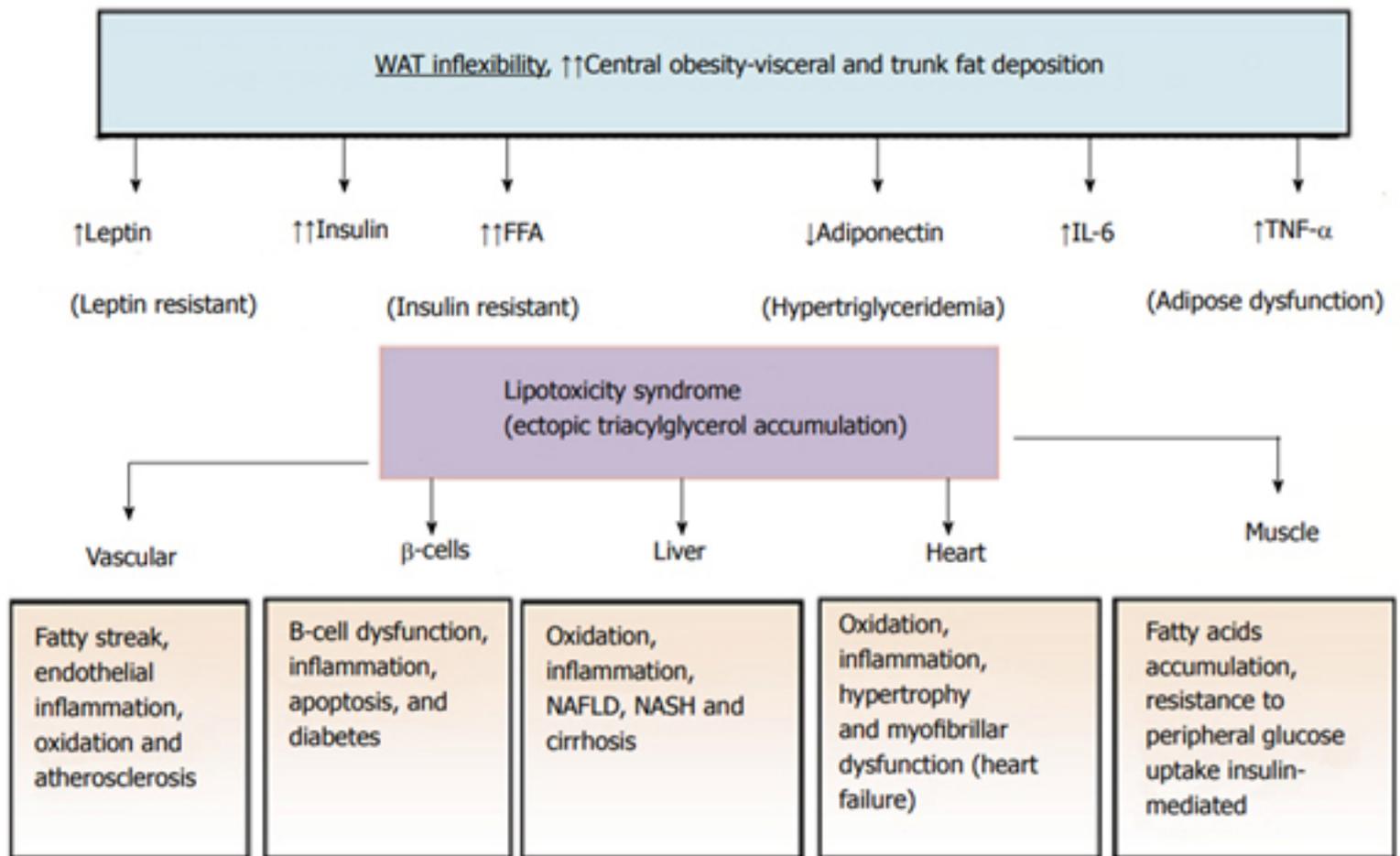
Paniagua (2016) proposes the following model explaining how metabolic syndrome and insulin resistance occur (Figure 3). This model states that people with sedentary lifestyles and obesity, as well as some people who may have genetic mutations and other biological factors, face problems associated with the malfunctioning immune response to chronic inflammation, which results in the increase of Leptin, Insulin, FFA (Fatty Acids), IL-6 and TNF- α , while Adiponectin is decreased (Paniagua et al., 2014). An increase in Insulin and FFA contribute to

insulin resistance, as well as other problems associated with metabolic syndrome (Vidal-Puig & Unger, 2009). It creates a vicious circle because adipose tissue starts to function improperly, which results in even more problems and worsens insulin resistance. Insulin responsiveness in patients with metabolic disorders and those who have insulin resistance can be improved by reducing body weight and encouraging them to exercise more (Melanson et al., 2009). Apparently, lower body weight reduces inflammatory processes inside the body, which stimulate the body to respond to inflammation more efficiently and adequately. Hence, the primary goal should be weight loss, because without a weight loss insulin resistance can't be addressed effectively as was found by Stuart et al., (2013).

Interestingly, people with certain hormonal problems may be at a higher risk of developing insulin resistance. The study by Arlien-Søborg et al., (2022) has focused on understanding how to reverse insulin resistance induced by growth hormone (GH) in patients suffering from acromegaly. However, the underlying molecular mechanisms still remain unknown. For now, it is clear that GH can induce insulin resistance through activating lipolysis. By suppressing the production of GH with somatostatin, it is possible to reduce insulin resistance in patients with acromegaly (Melmed et al., 2005). GH may affect tissues through the JAK/STAT pathway, leading to phosphorylation and dimerization of STAT5 Arlien-Søborg et al., (2022). The expression of GH-regulated genes CISH and IGF-I were detected in muscle and fat and were induced by GH signaling (pSTAT5) activation (Arlien-Søborg et al., 2022). Studies have found that the IGF-I factor is quite similar to insulin in its functions because it regulates growth and development. The studies have found that lower IGF-I is associated with higher insulin resistance (Belfiore et al., 2009; Hakuno & Takahashi, 2018; Succuro et al., 2009). Hence, higher exposure to GH induced by acromegaly may result in lower IGF-I factor, which could lead to the development of insulin resistance and other problems.

It can be concluded that biological and genetic mechanisms underlying the development of insulin resistance in metabolic syndrome are complex (Brown & Walker, 2016). There are hundreds of factors associated with the development of the abovementioned disorders, and more studies should be conducted to identify all possible loci and genes associated with these problems. For now, it is known that insulin resistance in metabolic syndrome develops due to malfunctioning insulin response pathway, or malfunctioning chronic inflammation response system, and other problems associated with energy and fatty acid metabolism (Vidal-Puig & Unger, 2010; Weisberg et al., 2003; Xu et al., 2003; Rung et al., 2009; Paniagua, 2016; Rosen et al., 1989; Prieur et al., 2011; Chadli et al., 2012). Insulin resistance may be observed in patients with various hormonal pathologies, including those suffering from acromegaly, when the body produces too much growth hormone (Arlien-Søborg et al., 2022) Considering that the rates of obesity and T2D in developing countries are alarming, it is highly important to develop effective evidence-based interventions targeting this problem.

Figure 3: Adipose Tissues Expandability and Metabolic Syndrome



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