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Peculiarity of Insulin Resistance in Men with Type 2 Diabetes Mellitus and Overall, Gender Comparison of Associated Complications

Victor E. Esenabhalu*

South Georgia State College, Douglas, Georgia [University System of Georgia], USA

Corresponding author: Bekalu Mekonen Victor E. Esenabhalu, MSc, Ph.D. South Georgia State College, Douglas, Georgia [University System of Georgia], USA

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Abstract

Insulin is a polypeptide hormone composed of 51 amino acids and secreted by the β cells of the pancreatic islets of Langerhans. Insulin regulates and maintains healthy blood glucose levels within the body, overseeing the control of plasma glucose levels. In the process, it stimulates cells to utilize the available plasma glucose for the Adenosine triphosphate (ATP) synthesis and coordinates the conversion of glucose into glycogen that is stored away in the liver and partly in the muscle as fatty acids. On the other hand, insulin resistance is a condition where normal sensitivity of the cells to insulin is impaired and cannot respond to the stimulation of insulin. When the pancreas produces normal or even elevated amounts of insulin, the body's response to the insulin is poor. While the body can adjust normal functioning amounts of insulin and/or β cells being produced, insulin resistance can often result in a condition called diabetes mellitus, a group of diseases that affect the way the body regulates blood glucose levels. Diabetes mellitus is a condition characterized by chronic hyperglycemia. Hyperglycemia can be caused by many factors, one being insulin resistance. Though diabetes mellitus occurs in many forms and affects people of all genders and ethnicities, this article specifically discussed the peculiarity of insulin resistance in men with type 2 diabetes mellitus. Areas such as normal and abnormal forms of insulin secretion, insulin resistance syndrome, causes of the insulin resistance form of type 2 diabetes mellitus, its epidemiology, worldwide prevalence, and global burden, gender differences in insulin resistance, and management of insulin resistance type 2 diabetes mellitus were researched. The etiology of the complications associated with insulin resistance was also researched.

Keywords: *Hyperglycemia, Hypoglycemia, Insulin resistance, Glucose, Diabetes mellitus, Pancreatic islets, Hyperinsulinemia, Beta cells*

Objectives and Design

This review is intended to investigate the peculiarity of insulin resistance in men with type 2 diabetes mellitus. Areas of interest include normal and abnormal forms of insulin secretion, insulin resistance syndrome, causes of the insulin resistance form of diabetes mellitus, epidemiology, worldwide prevalence, and global burden, gender differences in insulin resistance, and management of insulin resistance in men with type 2 diabetes mellitus. Although the topic of diabetes mellitus as a health condition has been studied extensively, this is different from insulin resistance in men with type 2 diabetes mellitus. This article is designed to specifically research the peculiarity of this disease in men. The article also extends to cover a gender comparison in the causes and complications of this disease. Currently, there is inadequate information on insulin resistance type 2 form of DM-related men. Our objective is to shed more light on the subject and raise awareness of pathogenesis and management of the disease.

Methods

Sources of information for this article included Medeley.com, PubMed, NCBI, JMIG, A, Medrxiv.org, Medical News Today, and Mayo Clinic.

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by the presence of an abnormally high level of sugar in the blood, (hyperglycemia) resulting from either inadequate insulin production or impaired insulin utilization [1]. There are three main types of diabetes mellitus: type 1 diabetes mellitus, type 2 diabetes mellitus, and gestational diabetes mellitus. Type 1 diabetes mellitus is where the pancreas is unable to produce enough, if any, insulin to regulate blood glucose levels. Type 2 diabetes mellitus (T2D) is the most common form of diabetes, accounting for approximately 90% of all cases. It results from a combination of insulin resistance, where cells become less responsive to insulin, and inappropriate insulin production by the pancreas [2]. Insulin resistance results from the event that the pancreas produces normal, or excess, amounts of insulin, but the body does not respond properly, preventing blood glucose levels from being regulated [3]. It is characterized by insulin insensitivity, decreased production of insulin, and the eventual failure of pancreatic β cells. Hyperglycemia will result from increased levels of insulin and with so much circulating glucose in the blood compounded with lower sensitivity membranal glucose receptors other complications resulting in stronger insulin resistance will eventually lead to T2D [3]. Many patients with T2D have hyperglycemia because of deficiencies in both insulin secretion and the inability of secreted insulin to convert

glucose to glucagon, which is a result of either β-cell dysfunction or insulin resistance complications [4]. While it is challenging to prevent a genetic inclination towards T2D, individuals who maintain insulin sensitivity can still uphold normal sugar levels by adopting lifestyle adjustments and utilizing medications, it is possible to enhance insulin sensitivity, insulin secretion, and glucose utilization. These actions can effectively lower the prevalence of T2D [4]. Gestational diabetes mellitus is diabetes that occurs in women when they are pregnant; though it usually goes away after pregnancy, it can increase the risk for type 2 diabetes mellitus later in life [4]. Gestational diabetes mellitus is characterized by a higher level of glucose in the blood, or a form of diabetes mellitus diagnosed around the second or third trimester of pregnancy [5]. It occurs when hormonal changes during pregnancy lead to insulin resistance, causing elevated blood glucose levels (Figure 1) [6].

Epidemiology of T2D and Insulin Resistance T2DM

Insulin resistance is cosmopolitan as it affects all races and ethnicities. Although there are currently limited information on its prevalence across specific ethnic group, a study of a sample of 3305 black, 3477 Mexican American, and 5581 white men and nonpregnant or lactating women aged 20 years and older by the National Health and Nutrition Examination Survey (NHANES) reveals that Insulin Resistance Syndrome (IRS) affects 24% of American within the age of 20 years and older and particularly more prevalent among the Mexican Americans and lowest in Blacks [8,9]. Another report in 2021 that conducted a survey on 6247 young Americans has it that the prevalence of IRS among Americans is 44.2%. It is recommended that 4 out of 10 Americans of 18 to 44 years of age without diabetes and preexisting cardiovascular disease are at risk of cardiometabolic risk factors, so screening efforts for IRS should be intensified irrespective of their BMI [10].

The prevalence of diabetes has reached epidemic proportions, making it a significant global health challenge [11]. Recent records have shown a total of 37.3 million people in the world have diabetes mellitus with 28.7 million being diagnosed and 8.2 million undiagnosed [5]. Type 2 diabetes remains more prevalent as worldwide obesity continues to increase. Studies linked to the amount of visceral fat in elderly men and women have statistically reported that men are ~2 times more likely to develop type 2 diabetes than women [6]. Obesity plays a role in insulin resistance as the body struggles to function outside of a healthy weight. In recent times, the peculiar signs and symptoms that are characteristic of men with this condition are beginning to gain some attention. This research paper is intended to focus in detail on several factors that are either the cause or are associated with this peculiarity in men.

Insulin Hormone

Normal Insulin Secretion

Insulin is a polypeptide hormone secreted by the β cells of the pancreatic islets of Langerhans into the portal veins. It acts as an endocrine ligand that binds plasma membrane-bound receptors in target cells to orchestrate an integrated anabolic response to nutrient availability [12,13]. They do this by transporting glucose into insulin-dependent tissues such as skeletal muscles, liver and white adipocytes thereby upholding the equilibrium of glucose within the body. Although these tissues perform distinct roles in maintaining metabolic balance, which requires specific pathways for insulin signaling. In skeletal muscle, insulin enhances the utilization and storage of glucose by boosting glucose transport and promoting net glycogen synthesis. In the liver, insulin activates glycogen synthesis, upregulates genes involved in lipogenesis, and downregulates genes related to gluconeogenesis. In white adipose tissue (WAT), insulin inhibits the breakdown of fats (lipolysis), while simultaneously increasing glucose transport and promoting the production of fats (lipogenesis) [13] Despite these distinct effects, the fundamental components involved in

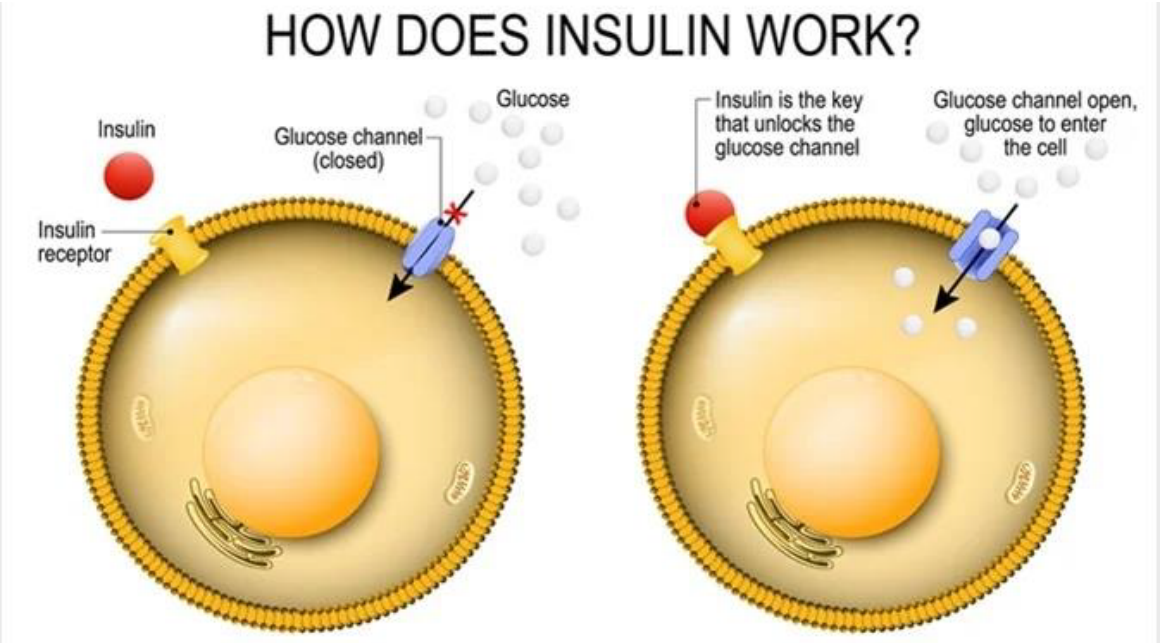

Figure 1: Illustrates the interaction between insulin and the appropriate receptor (membrane-bound receptor) prior to glucose entry into the cell [7].

insulin signal transduction are surprisingly similar in all cells responsive to insulin. It aids the absorption, utilization, and storage of glucose in these tissues. When circulating blood glucose is high, the β cells of the pancreas respond by producing a burst of insulin followed by a more sustained release of the hormone. Research has shown that glucose appears to stimulate the β cells by increasing intracellular ATP and the closing of KAMP channels. Glucose is not the only stimulant for the secretion of insulin. Other peptide hormones such as GLP-1 can also influence insulin secretion by enhancing or inhibiting it. Hormones like GLP-1 appear to be influenced by cAMP and the activation of cAMP-responsive protein kinase [14,15]. After a meal, as blood glucose levels escalate, the pancreas reacts to the availability of glucose, it generates a surge of insulin, succeeded by a more sustained release of the hormone [16]. Insulin secretion is tightly regulated by several factors, including blood glucose levels, gastrointestinal hormones, neural inputs, and other metabolic signals. The pancreatic β cells act as glucose sensors, responding to fluctuations in blood glucose to release appropriate amounts of insulin [2]. Apart from facilitating the uptake of glucose into insulin-sensitive tissues, such as skeletal muscles and adipose tissues, where it is utilized as an energy source or stored as glycogen and triglycerides, insulin also suppresses gluconeogenesis in the liver, preventing excessive glucose production to keep the blood glucose level within a tolerable range [13]. Insulin stimulates protein synthesis and inhibits protein breakdown, contributing to tissue growth. Also, insulin promotes lipid synthesis and inhibits lipolysis in adipose tissue, leading to the storage of fatty acids such as triglycerides. The dysregulation of the blood glucose level by insulin leads to numerous metabolic consequences generally referred to as diabetes mellitus [17].

Abnormal Insulin Secretion

Insulin resistance is characterized by a less-than-normal response to a normal amount of insulin production [18]. Identified causes for insulin resistance are excess body fat and genetics [18,21]. When higher levels of the insulin hormone are required to facilitate the normal reduction of glucose, the patient is insulin resistant [11,22]. While the body counteracts this disturbance by overproducing insulin – hyperinsulinemia – to achieve glucose homeostasis, the pancreas will become exhausted, and the production of insulin will diminish and lead to a condition called insulin resistance syndrome [2]. Insulin resistance syndrome is made up of several characteristics. These characteristics include glucose intolerance, obesity, dyslipidemia, and hypertension which all contribute to the development of type 2 diabetes (Figure 2) [23].

Insulin Resistance Syndrome

Insulin Resistance Syndrome (IRS), also called Metabolic Syndrome, is a group of interrelated metabolic disorders that, when combined, lead to an increased risk of serious health issues. The Adult Treatment Panel III (ATP) of the National Cholesterol Education Program (NCEP) requires that a patient should be diagnosed with IRS when he or she shows symptoms of three of these metabolic disorders, using the following standards: People with obesity in their stomachs (over 102 cm for men and over 88 cm for women), high triglyceride levels (more than 150 mg/dL), low HDL cholesterol (less than 40 mg/dL for men and less than 50 mg/dL for women), high blood pressure (above 130 mm Hg or above 85 mm Hg), and high fasting plasma glucose (over 110 mg/dL) [18,25]. IRS is referred to as a Metabolic Syndrome because of its close association with these metabolic disorders. These disorders include Insulin Resistance, Abdominal Obesity, Dyslipidemia, Hypertension (High Blood Pressure), and Hyperglycemia (Elevated Blood sugar) [23]. These disorders increase the risk of several serious health issues such as Type 2 Diabetes, Heart Disease, and Non-Alcoholic Fatty Liver Disease (NAFLD) [3,23]. Insulin resistance is usually observed before the diagnosis of these associated diseases, so IRS is a keystone marker that potentially offers great preventive values for them (Figure 3) [3].

Causes of Insulin Resistance

Pathogenesis

The pathogenesis of insulin resistance syndrome involves a combination of genetic, environmental, and lifestyle factors. The

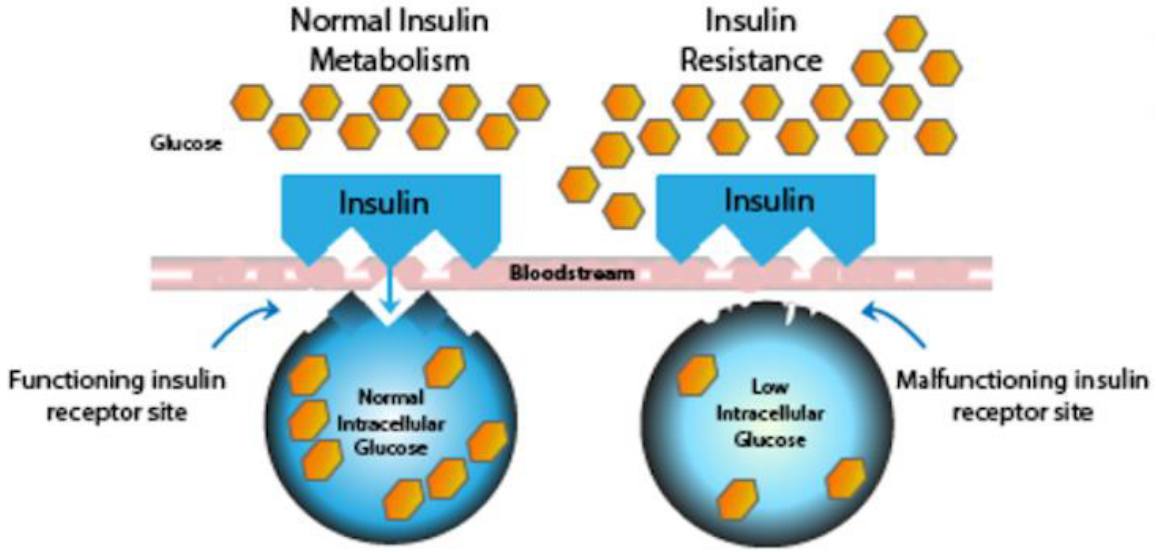

Figure 2: Illustrates insulin interactions at the functioning insulin receptor site[left] and malfunctioning insulin receptor site [24].

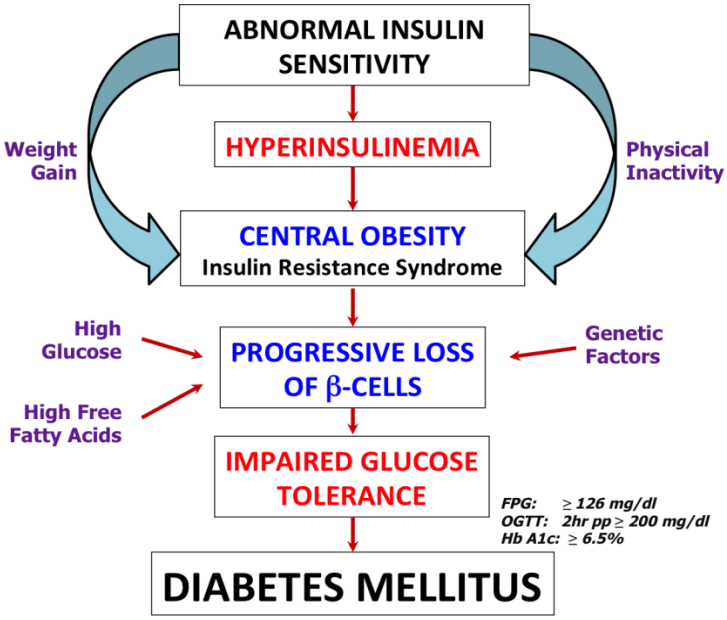

Figure 3: Illustrates insulin resistance syndrome and the characteristics of glucose intolerance, obesity, and hyperinsulinemia [26].

normal organ systems of Humans had originally evolved to be able to sustain events of scarce chemical energy in the form of nutrients, but due to the increase in wealth and excess availability of food as a result of industrialization, a level of toxicity that comes with this processed food and even our toxic environment, humans now consume more unhealthy foods than their body manage, these have caused majority of us to have ectopic lipids in our liver and skeletal muscles, which makes it hard for our bodies to respond to insulin [16]. Insulin insensitivity in men with type 2 diabetes can be either because target tissues are not able to give coordinated glucose lowering response to normal insulin signals [27] or due to other complications such as overeating, aging, hyperglycemia, increased levels of free fatty acids (FFAs), and the effects of some medications.[4] The accumulation of Ectopic lipids leads to adipocyte dysfunction, [28] adipocytes become metabolically active which makes it easier for macrophages to get in and causes lipolysis.[29] When blood plasma's Free Fatty Acid level rises our ability to metabolize carbs and fats in the liver becomes impaired either because Free Fatty Acid (FFA) inhibit glucose uptake, inhibits glycogen synthesis, and inhibits insulin stimulated glucose synthesis. [28] Which in return leads to hepatic insulin resistance [28]. The fatty acid flux increases the amount of fatty acid that can be esterified and the amount of triglyceride that can be synthesized in the liver, which worsens our steatosis.

Other Causes of Insulin Resistance

Mitochondrial Dysfunction

It has been known for many years that severe mitochondrial dysfunction can result in diabetes [17]. In a study using $^{13}C/^{31}P$ MRS, it was found that in healthy lean elderly volunteers with severe muscle insulin resistance, there is a ~40% reduction in the rates of oxidative phosphorylation activity associated with increased intramyocellular and intrahepatic lipid content [30]. This study suggests that an acquired loss of mitochondrial function associated with aging predisposes elderly subjects to intramyocellular lipid accumulation, which results in insulin resistance [31]. Further, it was found that mitochondrial density was reduced by 38%, intramyocellular lipid content was increased by 60%, and serine phosphorylation of IRS-1 was increased by 50% in the young insulin-resistant offspring of type 2 diabetes parents [32].

Adipokines

Insulin has three major target tissues-skeletal muscle, adipose tissue, and the liver. Not only is IR overexpressed in the cells of these tissues, but these are also the three places where glucose is deposited and stored; no other tissue can store glucose. About 75% of insulin-dependent postprandial glucose disposal occurs in the skeletal muscle [33]; it is therefore the major target organ. Patients suffering from insulin resistance and type 2 diabetes frequently display signs of abnormal lipid metabolism, increased circulatory concentration, and elevated deposition of lipids in the skeletal muscle [34]. An increase in plasma FFA reduces insulin-stimulated glucose uptake, whereas a decrease in plasma lipid content improves insulin activity in the skeletal muscle cells, adipocytes, and liver [35]. Studies have shown that raising plasma fatty acids in both rodents [36] and humans abolishes insulin activation of IRS-1-associated PI3-kinase activity in skeletal muscle where IRS-1 is most prevalent. Lipid-associated insulin resistance has also been shown to be linked to GLUT4 translocation defects. [37]

Worldwide Prevalence and Global Burden

Epidemiologic data indicate that insulin resistance is essential to the development of type 2 diabetes in most patients. Worldwide prevalence data indicates that diabetes has reached epidemic proportions. [38] Most cases of diabetes are type 2. Recent data collected by the World Health Organization (WHO) support the notion that the occurrence of diabetes is undergoing a rapid escalation and that the global burden of diabetes is undergoing a shift [39]. In

1995, approximately 135 million individuals were affected by diabetes, with a significant majority originating from just three nations: India, China, and the United States. Projected figures indicate that by 2025, the diabetes population will likely reach around 300 million: Once again, most of these cases will be concentrated in these same three countries, in more developed nations, the diabetes count will experience a 42% increase, growing from 51 million to 72 million, while in less developed countries, the surge is projected to be 170% escalating from 84million to 228 million. These surges in prevalence will not be solely attributed to population growth but rather to an elevated incidence of Insulin resistance [11].

Type 2 diabetes remains more prevalent as worldwide obesity continues to increase. Studies linked to the amount of visceral fat in elderly men and women have statistically reported that men are ~2 times more likely to develop type 2 diabetes than women [40]. Obesity plays a role in insulin resistance as the body struggles to function outside of a healthy weight. The prevalence of diabetes varies by region. Factors such as sedentary lifestyles, poor diet, and an aging population tend to lead to higher prevalence rates in high-income countries like the US and Western Europe. On the other hand, urbanization and changes in lifestyle patterns have led to a rapid rise in diabetes cases in low and middle-income countries, especially in South Asia, Southeast Asia, and Africa. Around the world, new diabetes cases vary by population and age group, with those aged 45 to 64 being the most likely to develop diabetes [41]. However, younger populations have seen an increase in diabetes cases due to the current prevalence of obesity, sedentary lifestyle, and poor diet [42,43].

Gender Differences in Insulin Resistance

The anatomy and physiology of men are completely different from that of women in several regard. Insulin sensitivity, body composition, and energy balance in men are completely different from that of women.[44] Gender difference in body fat distribution also plays a role in insulin resistance susceptibility. The above-enumerated factors have been studied extensively in physiology and nutrients. Some key findings include:

Insulin Sensitivity

Research have sown that men and women differ in their sensitivity to the hormone insulin [45]–[47]. This gender difference in sensitivity has also been observed in animals such as mice, for example, research conducted to investigate how insulin sensitivity and glucose metabolism differ in adipocytes between different fat depots of male and female mice and how sex steroids contribute to these differences reveal that female mouse is more sensitive to insulin that male mouse. This is because female adipocytes exhibit higher rates of lipid synthesis when compared to their male counterparts in both the perigonadal (PG) and subcutaneous (SC) depots. Additionally, in females, PG adipocytes demonstrate enhanced insulin sensitivity with respect to both lipogenesis and insulin signaling [48]. Women, in general tend to be more sensitive than men. This means that women body are often better at using insulin to regulate blood sugar levels. Hormonal differences, particular, difference in the Estrogen and Testosterone [49], [50] plays a role in this variation. Testosterone levels gradually decrease as men age. These diminishing testosterone levels are linked to the increased accumulation of visceral fat observed in aging men [47] but women with Polycystic ovary syndrome (PCOS) who often experience higher testosterone level are prone to insulin resistance syndrome [51].

Body Composition

Body Mass Index (BMI) is positively associated with the prevalence of Insulin resistance syndrome [52] and there is a strong association between android fat mass, gynoid fat mass and cardiovascular diseases [53] Wenzhi Ma. Because Men and women typically have different body compositions. Men tends to have a higher percentage of muscle mass and lower body fat percentage compared to women. Women often have a higher percentage of body fat, particularly subcutaneous fat which are stored under the skin, while men may carry more fat in the abdominal areas (visceral fat) [54]. There is also evidence that brain insulin action regulates eating behavior and energy fluxes throughout the body. High brain insulin sensitivity before lifestyle intervention has been shown to be associated with a more pronounced reduction in total and visceral fat during and less regain of fat [55].

Energy Balance

Gender can influence energy balance, which is the relationship between calories intake and expenditure, Men tend to have a higher resting metabolic rate (the calories burned at rest) due to their greater muscles mass [44]. This can result in men having a higher total daily energy expenditure (TDEE) compared to women. Women may have different hormonal fluctuations throughout the menstrual cycle, which can impact appetite and energy expenditure [56].

Body Fat Distribution

Studies have shown that men are more prone to developing insulin resistance due to larger amounts of visceral adipose tissue than women [57]. Estrogen, a hormone found in women, has been shown to favor insulin sensitivity and glucose homeostasis whereas men lack the estrogen hormone. Adiponectin, an insulin-sensitizing hormone, has also been shown to occur at significantly lower levels in men than in women [57]. The cause for this difference has not yet been established [44]. A study done with a sample size of 705 men and 688 women linked the amount of visceral fat in men and women, all aged 70, to the likelihood of developing insulin resistance and type 2 diabetes mellitus. This uncovered the statistic that men are ~ 2 times more likely to develop type 2 diabetes mellitus than women [58]. Furthermore, a comprehensive analysis of studies focusing on sex differences in insulin sensitivity and body fat distribution concluded that men are more susceptible to insulin resistance, especially in the presence of excess visceral fat [30].

Visceral Fat in Insulin Resistance

Visceral fat, also known as intra-abdominal fat, is a specific type of adipose tissue that surrounds and encases vital organs such as the liver, pancreas, and intestines in the abdominal Cavity. Unlike subcutaneous fat, which is found just beneath the skin, visceral fat is metabolically active and produces various hormones and inflammatory substances

[22]. This metabolic activity is a critical factor in the development of insulin resistance [13]. Research has consistently shown a strong association between visceral fat accumulation and insulin resistance in both men and women. However, studies have also indicated that men tend to have higher levels of visceral fat than women, especially as they age (Figure 4) [44].

Hormonal Differences

One of the primary factors contributing to gender differences in insulin resistance is the hormonal influence. Estrogen, a hormone found in women, plays a significant role in promoting insulin sensitivity and maintaining glucose homeostasis. Estrogen has been shown to improve insulin signaling and glucose uptake in cells, thereby reducing the risk of insulin resistance [56]. On the other hand, men lack estrogen, which may contribute to their increased susceptibility to insulin resistance. Additionally, adiponectin, an adipokine hormone secreted by adipose tissue, plays a crucial role in enhancing insulin sensitivity. Research has found that adiponectin levels are significantly lower in men than in women, further contributing to insulin resistance in the male population [59].

Hormonal Influence: Estrogen and Adiponectin

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Android vs. Gynoid in Fat Distribution

Gender differences in body fat distribution also play a role in insulin resistance susceptibility. Men tend to have an "android" pattern of fat distribution, characterized by excess fat accumulation around the abdomen and upper body. This android pattern, commonly referred to as an "apple-shaped" body, is associated with a higher risk of insulin resistance and other metabolic disorders [44]. In contrast, women often exhibit a "gynoid" pattern of fat distribution, where fat is more evenly distributed around the hips and thighs. This "pear-shaped" body type is typically associated with a lower risk of insulin resistance and related health complications [64].

The Connection Between Testosterone and Insulin Resistance

Low Testosterone and Insulin Resistance

Studies have shown that low levels of testosterone in men are associated with a higher prevalence of insulin resistance and type 2 diabetes [38]. As men age, mild deficiencies of testosterone can occur, making them more susceptible to increased adiposity and insulin resistance. These factors, when combined, contribute to the development of metabolic syndrome, a cluster of metabolic abnormalities, including central obesity, high blood pressure, dyslipidemia, and insulin resistance [39,65]. Untreated metabolic syndrome can further escalate the risk of developing type 2 diabetes mellitus. Severe deficiencies of testosterone in men not only increase susceptibility to increased adiposity and insulin resistance but also lead to β-cell dysfunction. The addition of β-cell dysfunction to these factors makes men more prone to developing type 2 diabetes mellitus (Figure 5) [66].

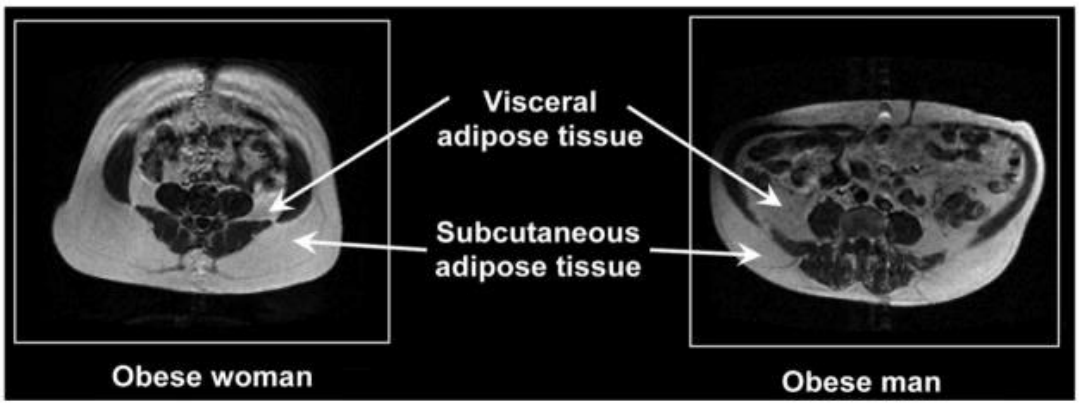

Figure 4: An illustration of visceral adipose tissue and subcutaneous adipose tissue [44].

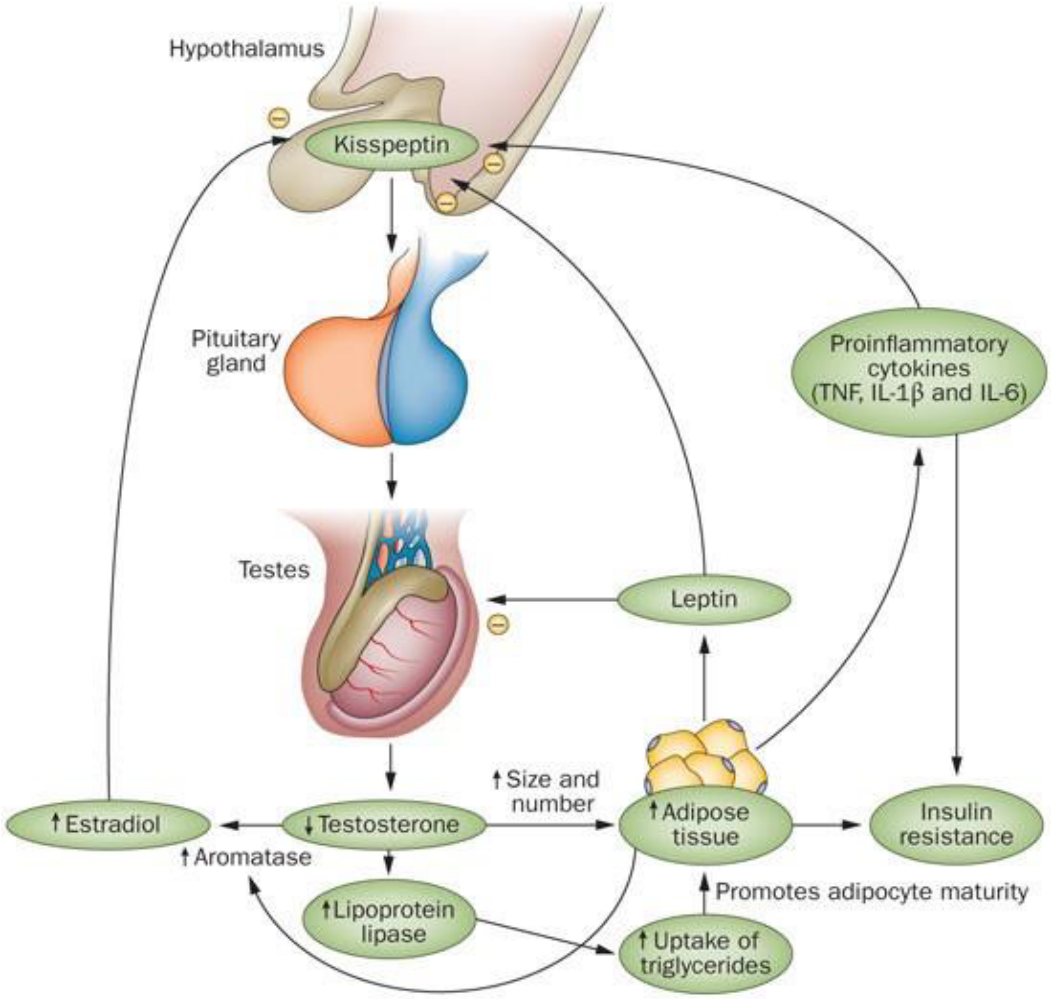

Figure 5: Illustration of hypothalamic-pituitary gonadal axis – Testosterone and Insulin Resistance in the metabolic syndrome and T2DM in men [50].

Testosterone and Glucose Utilization

Testosterone has been shown to play a significant role in glucose metabolism. It stimulates insulin secretion by pancreatic β-cells, enhances glucose uptake by tissues, promotes glycolysis (glucose breakdown), and increases mitochondrial oxidative phosphorylation (energy production). These beneficial effects of testosterone on glucose utilization are crucial in maintaining insulin sensitivity and preventing insulin resistance [44]. Therefore, a decline in testosterone levels with an increase in age would make a male lose all the numerous roles of testosterone in glucose utilization. This also contributes to a decrease in insulin sensitivity as it occurs in insulin resistance in men with type 2 diabetes (Figure 6) [65].

Testosterone Therapy and Metabolic Health - Interventional Studies

The potential benefits of testosterone therapy in improving type 2 diabetes and insulin resistance have been demonstrated through various interventional studies. Testosterone replacement therapy (TRT) in men with low testosterone levels has shown positive effects on insulin sensitivity, glucose metabolism, and body composition [38,67]. These studies suggest that TRT may have a role in managing insulin resistance in men with testosterone deficiencies.

Insulin Resistance in Men

Testosterone and cAMP-PKA Pathway

Testosterone increases the stimulation and release of insulin by increasing cAMP production and the activation of cAMP-dependent protein kinase (PKA) [68] (Figure 6). Low levels of testosterone, an androgen hormone in men, have been associated with the prevalence of insulin resistance and type 2 diabetes in men [69]. Mild deficiencies of testosterone in aging men can cause men to become more susceptible to increased adiposity and insulin resistance [68]. These factors can lead to a condition known as metabolic syndrome (Figure 7). When metabolic syndrome is left untreated, it can further increase the risk of developing type 2 diabetes mellitus. Severe deficiencies of testosterone in men not only increase susceptibility to increased adiposity and insulin resistance but also β-cell dysfunction. The addition of β-cell dysfunction to these factors causes men to become more prone to developing type 2 diabetes mellitus [68] (Figure 2.2). Testosterone has been scientifically shown to play a role in the utilization of glucose by stimulating insulin secretion, glucose uptake, glycolysis, and mitochondrial oxidative phosphorylation [68,69]. Beneficial effects of testosterone on type 2 diabetes and insulin resistance have also been shown through interventional studies [69]. While testosterone in the β-cells of men prevails to be beneficial, excess

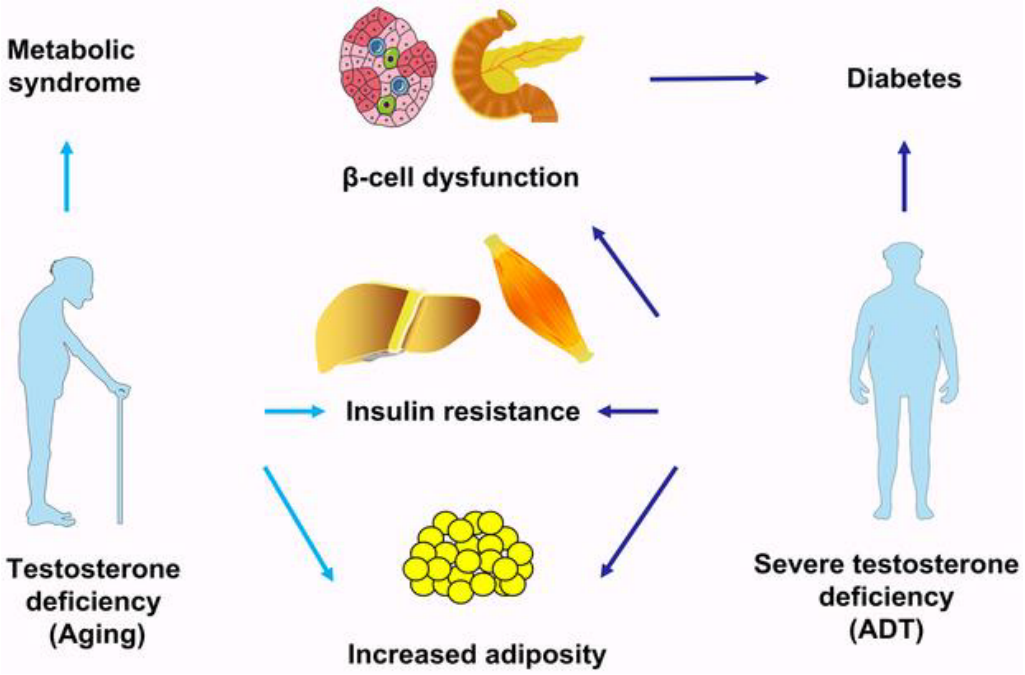

Figure 6: Illustration of the effects of testosterone deficiency and severe testosterone deficiency in men on increased adiposity [15].

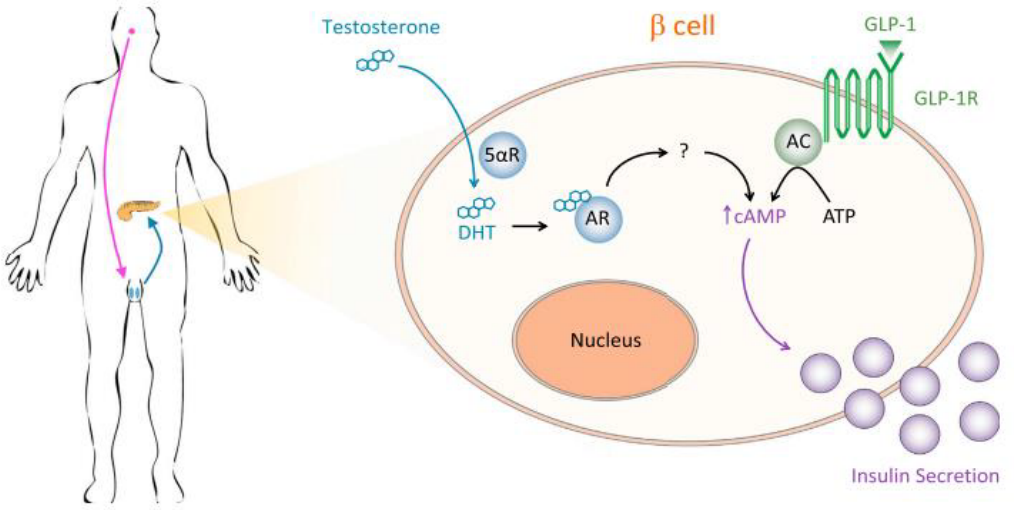

Figure 7: Illustration of the mechanism of testosterone stimulating the release of insulin [70].

testosterone in the β-cells of women can cause harmful effects such as hyperinsulinemia and increased susceptibility of β-cell dysfunction and failure (Figure 7) [68].

Management of Type 2 Diabetes Mellitus and Insulin Resistance DM

Treatments Availability

There are several treatments for type 2 diabetes, while only a few have been studied for insulin resistance. Medications like concentrated insulins, Metformin, and glucagon-like peptide 1 (GLP-1) receptor agonists are found to be helpful to patients with type 2 diabetes.

Treatment Usage

Metformin is usually the first line of defense when it comes to patients with type 2 diabetes and can be used with other insulin therapy treatments to regulate blood glucose levels. Concentrated insulins are the most clinically experienced, but they still run into issues such as an increased risk of hypoglycemia when doses need to be increased over time [71]. However, interest in GLP-1 receptor agonists for the treatment of type 2 diabetes and insulin resistance is on the rise as it does not pose an increased risk of causing hypoglycemia when paired with basal insulin. GLP-1 receptor agonists improve glycemic control and reduce body weight in patients with type 2 diabetes and insulin

resistance [71]. Other treatment options for insulin resistance in patients with type 2 diabetes mellitus still need to be explored as this condition continuously takes over.

Prevention Measures and Lifestyle Modifications

Lifestyle modifications are crucial in preventing and managing insulin resistance in men. Adopting a balanced diet that is rich in whole grains, fruits, vegetables, lean proteins, and healthy fats can help control weight and reduce visceral fat accumulation. Avoiding sugary and processed foods is also essential in preventing insulin resistance [72]. Physical activity has been advocated in the treatment of diabetes mellitus from as early as the 5th century [73], [74]. Regular physical activity, including both aerobic exercises and strength training, can improve insulin sensitivity and promote weight loss. Aim for at least 150 minutes (about 2 and a half hours) of moderate-intensity exercise per week to reap the full benefits [72,73]. Several other lifestyle modifications have also been found to be helpful in the management of insulin-resistant diabetes mellitus. They include glycemic control, blood pressure control, and smoking cessation.

Hormone Therapy

In some cases, hormone therapy may be considered for men with hormone imbalances that contribute to insulin resistance. Testosterone replacement therapy has shown promising results in improving insulin sensitivity and reducing visceral fat in men with low testosterone levels [8,62].

Pharmacological Interventions - Medications

Medications targeting insulin resistance and related conditions may also be prescribed under a healthcare professional's guidance. These may include antidiabetic medications to manage blood sugar levels, lipid-lowering drugs to control cholesterol, antihypertensive medications to manage blood pressure, and antiplatelet therapy aspirin to manage vascular thrombosis [75].

Weight Management Surgery

In severe cases of obesity and insulin resistance, weight management surgeries, such as bariatric surgery, may be considered. These surgeries can lead to significant weight loss, improvement in insulin sensitivity, and reduction in visceral fat accumulation [76,77].

Complications

Many diseases are associated with insulin resistance syndrome. The associated syndrome is a cluster of abnormalities, including hypertension and other cardiovascular dysfunctions, dyslipidemia, obesity, retinopathy (eye complication), nephropathy (kidney complication), neuropathy (nerve/foot) complication, and type 2 diabetes [78]. The compensatory effect of insulin resistance in hyperinsulinemia is one of the complications.

Insulin Resistance Syndrome and Cardiovascular Diseases

Diabetes as a Cardiovascular Disease Risk Factor

There is a strong direct correlation between insulin resistance and cardiovascular diseases. [79,81] Alterations of vascular smooth muscle function have been implicated in the development of vascular complications and circulatory dysfunction in diabetes [40,82]. In many cases, this vascular smooth dysfunction is characteristic of hypertension. About 50% of patients with essential hypertension are insulin-resistant and hyperinsulinemia [52,83]. There is evidence that blood pressure is linked to the degree of insulin resistance [84]. Exactly how insulin resistance influences blood pressure, however, is controversial [84,85]. Furthermore, a strong relationship between insulin resistance and blood pressure may not occur in many patients, especially black patients [86]. The link between insulin resistance type 2 diabetes and hypertension is speculated to be associated with the damage done to the innermost layer of the blood vessel endothelial cells by elevated plasma glucose levels in type 2 diabetes mellitus. The life of the blood vessel rests on the proper function of this vascular layer because the nitric oxide (NO) that enables blood vessel relaxation is derived from this layer [87]. This endothelial damage is implicated in the damage of the microcirculation (microvascular complications) in the lower extremities and the high rate of amputation in diabetic patients.

Major organ health issues associated with diabetic complications result from microcirculation damage. Diabetic retinopathy (eye complication) is caused by damage to the blood vessels in the tissue at the back of the eye (retina) and poorly controlled blood sugar is a risk factor. Uncontrolled high blood sugar on a long-term lead to damage to nerves, a condition called diabetic neuropathy (foot complication). This damage in the microcirculation weakens the walls of the micro vessels (capillaries) and interferes with the ability of these vessels to deliver oxygen and nutrient-rich blood to them. Similarly, diabetic nephropathy (kidney complication) is a common complication of type 1 and type 2 diabetes, which also results from poorly controlled diabetes that causes damage to blood vessel clusters in the kidneys. In line with this microvascular damage, high blood pressure can cause further kidney damage. The etiology of microvascular complications is the same in both males and females [78]. But the development of insulin resistance type 2 DM in men is different from women.

The lipid profile of patients with type 2 diabetes includes decreased high-density lipoproteins (HDL) cholesterol levels and this constitutes a significant risk factor for heart disease. Increased serum very-low-density lipoprotein cholesterol (VLDL) and triglyceride levels and, sometimes, a decreased low-density lipoprotein (LDL) cholesterol level is also part of the type 2 diabetes patients' profile [87]. Hyperlipidemia represents a major risk factor for the development of vascular dysfunction and atherosclerosis. The findings by Esenabhalu et. al. (2003) [87] revealed that attenuated endothelial nitric oxide synthase (eNOS) activity was associated with superoxide anion [O (2) (-)] release in free fatty acids (FFAs) - loaded cells. These data indicate that FFAs significantly affect endothelial Ca (2+) signaling, eNOS activity, and. O (2) (-) release and, thus, might contribute to vascular dysfunction in atherogenesis. Interestingly, insulin resistance has been found in persons with low levels of high-density lipoprotein (HDL) [88]. Insulin levels have also been linked to very low-density lipoprotein (VLDL) synthesis and plasma triglyceride levels [89].

The Link Between Obesity and Insulin Resistance

Obesity stands as a prevalent and significant issue not only in the United States but also in other developed nations. Among the numerous health challenges linked to obesity are insulin resistance and type 2 diabetes. Insulin resistance consistently accompanies obesity [90]. Furthermore, there is substantial evidence from both animal studies and human research that establishes a direct cause-and-effect link, that is Obesity causes insulin resistance [91,92]. Boden, M.D., and his colleagues hypothesized that the expanding adipose tissue of obese subjects produces compounds that are either released into the bloodstream and cause insulin resistance through endocrine mechanisms in remote targets (For instance, in skeletal muscle or liver) or released in close vicinity to target organs acting through paracrine mechanisms [28]. A few years later, the cytokine Tumor Necrosis Factor-α (TNF- α) and leptin were identified as a candidate for such a role [93,94]. Increasing evidence has shown that free fatty acids (FFAs) are an important link between obesity and insulin resistance. Plasma FFA levels are usually increased in obesity [95,96]. Goutham Rao M. D. (2001) asserted that obesity is a component of the syndrome, but it promotes insulin resistance rather than resulting from it. Weight loss can improve insulin sensitivity and reduce insulin levels [3].

Severe Insulin Resistance (SIR)

An increasing number of patients have severe insulin resistance and require large doses of insulin [97]. It is quite challenging to effectively control the blood sugar levels of patients dealing with severe insulin resistance due to the limitations of conventional treatment methods [98]. Insulin resistance is characterized by an impaired response to either endogenous or exogenous insulin [99]. Although insulin resistance is a common feature of type 2 diabetes, cases of severe insulin resistance remain uncommon but are increasing as the prevalence of diabetes and obesity surges [97]. Some known causes of severe insulin resistance include overuse of some medications (Glucocorticoids, Atypical antipsychotics, Calcineurin inhibitors, protease inhibitors, Oral contraceptives); Endocrine disorders (Acromegaly, Glucagonoma, Thyrotoxicosis, Cushing's syndrome, and Pheochromocytoma); Anti-insulin antibodies; HIV-associated lipodystrophy; Physiological causes (Trauma, Sepsis, Surgery, Diabetic ketoacidosis) [97].

There are currently no guidelines or consensus statements describing how best to treat patients with severe insulin resistance. Until recently, insulin was the only therapy available to treat those with severe insulin resistance. Despite the use of high doses of insulin, however, many patients do not reach their glycemic targets and are hampered by undesirable adverse effects such as hypoglycemia and weight gain. To mitigate some of these challenges, several new therapies have emerged and can be used in combination with insulin [97], Examples are concentrated insulin products [100]; Metformin [101]; Glucagon-like Peptide 1 Receptor Agonists [102]; Dipeptidyl Peptidase-4 Inhibitors; Sodium-Glucose Cotransporter 2 Inhibitor [103].

Conclusion

Insulin is a peptide hormone secreted by the pancreas to be used for the regulation of blood glucose levels. When insulin is being produced properly but not utilized, insulin resistance occurs. Several health factors can be caused by insulin resistance with the most prioritized being hyperglycemia. As the pancreas begins to overproduce insulin to counteract hyperglycemia, it causes hyperinsulinemia. Though this will temporarily solve hyperglycemia, the pancreas will become tired and slow insulin production. This condition left untreated will lead to a condition known as insulin resistance syndrome. Insulin resistance syndrome will cause the body to produce conditions such as glucose intolerance, obesity, dyslipidemia, and hypertension which all contribute to the development of type 2 diabetes mellitus. Type 2 diabetes is caused by many factors, one specifically being insulin resistance. Men are more likely to develop type 2 diabetes mellitus due to the excess visceral and hepatic adipose tissue and low levels of adiponectin. Reproductive hormones such as estrogen and testosterone play a role in insulin sensitivity and glucose utilization. With men lacking estrogen and having the potential to experience low levels of testosterone, their chances of developing insulin resistance and type 2 diabetes are higher than women. While there are several treatments for type 2 diabetes mellitus, GLP-1 receptor agonists (when paired with basal insulin) have shown the most benefits for regulating blood glucose levels and reducing body weight without causing hypoglycemia. For future studies on treatments for insulin resistance in men with type 2 diabetes, indirect factors such as testosterone levels should be taken under further consideration. Although there is a sharp contrast in the etiology of insulin resistance type 2 diabetes in men and women, the complications of insulin resistance form of type 2 diabetes mellitus in males and females are similar.

Limitation(s)

Although this article researched insulin resistance in men with type 2 diabetes mellitus, no literature is provided for ethnic/racial variation of this disease or the most impactful causative factor. However, it is obvious that we can ameliorate or diminish its prevalence by modifying our lifestyle. No literature is provided to support the speculation that females lose the advantage that is conferred on them by estrogens in their postmenopausal years thus placing them at the same risk level for developing insulin resistance type 2 form of diabetes mellitus as men.

Dedication

This research article is dedicated to all men and women across the globe who are suffering from insulin resistance type 2 diabetes mellitus and the associated complications.

References

1. J Vijayaraghavan, J S Crabtree (2017) DIABETES : What is Diabetes ? Types of diabetes : Symptoms *Hum Heal*
2. R Taylor (2012) Insulin resistance and type 2 diabetes. *Diabetes* 61(4): 778-779
3. M Goutham Rao, Insulin resistance syndrome. *Am Fam Physician* 63(6): 9-14, 2001
4. W Y Fujimoto (2000) The importance of insulin resistance in the pathogenesis of type 2 diabetes mellitus. *Am J Med* 108(61): 9-14
5. M Z Banday, A S Sameer, S Nissar (2020) Pathophysiology of diabetes: An overview *Avicenna J Med* 10(4): 174-188
6. What is diabetes? | CDC. https://www.cdc.gov/diabetes/basics/diabetes.html (accessed Aug. 01, 2023)

7. A. Mandal (2019) The Genetics of the Insulin Gene. *News Med Life Sicence* 5: 1-4
8. YW Park, S Zhu, L Palaniappan, S Heshka, M R Carnethon, S B Heymsfield (2003) The Metabolic Syndrome: Prevalence and Associated Risk Factor Findings in the US Population From the Third *Arch Int Medcine* 163(4): 427-436. [crossref]
9. J B Meigs (2003) Epidemiology of the insulin resistance syndrome. *Curr Diab Rep* 3(1): 73-79
10. V Parcha (2022) Insulin Resistance and Cardiometabolic Risk Profile among Nondiabetic American Young Adults: Insights from NHANES. *J Clin Endocrinol Metab* 107(1): E25-E37. [crossref]
11. A Astrup (2001) Healthy lifestyles in Europe: prevention of obesity and type II diabetes by diet and physical activity. *Public Health Nutr* 4(2b): 499-515. [crossref]
12. R A Haeusler, T E Mcgraw, D Accili, C Medicine, C Surgery(2019) Biochemical and cellular properties of insulin receptor signalling. *Nat Rev Mol Cell Biol* 19(1): 31-44. [crossref]
13. M C Petersen, G I Shulman (2018) Mechanisms of insulin action and insulin resistance. *Physiol Rev* 98(4): 2133-2223
14. W. Xu(2023) Architecture of androgen receptor pathways amplifying glucagon-like peptide-1 insulinotropic action in male pancreatic β cells. *Cell Rep* 42(5) May. [crossref]
15. W Xu, J Morford, F Mauvais-Jarvis (2019) Emerging role of testosterone in pancreatic β cell function and insulin secretion. *J Endocrinol* 240(3): R97-R105
16. M S Rahman(2021) Role of insulin in health and disease: An update. *Int J Mol Sci* 22(12: 1-19. [crossref]
17. A M A Brands, R P C Kessels, E H F De Haan, L J Kappelle, G J Biessels (2004) Cerebral dysfunction in type 1 diabetes: Effects of insulin, vascular risk factors and blood-glucose levels. *Eur J Pharmacol* 490(1-3): 159-168. [crossref]
18. National Cholesterol Education Program (NCEP) (2001) Executive summary of the Third Report of the National Cholesterol Education Programme. *(Ncep)* 85(19): 2486-2497
19. A R Saltiel, C R Kahn (2001) Insulin signalling and the regulation of glucose and lipid metabolism. *Nature* 414(6865): 799-806. [crossref]
20. Insulin Resistance: What It Is, Causes, Symptoms & Treatment
21. S I Itani, N B Ruderman, F Schmieder, G Boden (2002) Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and IκB-α. *Diabetes* 51(7): 2005-2011. [crossref]
22. V T Samuel, G I Shulman (2016) The pathogenesis of insulin resistance: Integrating signaling pathways and substrate flux. *J Clin Invest* 126(1): 12-22. [crossref]
23. A Reza Khoshdel, S L Carney, A Gillies (2012) Circulatory Syndrome: An Evolution of the Metabolic Syndrome Concept!. *Curr Cardiol Rev* 8(1): 68-76. [crossref]
24. How does insulin change in type 2 diabetes?
25. K G M M Alberti, P Zimmet, J Shaw (2006) Metabolic syndrome - A new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabet Med* 23(5): 469-480. [crossref]
26. PDB-101: Diabetes Mellitus: Diabetes Mellitus: About: Causes of Diabetes
27. H P Himsworth (2013) Diabetes Mellitus: Its differentiation into insulin-sensitive and insulin-insensitive types. *Int J Epidemiol* 42(6): 1594-1598. [crossref]
28. G Boden (2001) Free fatty acids - The link between obesity and insulin resistance. *Endocr Pract* 7(1): 44-51. [crossref]
29. E E Kershaw, J S Flier (2004) Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* 89(6): 2548-2556. [crossref]
30. S G Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW (2003) et.al, Mitochondrial dysfunction in the elderly: possible role in insulin resistance *Science (80-)* 00: 1140-1142. [crossref]
31. S G Morino K, Petersen KF (2006) Molecular mechanisms of insulin resistance in humans and their potential links with mitochondrial dysfunction. *Diabetes* 55(2): 9-15. [crossref]
32. G I Morino, K Petersen, K F Dufour, S Befroy, D Frattini, J Shatzkes N., . & Shulman, Reduced mitochondrial density and increased IRS-1 serine phosphorylation in muscle of insulin-resistant offspring of type 2 diabetic parents. *J Clin Invest* 115(12): 3587-3593, 2005. [crossref]
33. A Klip, M Pâquet (1990) Glucose transport and glucose transporters in muscle and their metabolic regulation. *Diabetes Care* 13: 228-243. [crossref]
34. B lecture. McGarry, Dysregulation of fatty acid me-tabolism in the etiology of type 2 diabetes. *Diabetes* 51: 7-18, 2001. [crossref]
35. D Moller (2001) New drug targets for type 2 diabetes and the metabolic syndrome. *Nature* 414: 821-827. [crossref]
36. J Kim 2004 PKC-theta knockout mice are protected from fat-induced insulin resistance. *J Clin Invest* 114: 823-827. [crossref]
37. J Pessin, D Thurmond, J Elmendorf, K Coker, S Okada 1999, Molecular basis of insulin-stimulated GLUT4 vesicle trafficking. Location! Location! Location!. *J Biol Chem* 274: 2593-2596. [crossref]
38. E Musa, J M El-Bashir, F Sani-Bello, A G Bakari (2021) Clinical and biochemical correlates of hypogonadism in men with type 2 diabetes mellitus. *Pan Afr Med J* 38. [crossref]
39. G Navarro (2016) Extranuclear Actions of the Androgen Receptor Enhance Glucose-Stimulated Insulin Secretion in the Male. *Cell Metab* 23(5): 837-851. [crossref]
40. What Is Type 1 Diabetes? | CDC. https://www.cdc.gov/diabetes/basics/what-is-type-1-diabetes.html (accessed Aug. 01, 2023)
41. H King, R E Aubert, WH Herman (1998) Global burden of diabetes, 1995-2025: Prevalence, numerical estimates, and projections. *Diabetes Care* 21(9): 1414-1431. [crossref]
42. L Samsell, M Regier, C Walton, L Cottrell (2014) Importance of Android / Gynoid Fat Ratio in Predicting Metabolic and Cardiovascular Disease Risk in Normal Weight as well as Overweight and Obese Children. 2014. [crossref]
43. C I Sari (2019) Android Fat Deposition and Its Association With Cardiovascular Risk Factors in Overweight Young Males 10: 1-9. [crossref]
44. E B Geer, W Shen Gender differences in insulin resistance, body composition, and energy balance. *Gend Med* 6(1): 60-75, 2009, doi: 10.1016/j.genm.2009.02.002. [crossref]
45. S Lemieux, D Prud'homme, C Bouchard, A Tremblay, J P Despres (1993) Sex differences in the relation of visceral adipose tissue accumulation to total body fatness. *Am J Clin Nutr* 58(4): 463-467, Oct. [crossref]
46. M Keuper and M Jastroch (2021) The good and the BAT of metabolic sex differences in thermogenic human adipose tissue. *Mol Cell Endocrinol* 533, Aug. [crossref]
47. J L Faulkner, E J B De Chantemèle (2019) Sex hormones , aging and cardiometabolic syndrome. 6: 1-9. [crossref]
48. Y Macotela, J Boucher, T T Tran, C R Kahn,(2009) Sex and depot differences in adipocyte insulin sensitivity and glucose. *Diabetes* 58(4): 803-812, Apr. [crossref]
49. V Muraleedharan and T H Jones (2010) Testosterone and the metabolic syndrome.: 207-223
50. P M Rao, D M Kelly, T H Jones (2013) Testosterone and insulin resistance in the metabolic syndrome and T2DM in men. *Nat Rev Endocrinol* 9(8): 479-493. [crossref]
51. S Z (2019) Lutz Sex-Specific Associations of Testosterone With Metabolic Traits. 10: 1-5. [crossref]
52. I ZAVARONI, S MAZZA, E DALL'AGLIO, P GASPARINI, M PASSERI, G M REAVEN (1992) Prevalence of hyperinsulinaemia in patients with high blood pressure. *J Intern Med* 231(3): 235-240
53. W Ma (2023) Association between android fat mass, gynoid fat mass and cardiovascular and all-cause mortality in adults: NHANES 2003-2007. 65. [crossref]
54. P Wiklund, F Toss, L Weinehall, P W Franks, A Nordstro (2008) Abdominal and Gynoid Fat Mass Are Associated with Cardiovascular Risk Factors in Men and Women. 93: 4360-4366. [crossref]
55. S Kullmann (2020) Brain insulin sensitivity is linked to adiposity and body fat distribution. *Nat Commun.* [crossref]
56. F Mauvais-Jarvis, D J Clegg, A L Hevener (2013) The role of estrogens in control of energy balance and glucose homeostasis. *Endocr Rev* 34(3): 309-338. [crossref]
57. S Diego, L Jolla (2018) Association with a Weight Loss Intervention. 8(1): 1-12
58. A Nordström, J Hadrévi, T Olsson, P W Franks, P Nordström (2016) Higher prevalence of type 2 diabetes in men than in women is associated with differences in visceral fat mass. *J Clin Endocrinol Metab* 101(10: 3740-3746. [crossref]

59. K Khoramipour (2021) Adiponectin: Structure, Physiological Functions, Role in Diseases, and Effects of Nutrition.: 1-15. [crossref]

60. C Chabrolle, L Tosca, C Ramé, P Lecomte, D Royère, J Dupont (2009) Adiponectin increases insulin-like growth factor I-induced progesterone and estradiol secretion in human granulosa cells. *Fertil Steril* 92(6): 1988-1996. [crossref]

61. G Slama (2012) The history of insulin therapy. *Med des Mal Metab* 6(4): 352-357

62. I Bitoska (2016) Effects of hormone replacement therapy on insulin resistance in postmenopausal diabetic women. *Open Access Maced J Med Sci* 4(1): 83-88. [crossref]

63. A Kautzky-Willer, J Harreiter, G Pacini (2016) Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocr Rev* 37(3): 278-316, Jun. [crossref]

64. JP Despres (1997) Visceral obesity, insulin resistance, and dyslipidemia: contribution of endurance exercise training to the treatment of the plurimetabolic syndrome. *Exerc Sport Sci Rev* 25(1): 271-300. [crossref]

65. G Wittert, M Grossmann (2022) Obesity, type 2 diabetes, and testosterone in ageing men. *Rev Endocr Metab Disord* 23(6): 1233-1242. [crossref]

66. D E Laaksonen (2004) Testosterone and Sex Hormone-Binding Globulin Predict the Metabolic Syndrome and Diabetes in Middle-Aged Men. *Diabetes Care* 27(5): 1036-1041. [crossref]

67. K Kumari (2023) Treatment with Testosterone Therapy in Type 2 Diabetic Hypogonadal Adult Males: A Systematic Review and Meta-Analysis. *Clin Pr* 13(2): 454-469. [crossref]

68. Chris Strakosch (1947) The discovery of insulin. *Physician's Bull* 12(5): 16-18. [crossref]

69. W Gisela (2005) Insulin and insulin resistance. *Clin Biochem Rev* 26(2): 19

70. M Wortham, M Sander (2016) High T Gives b Cells a Boost. no. 2011

71. M Bliss (1993) The history of insulin. *Diabetes Care* 16(3): 4-7

72. W G Oakley, VE Jones, A C Cunliffe, (1967) Insulin Resistance. *British Medical Journal* 2(5545): 134-138

73. L B Borghouts, H A Keizer (1999) Exercise and Insulin Sensitivity : A Review

74. S R Colberg (2016) Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. *Diabetes Care* 39(11): 2065-2079. [crossref]

75. F Zaccardi, D R Webb, T Yates, M . Davies, (2016) Pathophysiology of type 1 and type 2 diabetes mellitus: A 90-year perspective. *Postgrad Med J* 92(1084): 63-69. [crossref]

76. D Care, S S Suppl (2021) 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2021. *Diabetes Care* 44: S15-S33. [crossref]

77. S Azim, S R Kashyap (2016) Bariatric Surgery: Pathophysiology and Outcomes. *Endocrinol Metab Clin North Am* 45(4): 905-921

78. S D, S B (2011) Late Stage Complications of Diabetes and Insulin Resistance. *J Diabetes Metab* 02(09

79. V Ormazabal, S Nair, O Elfeky, C Aguayo, C Salomon and F A Zuñiga (2018) Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol* 17(1): 1-14. [crossref]

80. A A Gupte (2015) Association between insulin resistance and estrogen in sexual precocity of obese children. *Diabetes* 12(9): 2497-2500. [crossref]

81. M Laakso, J Kuusisto (2014) Insulin resistance and hyperglycaemia in cardiovascular disease development. *Nat Rev Endocrinol* 10(5): 293-302. [crossref]

82. E Fleischhacker (2000) Human diabetes is associated with hyperreactivity of vascular smooth muscle cells due to altered subcellular Ca2+ distribution. *Diabetes* 48(6): 1323-1330. [crossref]

83. H Kawano (2010) The relationship between testosterone and metabolic syndrome. *Hypertens Res*537-538

84. K Osei (1999) Insulin resistance and systemic hypertension. *Am J Cardiol* 84(1A): 33-36. [crossref]

85. C. Ferri (1999) Relationship between insulin resistance and nonmodulating hypertension: Linkage of metabolic abnormalities and cardiovascular risk. *Diabetes* 48(8): 1623-1630. [crossref]

86. M F Saad (1991) Racial Differences in the Relation between Blood Pressure and Insulin Resistance. *N Engl J Med* 324(11): 733-739. [crossref]

87. V E Esenabhalu, G Schaeffer, W F Wolfgang (2003) Free Fatty Acid Overload Attenuates Ca2+ Signaling, NO Production in Endothelial Cells. 5(1. [crossref]

88. A Garg (1996) Insulin resistance in the pathogenesis of dyslipidemia. *Diabetes Care* 19(4): 387-389

89. A B CRUZ, DS AMATUZIO, F GRANDE, L J HAY (1961) Effect of intra-arterial insulin on tissue cholesterol and fatty acids. *Circ Res* 9: 39-43. [crossref]

90. E Ferrannini, A Natali, P Bell, P Cavallo-Perin, N Lalic, G Mingrone (1997) Insulin resistance and hypersecretion in obesity. *J Clin Invest* 100: 1166-1173

91. W S Pascoe, L H Storlien (1990) Inducement by fat feeding of basal hyperglycemia in rats with abnormal beta-cell function: model for study of etiology and pathogenesis of NIDDM. *Diabetes* 39: 226-233. [crossref]

92. V Schliack (1954) Mangelernahrung und Diabetes Morbiditat. 1954;151: 382-396. *Z Klin Med* 151: 382-396

93. Y Zhang, R Proenca, M Maffei, M Barone, L Leopold, J M Friedman (1994) Positional cloning of the mouse obese gene and its human homologue. [published erratum appears in Nature]. *Nature* 372: 425-432. [crossref]

94. J Caro, M Sinha, J Kolaczynski, P Zhang, , R Considine (1996) Leptin: the tale of an obesity gene. *Diabetes* 46: 1455-1462. [crossref]

95. E Gorden (1960) Non-esterified fatty acids in blood of obese and lean subjects. *Am J Clin Nutr* 8: 740-747

96. G Reaven, C Hollenbeck, C Jeng, M Wu, Y Chen (1988) Measurement of plasma glucose, free fatty acid, lactate, and insulin for 24 h in patients with NIDDM. *Diabetes* 37, pp. 1020-1024. [crossref]

97. T J Church, S T Haines (2016) Treatment approach to patients with severe insulin resistance. *Clin Diabetes* 34(2): 97-104

98. W Crasto (2009) Insulin U-500 in severe insulin resistance in type 2 diabetes mellitus. *Postgrad Med J* 85(1002: 219-222

99. American Diabetes Association (1997) Consensus development conference on insulin resistance. Diabetes Care. *Diabetes Care* 21: 310-314

100. W S Lane (2009) High-dose insulin therapy: is it time for U-500 insulin?. *Endocr Pr* 15: 71-79. [crossref]

101. American Diabetes Association (2017) American Diabetes Association. (2017) . American Diabetes Association Standards of medical care in diabetes-2017. *Diabetes Care* 40(1

102. A J Garber (2011) Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. *Diabetes Care* 34(2): S279. [crossref]

103. V Valentine (2012) The role of the kidney and sodium-glucose cotransporter-2 inhibition in diabetes management. *Clin Diabetes* 30(4): 151-155.

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