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Consequences of Insulin Resistance Long Term in the Body and Its Association with the Development of Chronic Diseases

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Abstract

Insulin resistance (IR) has become more common in recent years, and it has been related to a number of metabolic disturbances such as obesity, non-alcoholic fatty liver disease (NAFLD), Diabetes mellitus (DM), metabolic syndrome (MetS), cardiovascular disease (CVD), polycystic ovary syndrome (PCOS), and others. IR is defined by a decreased ability of cells to respond to insulin action, as well as hyperglycemia and hyperinsulinemia. There are many factors responsible for the evolution of IR, most notably genetic factors and the modern lifestyle in which an unhealthy diet and lack of physical activity have contributed to an increase in the spread of IR worldwide at various ages. Since insulin is the dominant hormone that drives metabolism and many important functions. Therefore, any alteration in normal insulin, such as high or low insulin levels has a significant influence on the body. Furthermore, to understand IR, it is essential first to know how insulin functions under natural physiologic conditions. This review aims to contribute to an understanding of insulin and insulin resistance, as well as the role of genetics and lifestyle in the evolution of insulin resistance and knowledge of the many common diseases associated with insulin resistance; in the final section of the review, certain diets and exercises have been suggested to help reduce insulin resistance.

Keywords

Cardiovascular, Obesity, Diabetes, (PCOS), Metabolic Syndrome, Insulin

1. Introduction

Insulin resistance (IR) is the main danger factor for many diseases and is a de-

fining feature of metabolic disorders, which are thought to be the pathogenic driver of many modern diseases [1] [2] [3]. IR causes a broad range of clinical symptoms and is involved in a variety of pathological states, such as type 2 diabetes (T2DM) polycystic ovary syndrome (MetS), non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, obesity, and glucose intolerance [2] [4]. Furthermore, it is widely accepted that IR is involved in the pathogenesis of most metabolic disorders, cardiovascular disease (CVD), atherosclerosis, certain cancers, and neurodegenerative diseases. IR is thus regarded as the primary cause of many diseases and contributes significantly to the chronic disease epidemic [3] [5]. IR is a pathological state defined as a disruption in insulin production and as the tissue response to insulin decreases, resulting in impaired glucose homeostasis [4]. Because insulin performs multiple activities in the body, therefore, the hyperinsulinemia which may occur as a result of a failure to regulate carbohydrate metabolism causes a slew of health problems [6]. According to the latest studies, IR has a wide-ranging impact on working-age people, and it is related directly to obesity. It has been found that 15.5 - 51.0 percent of adults in highly developed countries are affected by IR. [4]. However, research has shown that IR can impact people who are seemingly healthy and they don't have weight gain [4]. Moreover, genetics and lifestyle are thought of as being the major determinants of these IR disturbances. Nonetheless, genetic factors and lifestyle cannot account for the recent significant increase in the prevalence of IR; therefore, it is thought fetal growth factors may also be involved so changes in the hormonal environment during fetal growth can contribute to the evolution of IR [2]. In addition, chronic low-grade inflammation is a major contributor to the evolution of IR. Also, immune system cells have been linked to metabolic disease [7]. Moreover, notwithstanding extensive research, the underlying factors that underlie insulin resistance are still unknown; however, extracellular disorders like an overabundance of nutrients, hyperinsulinemia, and inflammation are universally accepted to cause intracellular stress in target tissues, like adipose and muscle tissue, impairing insulin's ability to start these cells' usual metabolic processes [1]. Furthermore, because insulin resistance is a major and prevalent factor of metabolic disease, it ought to be thought of as a treatment aim for these disorders such as diabetes mellitus; however, there is no widely recognized explanation that describes the mechanism underlying IR. Moreover, mounting evidence suggests that ectopic lipid accumulation is more significantly associated with diabetic physiology, which includes plasma inflammatory cytokine levels and Endoplasmic reticulum stress (ER stress) [3]. In addition, many studies have demonstrated that the evolution of IR is significantly influenced by the accumulation of diacylglycerol (DAG) in plasma membrane fractions as a result of ectopic fat deposition, which activates nPKC in skeletal muscle and liver tissues, depending on this pathophysiological mechanism of IR, the inhibition of lipid production in the liver and the activation of fat oxidation in skeletal muscle can help prevent ectopic lipid buildup, and possibly has an advantageous

impact on insulin sensitivity [3]. This review paper aims to contribute to an understanding of insulin and insulin resistance, as well as the role of genetics and lifestyle in the evolution of insulin resistance and knowledge of the many common diseases associated with insulin resistance, in the final section of the review, certain diets and exercises have been suggested to help reduce insulin resistance.

2. Insulin and Insulin Resistance

2.1. Insulin

Insulin is a peptide hormone that controls the metabolic process of glucose. In 1921-1922, Banting and Best unearthed insulin at the University of Toronto. It aids in the transport of glucose from the blood into the cells, in which it is metabolized to generate energy [8]. It keeps blood sugar levels stable. When blood glucose levels rise. Insulin lowers them by raising the absorption of glucose in the liver, muscle, and fatty cells, these tissues use surplus glucose to produce glycogen, and glycogen is converted into glucose when blood sugar falls. It increases DNA replication and protein synthesis, which influences amino acid absorption. Insulin promotes the production of fatty acids by allowing fat cells to take lipids from the blood. Proteolysis, lipolysis, and gluconeogenesis are also reduced [8]. The role of insulin in glucose balance is distinguished by its direct effects on the liver, white adipocytes, and skeletal muscle, each of these tissues plays a unique role in metabolic homeostasis [9]. When nutrients are abundant under these conditions, Insulin shifts from nutritional output to stockpiling. Blood glucose levels reach a critical level following nutritional status, which induces insulin production from β-cell. Insulin enhances carbohydrate absorption in skeletal muscle and adipose tissue, where proteins and carbohydrates are kept as fats. Moreover, overeating and inactivity, on the other hand, impede this mechanism and therefore can lead to significant health risks such as heart problems and T2DM [3]. In contrast, in the fasted state, to sustain normal glucose levels in the blood, the liver releases glucose in the bloodstream; hepatic glucose production (HGP) is a process that includes the degradation of liver cell glycogen and the production of glucose from scratch utilizing glycerol and fatty acids [3]. As previously stated, insulin's function is to keep glycemia stable by stimulating glucose absorption in adipose tissue, and skeletal muscle while inhibiting liver glucose production [10]. Insulin influences target tissue both directly and indirectly. Since of their incorporated nature, these spillovers are complicated in cultured cells and, as a result, are more complicated to understand than insulin's direct, cell-independent impact. The suppression of hepatic acetyl-CoA content by insulin-induced lipolysis demonstrates the indirect action of insulin. This mechanism combined with glycerol turnover suppression, allows insulin to inhibit lipolysis and thus prevent gluconeogenesis in the liver. Other important indirect insulin action pathways include insulin inhibiting glucagon synthesis via paracrine sending signals and central nervous system insulin action [9]. Physiologically, The interactions of some of the other hormones at the whole-body lev-

el affect the actions of insulin. Although insulin is the primary hormone trying to drive metabolic activities, it works in collaboration with IGF-1 and growth hormone [11]. Insulin, on the other hand, is a pleiotropic hormone that influences amino acid and ion transfer, protein and fat metabolism, nitric oxide production, reproduction, and distinctions [12].

2.2. Insulin Resistance

Insulin resistance (IR) is categorized as a reduced capacity of target tissues to be responsive to insulin action. In addition, IR contributes to the development of metabolic disorders and T2DM, and is frequently linked to CVD [13]. This phenomenon is caused by significant defective in insulin-mediated glucose absorption, specifically glycogen composition, and glucose oxidation. Moreover, The influences of IR are determined by metabolic and physiological functions in different parts of the body. As also liver tissue, adipocytes, and skeletal muscle are all affected by IR, as it is the primary site in inside cells glucose transfer and lipid and glucose metabolic [14]. As previously stated, IR is biologically known as the failure of certain body tissues to react to normal insulin levels, which would need IR levels to keep insulin normal processes. It is worth noting, Insulin's glucose organization impacts, like suppression of hepatic glucose production and, cellular absorption of glucose, lipolysis, lipolysis, and synthesizing of glycogen, is not found in insulin-resistant tissues at normal plasma levels [3]. Insulin resistance and hyperinsulinemia occur before hyperglycemia [10]. Approximately 70 percent and 10 percent of glucose absorption are catalyzed by insulin through the GLUT 4 receptors in adipocytes, and skeletal muscle, respectively. Furthermore, inhibiting lipoprotein lipase active in fat cells increased free fatty acid release additionally, Insulin resistance impairs synthesizing of glycogen and proteolysis in skeletal muscles. As well as because the liver is responsible for 30% of glucose elimination, IR causes the liver to secrete more triglycerides and very low-density lipoprotein [14]. Peripheral insulin resistance increases insulin requirements while also inducing β-cell adjustment by continuing to increase β-cell lump and activity in order to produce an adequate amount of insulin to keep normal blood glucose levels; as a result of this compensating response, hypersecretion of insulin and hyperinsulinemia occur, and insulin rotates at higher levels, which contributing the metabolic abnormalities seen in T2DM [10]. Insulin, lack of insulin, and IR has various impacts depending on the biological properties of organs and tissues. Involved, as well as their reliance on insulin for metabolic processes. Insulin-dependent tissues are primarily adipose tissue and skeletal muscle, based on intracellular glucose transport. Insulin's actions, on the other hand, Insulin has numerous and diverse impacts [11]. Skeletal muscles are the primary depreciation of glucose; therefore, IR in these muscles impairs muscle glycogen production, which demonstrates that the primary cause is decreased intracellular glucose transport. As a result, muscular insulin resistance may have an impact on whole-body metabolism [3] [11]. The

effects of IR on the liver increase free fatty acid flow and promote the output of very low-density lipoprotein [11]. Moreover, hepatic IR leads to IR in other tissues [15]. Knowledge of the mechanisms underlying IR is possible, through skeletal muscles, fatty tissues, and the liver because muscles are a quantitative tissue for eliminating insulin-induced glucose and fatty tissues and the liver are qualitatively important sites for insulin signals caused by glucose [3]. Surprisingly, IR and low insulin levels influence metabolic adjustment during famine and prenatal. Insulin levels fall as a result of famine. In response to low glucose levels, it is simple to mobilize glucose from the liver, glycerol and fatty acids from lipid cells, and amino acids from muscle tissues, which helps to maintain glycemia. While IR during pregnancy guarantees that the fetus receives sufficient nutrients and metabolic pillars for growth [14]. Moreover, because insulin action provides multiple roles in various cell types, IR has a wide range of functional consequences in the insulin targettissues [9]. The disruption of peripheral vascular resistance, which is a result of IR, raises blood pressure. IR contributes to the evolution of target organ damage in arterial hypertension. As well, the metabolic changes that lead to the onset of T2DM are brought on by the persistence of IR. The two main external factors that contribute to the evolution of IR are an increase in caloric intake and sedentary behavior as shown in **Figure 1** [12].

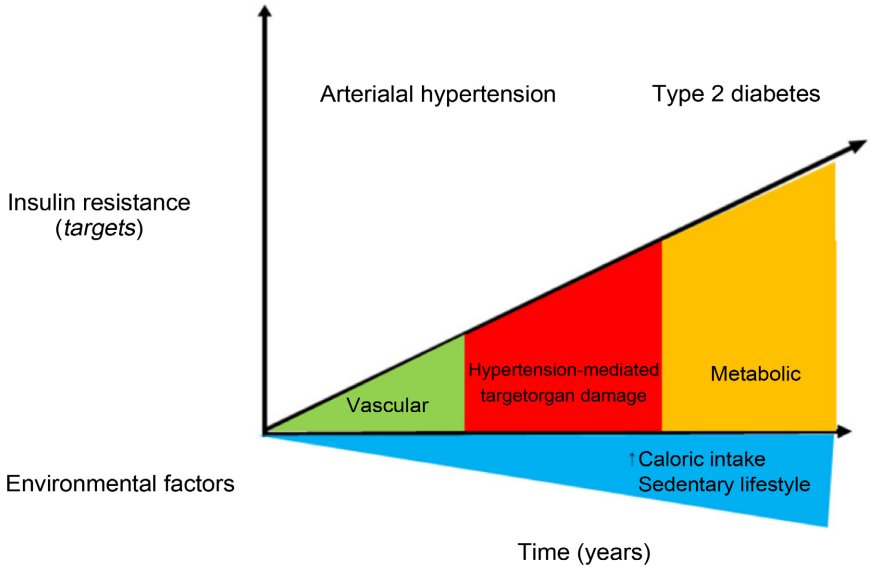

Figure 1. Insulin resistance is a tissue- and organ-specific phenomenon that occurs over time [12].

3. The Role of Genetics and Lifestyle in Insulin Resistance

IR is caused primarily by a combination of genetic and environmental factors (low physical activity and overeating) [16].

3.1. Genetic Factors

Early familial genetic investigations showed that IR, as well as MetS, had a

hereditary foundation. Since 2007, around 88 loci have been linked to the likelihood of having T2DM in genome-wide association studies (GWAS) The great majority of T2DM-related loci appear to be linked to β-cell performance and insulin production [17]. Furthermore, In rare cases, IR is caused by mutations in genes involved in insulin release [1]. Even though being a heritable trait, IR is typically only medically demonstrated in the context of being overweight. However, in the absence of obesity, IR of severe severity evolves in a minority of patients; many of these patients had genetic mutations, which some recently discovered [18]. More than 15 different genes have now been identified as having flaws in people with severe IR [19]. Despite continued success in defining risk locations of IR, besides T2DM, estimates show that they represent just 25 - 44 percent of inherited IR [17].

3.2. Lifestyle Factors

Overeating calorie-rich food and unsaturated enough has resulted in unprecedented increases in obesity in industrialized nations [9]. Furthermore, central obesity has been linked to IR. But even so, the molecular mechanism by which fat leads to IR is Incomprehensible [14]. The leading causes of IR are a diet containing full of fat, and refined carbohydrates, and a lack of exercise, as also aggravated by genetic factors like the onset of central obesity [7]. Physical inactivity and obesity can they a role in the evolution of IR [14]. According to the latest research inadequate sleep has an effect on IR and insulin action; besides, a lack of sleep is linked to an increase in body mass index (BMI) [11].

4. The Most Common Diseases Associated with Insulin Resistance

4.1. Metabolic Syndrome

Metabolic syndrome (MetS) is defined as a group of metabolic disorders that includes hypertension, IR, obesity, and dyslipidemia, as well as it, has been linked to an increased risk of heart disease and T2DM [7]. In 2009, the World Health Organization and other organizations issued a scientific statement characterizing metabolic syndrome as high blood pressure, high triglyceride, LDL/HDL cholesterol levels, dyslipidemia, and abdominal obesity [17]. According to global statistics, the metabolic syndrome occurs in approximately 25% of the young population. In India, people aged 20 to 25 have a 24 percent incidence, 28 percent in the United States, 30.1 percent in Tehran, 33.4 percent in Turkey, and 39.3 percent in the United Kingdom (Saudi Arabia) [20]. IR is associated with a rise in body fat as well as a preference for fat accumulation in the upper body. Women who are overweight and have a higher percentage of fat in their bodies In the abdominal and chest region have higher levels of IR, glucose intolerance, dyslipidemia, and hyperinsulinism than women who are overweight but have the least amount of body fat. As a result, the proportion of body fat is an essential factor of MetS [20]. IR in adipose tissue leads to hyperlipidemia, a significant

characteristic of Mets [15]. The Mets are also characterized by hyperinsulinemia, knowledge of the underlying factors that underlie insulin action and resistance is essential for managing this syndrome [15]. The first step in treating Mets is to control risk factors including, obesity, lack of activity, and an unhealthy lifestyle [20].

4.2. Obesity

Since the 1970s, the global prevalence of obesity has nearly tripled becoming a global epidemic. In 2016, over 1.9 billion persons (39 percent of adults worldwide) were overweight, with over 650 million obese [21]. Obesity is a significant contributor to hypertension, dyslipidemia, heart disease, and T2DM, as well as sleep apnea, and certain types of cancer. As a result, this largely preventable condition is regarded as one of the most serious healthcare issues [22]. Obesity, especially abdominal obesity, is associated with peripheral insulin resistance. IR, on the other hand, is not simply a result of being overweight or obese. IR varies greatly within obesity, and those with the highest level of IR have the highest risk of T2DM and heart disease. Although obesity is not always linked to IR, the vast majority of insulin-resistant people are obese or overweight. Furthermore, it is clear that lifestyle factors such as Excessive consumption of unhealthy foods and a lack of regular exercise play an important part in the rising prevalence of obesity [22] [23].

4.3. Diabetes Mellitus

Diabetes mellitus (DM) is a metabolic disorder in which glucose homeostasis is impaired, and it is on the rise around the world as it could be described as a global epidemic [10]. Diabetes affects 425 million populations globally, as per the World Health Organization. By 2045, this figure is predicted to rise by 50 percent. Moreover, also claimed the lives of 1.6 million people in 2016. Besides, retinopathy, nephropathy, neuropathy, and heart disease are common consequences in diabetic patients [10]. T1DM is a type of diabetes that affects approximately 5% - 10% of diabetics and is caused by β-cell failure, and decreased insulin production, and insulin is used to treat hyperglycemia in patients [15] [24]. As also T2DM affects 90 - 95 percent of diabetics. In developed countries, type 2 diabetes is also one of the most highly prevalent metabolic diseases. It is defined as a lack of insulin responsiveness and IR in peripheral tissues. Insulin therapy is not used for T2DM [15] [24] [25]. IR in the principal insulin-target tissues is a well-known defect that occurs prior to the onset of type 2 diabetes [13]. Hyperinsulinemia, a prominent hallmark of the MetS is caused by excessive insulin secretion from β-cell that has been linked to the evolution of cardiovascular disease and T2DM [15]. Moreover, IR is involved in the pathophysiology of T2DM. Additionally, IR has been associated with a higher risk of cardiovascular dysfunction in T2DM patients [26]. Muscle cells are destroyed by high blood sugar, causing weakness and mass loss, muscle weakness is a powerful indicator of diabetes-related deficits and disabilities [26]. In addition, obesity t is a

common contributor to T2DM [27]. 80% of T2DM patients are overweight or obese [26]. T2DM is characterized by IR. Diabetes treatment aims to reduce IR. As a result, assessing IR using the HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) is animportant step in preventing diabetes [28] [29]. Obesity, T2DM, as a result of changes in contemporary life like ample food and lack exercise [10].

4.4. Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a multifactorial syndrome distinguished by high levels of luteinizing hormone, as well as excess androgen and anovulation; it's also the most communist condition in women of reproductive age [30]. T2DM and glucose tolerance disorder are more common in women who have PCOS [31]. PCOS is often linked to obesity and has a negative effect on reproductive [30]. PCOS is a metabolic disease associated with IR. Where IR affects between 60 and 70 percent of women with PCOS. Obesity worsens IR in PCOS patients, even though thin women with PCOS may have it as well [32]. Androgen excess, which affects 60 - 80 percent of PCOS patients, is a major symptom of the condition. It aids in the pathophysiology of PCOS by keeping the abnormal hormone shareholders [30]. Moreover, obesity, metabolic complications, and cardiovascular risk IR are present in 60% - 80% of all PCOS women. IR is also linked to hyperandrogenism, anovulation, and an increased risk of CVD [33]. In spite of the fact that IR is frequently connected with obesity, it is as prominent in PCOS women who are not overweight [34]. Despite the many ideas presented to define the pathogenic cause of PCOS, the involvement of IR as a fundamental causative factor has remained undisputed and recognized. Hyperinsulinemia stimulates excessive ovarian androgen production, resulting in PCOS [30].

4.5. Cardiovascular

Cardiovascular disease (CVD) is the most common reason for mortality around the world. In spite of the progress in prognosis and therapy over the last 40 decades, but CVD has increased in tandem with older adults, rising obesity, and metabolic diseases [35]. Additionally, Obesity, aberrant lipid levels, and IR are all factors that contribute to the development of CVD. As well as, CVD is more common in people with a BMI of 30 kg/m^2 or above than in people with a normal BMI [14]. Besides, More than 80 years ago, when Banting and Best discovered insulin, they recognized that CVD is intimately linked to a group of metabolic diseases [35]. Moreover, people with T2DM have a two to eight times higher risk of CVD than people without diabetes as well as It is expected that diabetics have by 5 - 15-year reduction in life span due to higher vascular disease mortality [14]. Hyperinsulinemia and IR play important roles in other Mets disturbances and raise the risk of CVD [35]. IR and cardiometabolic disruptions may be influenced by the variability of fat content and adipose tissue distribu-

tion. In a sound heart, fatty acid oxidation creates around 50% - 70% of the ATP needed for cardiac fuel, while glycolysis contributes only about 10% of total ATP synthesis. Despite the fact that fatty acids appear to be the primary source of energy, the heart can switch to another ATP source based on what is available. But IR cause decreases metabolic flexibility, allowing fatty acids to become the primary source of energy. As a result of this change lipid absorption and aggregation in the heart increase, resulting in lipotoxicity [14]. IR and CVD are linked by several molecular mechanisms which include IR, such as its involvement in the evolution of atherosclerosis, vascular function, hypertension, and macrophage accumulation additionally, IR, hyperglycemia, and inflammation can start causing and predicting adverse cardiovascular events [14].

4.6. Atherosclerosis

The involvement of IR, hyperinsulinemia, and the pathophysiology of its clinical implications in the development of atherosclerosis are highlighted. The arterial wall is affected both directly and indirectly, as well as, there is significant evidence that insulin physiologically targets the endothelium, implying a relationship between IR and atherosclerosis [12]. IR induces endothelial cell malfunction by lowering nitric oxide production and boosting procoagulant chemical production, resulting in platelet accumulation. IR affects the PI3K pathway but not the MAP kinase pathway; as a result of insulin's mitogenic impact on endothelial cells, atherosclerosis develops [14]. In people who have IR, atherosclerosis is the biggest cause of mortality [19]. Furthermore, inflammatory mechanisms regulate the atherosclerotic process. Similarly, IR also was identified as a chronic inflammatory condition at a low level [12].

4.7. Hypertension

Hypertension is a common cause of CVD, such as cardiomyopathy, vascular dysfunction, and strokes. As well as excessive obesity is a significant component of main (primary) hypertension. The distribution of adipose tissue, on the other hand, plays an essential role in defining the effect of obesity on blood pressure. [35] In IR, hyperglycemia promotes a liquids transfer from the inside cells to the outside cells, which leads to an increase in plasma volume and an increase in blood pressure. Furthermore, increased insulin secretion enhances sodium reabsorption from kidney tubules, and reninexcretion, in addition to activation of the sympathetic nerve, which can cause an increase in blood pressure Chronically [36]. IR and Hyperinsulinemia are thought to be important causes of hypertension. Since 30 years ago, researchers have discovered. Patients with IR have higher blood pressure than people with healthy insulin levels [35].

5. Lifestyle Modification

According to health recommendations, people of any age should adopt healthy lifestyles in order to stay healthy and avoid non-communicable diseases. As well,

when there are risk factors for CVD keeping track of healthy eating habits is critical [37]. Moreover, weight loss and lifestyle modification (healthy food and physical activity) are the most common advice for improving insulin sensitivity [38]. The treatment approach includes lifestyle adjustments that aim at calorie reduction and weight loss, as well as regular exercise. Many dietary patterns, such as the Mediterranean, are thought to help maintain healthy body weight and reduce IR [6]. There are numerous dietary approaches for body weight loss available, such as a high-protein, low-calorie diet. Furthermore, there are other great advantages to losing weight that extend beyond glycemic maintenance [28]. Notably, consuming enough fiber is essential because it has multiple advantages, including improvement of insulin sensitivity and prevention of hyperglycemia [5]. In addition to the ketogenic diet (KD), which contains very few carbohydrates and relies primarily on lipids and proteins for energy, induces ketosis which has been shown to be beneficial for losing weight and enhancing blood sugar balance [28]. Besides, physical exercise has also been identified as a critical component in the primary protection of T2DM. Exercise has multiple benefits like glycemic control as well as lowering IR, enhancing physical fitness, and strengthening muscles [26]. Moreover, exercise for 30 minutes per day is beneficial to body health [6]. Exercise has a substantial several of proof supporting its involvement in decreasing insulin sensitivity and its positive effects on IR conditions, as well as scientific studies have found that lifelong regular exercise minimizes and considerably the incidence of T2DM [11]. According to the latest research, combining aerobic and resistance exercises is more useful than practicing one or the other separately. Additionally, resistance exercise enhances muscle mass, which increases blood glucose absorption by raising muscle mass, while aerobic exercise improves insulin sensitivity [26].

6. Conclusion

Insulin resistance is becoming more common in an alarming situation in which modern lifestyles and physical inactivity have aided in the evolution of IR. Despite the fact that underlying factors that underlie IR have not been identified until now. However, studies and research have provided some theories about the development of IR as well as evidence of the involvement of IR in the evolution of many metabolic disorders in addition to cardiovascular diseases. The first main treatment for many metabolic diseases and to improve IR is to modify diet, get adequate sleep, and exercise regularly. Moreover, has been shown Physical activity reduces IR with high efficiency in the short and long term.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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