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Review Article

The Association of A Sedentary Lifestyle with Glucose Metabolism and Insulin Resistance

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Abstract

Many people, including office workers, drivers, gamers, commuters, elderly people, and pregnant women, are at risk of a sedentary lifestyle. A sedentary lifestyle is characterized by spending more than 6-8 hours a day without doing intense or moderate physical activity, such as sitting on public transport, at work, or at home. Sedentary behavior is known as the main factor in the prevalence of obesity and non-alcoholic fatty liver disease (NAFLD). A sedentary lifestyle induces insulin resistance (IR) by elevating the workload of the islets and reducing their efficiency through various pathways, including inflammation, dysregulation of glucose and lipid homeostasis, and enhancing lipid storage. Furthermore, it leads to mitochondrial dysfunction, endoplasmic reticulum stress, beta cell apoptosis, and oxidative stress. In this manuscript, we explore the possible association between sedentary lifestyle and insulin resistance to increase the knowledge about the pathophysiology of sedentary lifestyle-dependent IR in the liver. Hence, in this review article, we focused on the relationship between sedentary lifestyle and lipid and carbohydrate metabolism in the liver, which can finally lead to insulin resistance.

Keywords: Sedentary lifestyle, Metabolism, Insulin resistance, Inactivity

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Introduction

Many people, including office workers, drivers, gamers, commuters, elderly people, and pregnant women, are at risk of a sedentary lifestyle. A sedentary lifestyle is characterized by spending more than 6-8 hours a day without doing intense or moderate physical activity, including sitting on public transport, at work, or at home (1). The term "sedentary" comes from the Latin "sedere" (to sit) and refers to lying behavior or any waking sitting with low energy expenditure. This description fits with the commonly cited technical definition of < 1.5 metabolic equivalent units (2). It has been established that a sedentary lifestyle is associated with many disorders (Figure 1) (3). Bed rest efficiently induces extreme sedentary behavior. Inactivity is known as the main factor in the prevalence of obesity and non-alcoholic fatty liver disease (NAFLD) (4). The liver is known as an insulin-sensitive tissue and plays an important role in energy homeostasis by generating over 80% of blood glucose, as well as performing numerous key functions in lipid and glucose metabolism. Various situations, such as liver damage, lipid accumulation and peroxidation, inflammation, reactive oxygen species (ROS), and mitochondrial dysfunction, can promote liver insulin resistance (IR) (5).

Different experiments have demonstrated that nutritional factors, overproduction of very-low-density lipoprotein (VLDL), and hepatic steatosis, as a result of a sedentary lifestyle, can lead to hepatic IR (6-8). The liver is recognized as a primary target of metabolic changes and can participate in inflammatory and metabolic changes in peripheral tissues that describe metabolic syndrome (9). In experimental settings, liver proteins such as hepatokines can promote IR in peripheral tissues like muscle and adipose tissue (10). In fact, the liver and the products derived from this organ, in addition to the effects on liver gluconeogenesis, can also change peripheral tissue insulin sensitivity (11). It has been well established that a sedentary lifestyle changes various factors in the liver (12). The severity of diabetogenic phenotypes is related to the duration of sedentary lifestyle, indicating that the liver is probably one of the main targets. Furthermore, previous experiments have indicated that physical inactivity is related to islet cell insufficiency. A sedentary lifestyle can induce IR by elevating the workload of islets and reducing their

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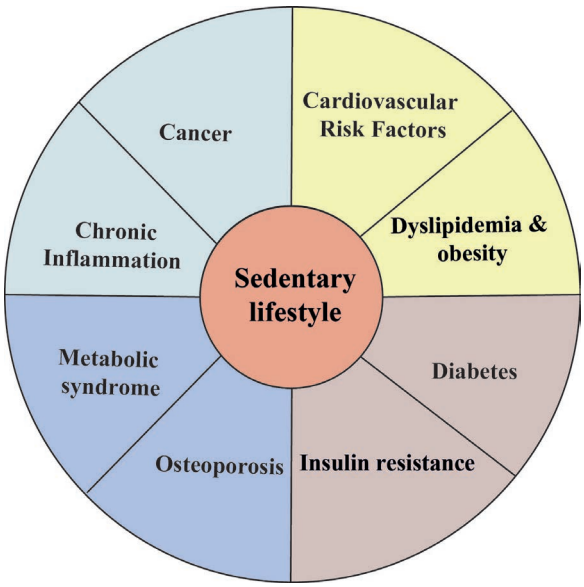


Figure 1. The Association of Sedentary Lifestyle with Many Disorders

efficiency via different pathways, including mitochondrial dysfunction, ER stress, inflammation, oxidative stress, and apoptosis of β-cells (13). The function of different factors participating in hepatic IR will be discussed in subsequent sections of this review.

Sedentary Lifestyle and Liver Insulin Resistance

Overweight and obesity are strongly linked with a sedentary lifestyle, which is a risk factor for insulin resistance (14). Sedentary behavior in the short and long term is associated with insulin resistance (15). A change in the insulin signaling pathway is an early response to prolonged sedentary behavior (16). In type 2 diabetes (T2D) and obesity, insulin cannot properly regulate hepatic metabolism, leading to excess glucose production and lipid synthesis, a situation referred to as "selective hepatic insulin resistance". Furthermore, elevated lipogenesis and hepatic glucose production are well recognized in insulin-resistant individuals (17). Insulin is the main regulator of lipogenesis, gluconeogenesis, and glycogenesis in the liver, and IR conditions are accompanied by NAFLD (18). It has been reported that lipogenesis was twofold in sedentary individuals compared with controls (19).

Increased circulating FFA levels and chronic inflammation are linked with obesity and have a vital role in the pathogenesis of hepatic IR. Inflammatory markers activate c-Jun NH (2)-terminal kinase (JNK) and inhibitor of kappa B kinase beta (IKKβ), which lead to activation of nuclear factor-κB (NF-κB), and degradation of the inhibitor of κB (IκBα). NF-κB activation further induces the expression of inflammatory genes and suppresses insulin signaling via serine phosphorylation of IRS-1, leading to hepatic IR. Moreover, the inflammatory markers increase the suppression of the expression of cytokine signaling (SOCS)3 via activation of transcription (STAT)- and NF-κB-mediated pathways. It has been established that SOCS3 can bind to the insulin receptor and inhibit the phosphorylation of IRS-1 and IRS-2 (18).

Increased FFA levels can also activate inflammatory pathways via the toll-like receptor 4 (TLR4), which stimulates the NF-κB inflammatory pathway. Furthermore, high FFAs levels lead to a high net intracellular diacylglycerol (DAG) concentration in the liver. Elevated DAG activates PKC, which phosphorylates the insulin receptor, causing impairment in the interaction of insulin receptor substrate 1 and 2 with insulin receptor (18). A previous study showed that TLR4 is a link between inflammation, sedentary lifestyle, and disease (20).

Sedentary behavior is related to islet cell deficiency. Inactivity can induce insulin resistance by elevating the workload of islets and reducing efficiency via different pathways, such as inflammation, mitochondrial dysfunction, endoplasmic reticulum stress, beta cell apoptosis, and oxidative stress (13). Increased ROS production and hyperlipidemia can cause activation of hepatic stellate cells (HSC) (21) and lead to liver fibrosis. Certainly, in medical conditions such as hyperinsulinemia and insulin resistance, as well as in a sedentary lifestyle, the production of ROS is increased in part by the augmented activity of cytochrome P450 2E1 (CYP2E1) (22). This change is due to the decrease in the repressive influence of insulin on the CYP2E1 gene (22). Augmented ROS can then directly raise collagen generation by activated HSCs (22, 23). Increased CYP2E1-mediated ROS production could further impair insulin signaling in the liver, aggravating the liver IR and injury (24). HSCs contribute to the pathogenesis of liver damage and HSC activation, a process involved in collagen secretion and represent the final common pathway in the response of the liver to an insult or injury. Therefore, ROS is a crucial and well-recognized component which is produced by inactivity (13).

Lipid accumulation in hepatocytes is greater in obese animals compared with controls, and this deposition is relatively higher beside the portal triad than near the central vein (25). Furthermore, changes in the structure of liver sinusoids are observed in obese animals as compared with a control group (26).

Liver function test markers, specially γ-glutamyltransferase (GGT) and alanine aminotransferase (ALT), predict the incidence of obesity and T2D. Elevated levels of liver enzymes were reported in sedentary behavior (27). In an experiment which involved 3 bed rests of various periods in men and women (42, 60, and 90 days), AST and ALT levels were significantly above normal laboratory values, with an increase of 50% (28). It is important to note that epidemiological studies suggest that elevation of activity of transaminases (especially ALT), even within the normal value, predicts the incidence of fatty liver and new-onset diabetes, independently of classical risk factors (29).

The upregulation of ALT during bed rest may reflect the development of fatty liver. In this context, Perseghin et al (30) have demonstrated a positive association between

intrahepatic fat accumulation and high habitual physical activity in humans. It is noteworthy that the ALT and GGT levels are strongly related to peripheral and liver IR and decreased liver insulin extraction in healthy human subjects (31). It has been reported that increased levels of ALT and ALT/AST ratio are related to hepatic and peripheral insulin resistance (32).

Sedentary Lifestyle and Carbohydrate Metabolism

A sedentary lifestyle for a long time can increase the expression of phosphofructokinase (PFK), a key rate-limiting enzyme in the glycolysis pathway. Reduction in the hexokinase (HK) levels was reported after short-term (7 days) and long-term (84 days) bed rest (16).

It has been established that a sedentary lifestyle negatively influences the expression, translocation, and function of genes and proteins that participate in carbohydrate metabolism. Regular exercise increases the activity of glucose transporter 4 (Glut-4), the main and insulin-dependent glucose transporter. Therefore, any disturbance in the function or expression of GLUT4 can affect insulin signaling and induce IR (33). Previous studies reported that even 7 days of inactivity can decrease insulin action by reducing the GLUT4 levels (34). However, studies show that physical inactivity can induce IR by reducing Glut-4 levels (33). It has been reported that 9 days of bed rest change the expression of genes involved in insulin signaling, including hexokinase 2, Ras related glycolysis inhibitor and calcium channel regulator (RRAD), and GLUT4, which can consequently reduce insulin sensitivity in skeletal muscles. Another study showed that physical inactivity downregulates glycogen synthase, GLUT4, Akt proteins, and Hexokinase 2 (HK2) and decreases insulin sensitivity (13).

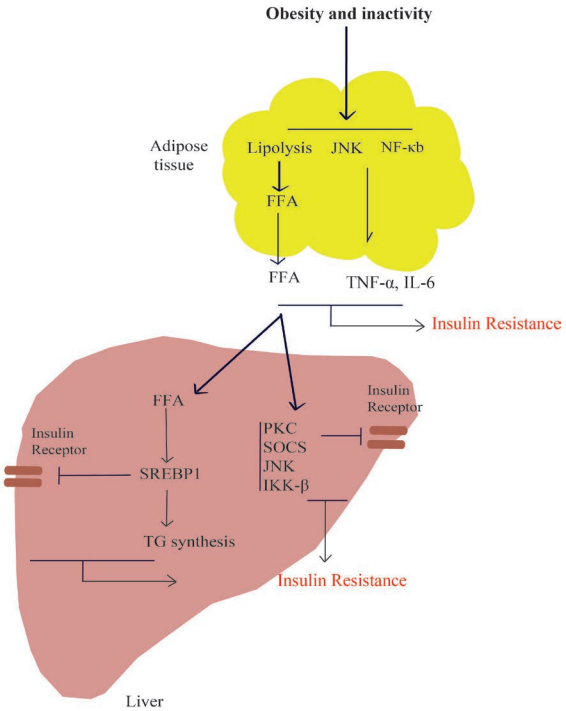


Figure 2. The Role of Obesity and Inactivity in the Induction of Insulin Resistance by Affecting Inflammatory Markers and Triglycerides Metabolism

Hepatic glucose homeostasis is important for maintaining blood glucose in the normal range. As a result, it is crucial to know whether these parameters are changed by inactivity. For instance, studies have revealed that glucose levels increase after spaceflight (SF) (12). Merrill et al have demonstrated a 20-fold increase in liver glycogen in SF animals in comparison with controls (35). Racine et al have conducted a morphometric study and demonstrated that the liver glycogen level of flight and tail-suspended animals is significantly increased (36). Abraham et al have measured (37) the activities of various enzymes involved in carbohydrate and lipid metabolism in rats after spaceflight. They have uncovered increased levels of palmitoyl-CoA desaturase and lactate dehydrogenase (LDH) and low levels of glycogen phosphorylase and 6-phosphogluconate dehydrogenase in rats exposed to prolonged SF (18.5 days). Furthermore, higher levels of liver palmitoleate and glycogen were significantly different from those of the control group, which may be due to the augmented activity of palmitoyl-CoA desaturase and reduced activity of glycogen phosphorylase, respectively (37, 38).

The amount of liver glycogen is also regulated by FFAs (39). Under fasting conditions, lipolysis is increased (40), blood FFA concentrations increase, and the generation of glucose adapts via preservation of gluconeogenesis and downregulation of the glycogenolysis pathway (41). In this context, it has been demonstrated that infusion of lipid/heparin restrains the breakdown of liver glycogen in fasting healthy human subjects (42). An in vitro experiment has revealed that FFAs raise liver glycogen levels by increasing the activity of glycogen synthase and by suppressing glycogen phosphorylase. The second process is inhibited by increased glucose-6-P from gluconeogenesis and by ATP derived from the oxidation of FFAs (43).

Sedentary Lifestyle and Liver Lipid Metabolism

The liver plays a key role in the systemic regulation of lipid and carbohydrate metabolism, and abnormal insulin function in the liver is thought to be a major cause of insulin resistance. During a normal fasting period, the glucagon-to-insulin ratio increases, which reduces glucose utilization and stimulates the liver to produce more glucose. First, glycogenolysis is activated and then gluconeogenesis is activated. During satiety, glucagon secretion decreases, but insulin levels increase, resulting in increased glucose utilization, decreased glucose production, and increased glycogen and lipid storage. In disease states such as type 2 diabetes and obesity, insulin fails to regulate hepatic metabolism, resulting in excessive glucose production despite increased lipid synthesis, a condition commonly referred to as selective hepatic insulin resistance. Therefore, disorders associated with insulin resistance, such as T2D and obesity, are closely

associated with NAFLD. The NAFLD usually precedes T2D, and individuals with NAFLD almost always exhibit hepatic insulin resistance, which plays a key role in the pathogenesis of NAFLD. NAFLD patients generally have elevated insulin levels. Individuals with NAFLD and those with increased hepatic steatosis have been shown to have twice the rates of de novo lipogenesis, insulin, and free fatty acid (FFA) levels compared to healthy individuals (17).

A sedentary lifestyle is accompanied by a reduced mitochondrial oxidative capacity and elevated content of lipotoxic metabolites. Only one day of sedentary intervention reduced the expression of mitochondrial stearoyl-CoA 9-desaturase-1 (SCD1), diacylglycerol O-acyltransferase 1 (DGAT1), and glycerol-3-phosphate acyltransferase (mGPAT) [75]. Reduced expression levels of these lipogenic enzymes lead to a lower disposal of fatty acids towards the intramuscular triglyceride synthesis and the accumulation of lipotoxic intermediates in the muscle (16).

Various experiments have shown that IR is a typical feature of NAFLD, even without obesity. Yang et al (44) established that patients with NAFLD (without obesity and T2D) have markedly higher IR than do individuals without NAFLD, regardless of abnormal levels of metabolic risk factors. Various factors, such as cytokines, adipokines, inflammation, and IR, are involved in NAFLD, and this disorder is considered the hepatic feature of metabolic syndrome and IR (44). It is noteworthy that 13-day SF in mice yields significant alterations in the liver, indicative of early NAFLD (45).

Studies conducted on bed rest models have also revealed high lipid accumulation in the liver, hypertriglyceridemia, and, consequently, IR development accompanied by a loss of fat uptake and oxidation by muscle. Two months of bed rest can raise the levels of liver markers of NAFLD, such as aspartate transaminase (AST), alanine transaminase (ALT), insulin, and HOMA-IR, as well as fragments of cytokeratin 18 (CK18), an indicator of hepatic apoptosis and steatohepatitis, in normal-weight subjects (46-48). SF animals have shown a loss of retinol from lipid droplets, along with fatty liver (45). Total triglyceride (TG) content of the liver is also markedly elevated in SF mice in comparison with the control group (45). It has been demonstrated that TG synthesis pathways are stimulated by a sedentary lifestyle, causing hepatic lipid accumulation, which, along with inflammation, can induce insulin resistance (49, 50).

The expression levels of PLIN3 and PLIN4, genes thought to mediate the formation of nascent droplets, as well as PLIN2 (45), a marker for hepatic steatosis, are markedly upregulated (51), indicating elevated biosynthesis and packaging of TGs (45). In another experiment, high TG contents and increased fatty acid synthesis were also observed in obese subjects (52). Hepatic lipids are well known as a vital predictor of hepatic IR (53). Hepatic diacylglycerol (DAG) and TG deposits, besides activation of protein kinase Cε (PKCε), impair insulin action in the liver. Hence, NAFLD is directly associated with hepatic IR (54). The aggravation of hepatic IR stimulates the development and progression of T2D (5).

FFAs: free fatty acids, SREBP-1: sterol regulatory element-binding protein 1, TNF-α: tumor necrosis factor alpha, IL-6: interleukin 6, NF-κB: nuclear factor kappa B, PKC: protein kinase C (PKC), SOCS: suppressor of cytokine signaling, JNK: janus kinase, IKK-β: inhibitory kappa B kinase beta

In a previous study, the association of metabolic dysfunctions, including increased triglycerides and decreased insulin sensitivity, with sedentary lifestyles was reported (49). Numerous mechanisms have been proposed to clarify the relationship between the TG index and IR. Elevated TG levels can lead to increased FFA levels and, consequently, raise the flux of FFAs from adipose tissues to non-adipose tissues, thus probably promoting IR. Elevated FFA levels are also lipotoxic and lead to mitochondrial dysfunction (55). Moreover, mitochondrial dysfunction in different tissues was reported to be caused by a sedentary lifestyle (56).

It has been found that upregulated liver and muscle TGs can interfere with glucose homeostasis in a target tissue. It has been reported that overproduction of liver VLDL correlates with suppression of insulin signaling in the liver, which leads to IR (55). On the other hand, insulin regulates VLDL metabolism in the liver. Insulin modulates liver VLDL by increasing the degradation of apoB. These studies support the significance of liver TGs in the pathogenesis of IR (57). In a study conducted by Krotkiewski et al, increased intracellular TG accumulation was observed in the muscle and liver (58) along with the development of IR in healthy subjects who were confined to bed rest (59).

Sedentary Lifestyle and Mitochondrial Dysfunction

Inactivity and a sedentary lifestyle simultaneously reduce the activity of antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and increase malondialdehyde level (MDA) (60). Sedentary lifestyle markedly decreases the total glutathione (GSH) levels, catalase activity, CuZn-SOD, GSH reductase, and glutathione sulfur transferases (GSTs) in the liver during a sedentary lifestyle (16, 23). Another study also revealed increased levels of liver MDA and LOOH radicals and low levels of total glutathione, CuZn-SOD, glutathione peroxidase, and catalase during and after long-term weightless in rat (61). Reduced catalase activity may diminish the ability of the liver to remove •OH generated in peroxisomes (62). Sedentary lifestyle increases the production of ·OH, which is small, mobile, and reactive; in other words, it can cause oxidative damage and increase lipid peroxidation (63).

The relationship of ROS and the pathogenesis of IR through the defect in the insulin signaling pathway, as well as abnormal secretion of adipocytokines, is well established (64, 65). In animal models, the increase of ROS

causes IR, and SOD can alleviate IR (66). The findings of the study conducted by Koroglu et al (67) indicate that patients with IR have higher MDA levels and lower SOD and GSH levels in the liver than do subjects without IR. They found that blood and liver MDA content, GSH level, and SOD activity, as well as the liver necroinflammatory stage, independently correlate with homeostatic model assessment of insulin resistance (HOMA-IR) (67). It should be noted that GSH depletion can inhibit the insulin signaling cascade and, consequently, lead to IR in animals without an upregulation of ROS markers (68). Glucose intolerance detected after GSH depletion is a direct effect of the liver GSH shortage, and not an indirect result of upregulated ROS (68). In agreement with this hypothesis, infusion of GSH has been shown to raise total glucose uptake in T2D subjects (69).

Baqai et al have found that many genes that contribute to scavenging of ROS (e.g., flavin-containing monooxygenase 2 (FMO2), glutathione peroxidase-6 (GPx-6), and cytoglobin) are upregulated in the liver of flight mice (70). They have also reported high levels of myoglobin, an important transporter of ROS. The increased expression of these genes could reflect the free radical-scavenging properties of cells (70). It has been determined that hyperglycemia is related to augmented ROS (71). ROS can activate NF-κB, which can lead to IR (72). It has been reported that activation of NF-κB promotes the production of apolipoprotein B100 in hamster liver, which consequently leads to IR (73). Therefore, activation of NF-κB-related signaling pathways may be triggered by ROS induced by an SF environment (74).

Sedentary lifestyles are associated with poor sleep (75). The loss of sleep predisposes the liver to ROS damage and significantly reduces liver phosphatidylcholine expression (76). This compound is known as the main phospholipid in mammalian cells (77). It has been documented that sleep disturbances, especially daytime sleepiness and insomnia, are involved in the development of IR and glucose intolerance, and consequently, T2D (78, 79). Moreover, previous studies have revealed high levels of total cholesterol (TC), triglycerides (TGs), glucose, HbA1c, oxidized low-density lipoprotein (ox-LDL), HOMA-IR, inflammatory factors, high blood pressure, and high body mass index (BMI) in shift workers compared with control groups (80-82). In fact, shift work is related to an elevated risk of IR, metabolic syndrome, obesity, T2D, CVD, and acute myocardial infarction (82). Shift work schedule is associated with sedentary behavior and physical activity (83, 84). In addition to shift work, our previous studies showed that high fat diet also induce IR and healthy diet or some supplementations normalize IR (85-89).

Conclusion

A sedentary behavior has been proposed to induce insulin resistance. Inactivity and a sedentary lifestyle reduce antioxidant enzyme activities, induce inflammation, mitochondrial dysfunction, and dysregulation of glucose and lipid homeostasis, and enhance lipid storage. Furthermore, a sedentary lifestyle increases beta-cell apoptosis and dysregulates insulin signaling.

Authors' Contribution

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Validation: Maryam Cheraghi Bedsorakhi, Ebrahim Abbasi
Visualization: Ebrahim Abbasi
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Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

Not applicable.

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