



Relationship between Stress and Insulin resistance

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Received: 04/09/2025

Accepted: 07/11/2025

Abstract:

Chronic stress is considered one of the fundamental factors contributing to the onset and progression of insulin resistance, which represents the central pathway in the development of both type 2 diabetes and metabolic syndrome. Accordingly, the present study aimed to highlight the causal and reciprocal relationship between psychological stress and insulin resistance by elucidating the physiological, neural, hormonal, and behavioral mechanisms mediating the link between these two variables. It was demonstrated how chronic psychological stress can directly affect insulin receptor sensitivity through activation of the hypothalamic–pituitary–adrenal (HPA) axis, leading to increased cortisol levels and pro-inflammatory cytokines. Furthermore, heightened sympathetic nervous system activity and elevated catecholamine secretion result in recurrent hyperglycemic episodes that further reinforce insulin resistance. In addition, the study addressed the behavioral consequences of stress, such as sleep disturbances, excessive consumption of calorie-dense foods, and reduced physical activity, all of which contribute to the progression of insulin resistance. Therefore, this study underscores that the relationship between psychological stress and insulin resistance is not incidental but rather constitutes a complex causal loop that reflects the intricate interplay between psychological, biological, and behavioral factors.

Keywords: Acute Stress; Chronic Stress; Diabetes; Insulin; Insulin Resistance.

I. INTRODUCTION

In recent decades, Type 2 Diabetes Mellitus (T2DM) has emerged as one of the most pressing global health challenges, with its prevalence rising at an alarming rate, reaching epidemic proportions in numerous countries. According to reports from the World Health Organization, type 2 diabetes accounts for approximately 90–95% of all diabetes cases worldwide.

Although traditionally viewed as a disorder of blood glucose regulation, recent scientific literature unanimously agrees that insulin resistance (IR) constitutes the primary physiological foundation that precedes the clinical manifestation of type 2 diabetes, making the understanding of its causes and mechanisms a critical factor in early prevention and intervention (DeFronzo, 2004).

Insulin resistance is defined as a condition in which cells—particularly those in the liver, muscles, and adipose tissue—lose their natural sensitivity to insulin, necessitating higher amounts of insulin to maintain glucose homeostasis. Over time, pancreatic β -cells fail to meet this increasing demand, leading to dysregulated blood sugar levels and the clinical onset of type 2 diabetes (Kahn, 2001).

Numerous contributions have aimed to explain the pathogenesis of insulin resistance. While these efforts have significantly advanced our understanding of the physiological mechanisms underlying IR, most research has continued to focus predominantly on direct biological factors, such as genetics, visceral obesity, and physical inactivity. However, such a reductionist approach often overlooks the pivotal role that chronic psychological stress may play as a triggering factor in disrupting neuroendocrine and metabolic homeostasis, thus contributing to the development of insulin resistance.

Recent studies have demonstrated that insulin resistance is the outcome of a complex interplay between biological, psychological, and behavioral factors. From the perspective of psychoneuroendocrinology, insulin resistance is increasingly understood within the dynamic interaction of the central nervous system, endocrine regulation, immune function, and daily behavioral patterns. Numerous studies have confirmed that chronic psychological stress, sleep disturbances, poor nutrition, and sedentary lifestyles can directly impact insulin receptor sensitivity through activation of the hypothalamic-pituitary-adrenal (HPA) axis, increasing cortisol secretion and pro-inflammatory cytokines (Chrousos, 2009).

Consequently, psychological variables—particularly chronic stress—have gained growing scientific attention in recent years as contributing and influential factors in the progression of insulin resistance. Recent empirical findings indicate that individuals with elevated levels of chronic stress and daily psychological strain exhibit significant alterations in HPA axis function, characterized by persistent cortisol hypersecretion, which in turn leads to sustained hyperglycemia and impaired insulin signaling (Joseph & Golden, 2017). In a longitudinal study by Hackett and al. (2022), high levels of psychological distress were significantly associated with an increased risk of developing insulin resistance over several years of follow-up, even after adjusting for variables such as body mass index, physical activity, and socioeconomic status. These results suggest a potential causal relationship not solely attributable to diet or obesity, but one that necessitates deeper exploration of neuropsychological mechanisms.

Additionally, research in the field of psychoneuroimmunology has shown that chronic stress is linked to elevated levels of low-grade systemic inflammation, marked by increased cytokines such as IL-6, TNF- α , and CRP, which have been proven to interfere with insulin signaling pathways within cells, thereby reinforcing insulin resistance (Black, 2006). Many studies have found that individuals exposed to chronic psychological stress display elevated inflammatory markers, even in the absence of infections or physical injuries, highlighting psychological stress as a primary source of inflammation, independent of physiological insults (Rohleder, 2019).

Despite this growing body of evidence, the relationship between psychological stress and insulin resistance remains insufficiently understood in terms of directionality, mediating mechanisms, and individual variability. Hence, the significance of this study lies in its aim to explore the causal and reciprocal relationship between stress and insulin resistance, by analyzing the physiological, neural, hormonal, and behavioral mechanisms that connect these two variables. This may open new horizons for preventive and multilevel therapeutic interventions, particularly in the context of the global rise in metabolic disorders.

II. Stress

stress constitute the focus of attention of many scholars in psychology, as they are considered the basis upon which the various types of pressures that an individual may face are built, such as: social pressures, family pressures, academic pressures, economic pressures, emotional pressures, physical pressures, and health pressures.

Some scientists, such as Lobson and others, point out the difficulty of establishing an appropriate definition of pressure that everyone agrees on. (لوکيا، 2006). Despite the diverse and varied writings on the subject of stress by those interested in mental and physical health, the term or concept of stress does not mean the same thing to all of them, due to the different perspectives they adopt. This is in addition to the fact that the concept is merely a hypothetical construct, rather than something tangible, clear, and easy to measure. Thus, Mona and Lazarus pointed out the confusion among the perspectives that attempted to define stress. Some considered it a stimulus, others considered it a response, and a third group viewed it as an interactive process between stimulus and response (Mona & Lazarus, 1977).

The integrative view of the concept of stress (stimulus and response) is more comprehensive and more precise in its definition. By analyzing the definitions that address stress as a stimulus and a response, the following can be concluded:

. Psychological stress is a comprehensive concept that encompasses several responses arising in response to extremely powerful stimuli, requiring the individual to adapt.

- These stimuli may be external, such as sudden changes in the environment, job loss, role conflict, or relational problems. They may also be internal, such as a threat, which indicates the subjective assessment and interpretation of a particular situation as dangerous and frightening.

- Psychological processes play a major role in the response to psychological stress.

- Psychological stress results in physical, psychological, behavioral, and cognitive effects.

Selye introduced the idea that a stress response can result in positive or negative outcomes based on cognitive interpretations of the physical symptoms or physiological experience. When a person tolerates stress and uses it to overcome lethargy or enhance performance, the stress is positive, healthy, and challenging; this is called eustress . On the other hand, stress is negative when it exceeds our ability to cope, fatigues body systems, and causes behavioral or physical problems. This is called distress. (Nader, 2019)

The level of stress that can be provoked from each event depends on the importance of the stressor for the person and its intensity, and the difficulties or easiness to cope with it. Therefore, the grade of stress depends on seven factors (Nader, 2019):

- Level of importance of the desired thing
- Grade of impediments to achieve them
- Sharpness of the appearance of stress
- Life experience

- Vitality level responsible for the resilience to face difficulties
- Duration of the stress
- Presence of other causes of stress

Acute stress vs. chronic stress

Selye (1956) introduced the concept of stress as a response model. According to Selye, stress is a physiological response pattern, or a “nonspecific response of the body to any demand,” focused on achieving or maintaining homeostasis, which is the stability of physiological systems that maintain life (e.g., body temperature, heart rate, glucose levels). (Nader, 2019, P1)

The Hungarian pathologist (Selye, 1956) concluded that chronic and constant environmental threats for a long period affect the autonomic processes and physiological balance of the organism. If this stage develops and continues, it leads to the emergence of organic disease. (باطة، 1998). He explained the relationship between stress and the accompanying physiological incompatibility with three stages that he called the general adaptation syndrome.

He believes that the general adaptation syndrome. (G.A.S.) incites the individual to defend, and helps the body to overcome difficulties. He believes that it is a syndrome because its symptoms are consistent and depend on each other. (الزراء، 2000). The general adaptation syndrome. consists of three stages: The first stage: the alert stage, in which the organism prepares and becomes ready to face the threat. The second stage: the resistance stage, in which the organism exerts effort to deal with the threat, as happens in the case of confrontation. The third stage is the exhaustion stage, and occurs if the organism fails to get rid of the threat, and exhausts all its physiological resources during its attempts to adapt to the event. (تايلور: 2008).

Hans Selye's theory is summarized in the occurrence of a disorder in the hormonal system that links three important parts of the nervous and endocrine systems (hypothalamus, pituitary gland, adrenal gland) as a result of continuous exposure to stress, which leads to an increase in hormonal defenses through the autonomic nervous system (عبد القوي: 2007). The appearance of the stressor alerts the hypothalamus, which results in the formation of the syndrome. This is done through the intervention of two pathways:

* **The first way:** It is by stimulating the sympathetic nervous system and the adrenal medulla, and this stimulation leads directly to a set of reactions known as the alarm reaction. The alarm reaction stage of the GAS prepares a person to respond to the stressor they are experiencing. This is often known as a “fight or flight” response. (Lana, 2023)

The most important reactions that characterize the alarm response can be summarized as follows:

1. Increased heart rate and intense contraction of the cardiac muscle. This reaction enables the rapid passage of substances through the blood to areas that need to counteract pressure.
2. Constriction of the blood vessels supplying the skin and viscera, except for the heart and lungs. Simultaneously, the blood vessels supplying the skeletal muscles and brain dilate. This reaction allows blood to be sent to the organs involved in the response and reduces the flow of blood to non-active organs.
3. The spleen contracts and releases stored blood into the general circulation to produce a large amount of blood. Red blood cell production accelerates, increasing the blood's clotting capacity. This property allows for the fight against bleeding.
4. The liver converts stored glycogen into large quantities of glucose and releases it into the circulation. Glucose levels decrease due to the active cells, providing the energy needed to counteract stressors.

5. Increased sweat production. This reaction helps lower body temperature, which rises due to increased circulation and catabolism.

6- Accelerated breathing and dilation of the respiratory tract to facilitate airflow. This reaction enables the body to take in the largest possible amount of oxygen when needed, enabling the body to respond to declining metabolism. It also allows the body to sequester a significant amount of carbon dioxide, a byproduct of metabolism.

7- Saliva production and decreased intestinal digestive enzymes. This reaction results from the fact that digestive activity is no longer necessary to cope with stress. (Tortora & Gabowski & Parent: 1995)

* **The second way:** It is known as the resistance phase, and it takes a while to appear, and both the adrenal cortex and the glandular part of the pituitary gland intervene in it, and this reaction takes time to appear, but its effects remain for a long time.

The parasympathetic branch of the ANS tries to return the body to normal by reducing the amount of cortisol produced. The heart rate and blood pressure begin to return to normal. If the stressful situation comes to an end, during the resistance stage, the body will then return to normal. However, if the stressor remains, the body will stay in a state of alert, and stress hormones continue to be produced. This physical response can lead to a person struggling to concentrate and becoming irritable. (Lana, 2023)

The resistance phase operates through regulatory hormones secreted by the hypothalamus (CRH, GH, RH, TRH). The most important biochemical changes that characterize this phase can be summarized as follows:

1. CRH stimulates the anterior lobe of the pituitary gland to increase the secretion of ACTH, which stimulates the adrenal cortex to secrete large quantities of its hormones. During this reaction, renal activity decreases, as does blood flow to the kidneys, as they are unable to effectively respond to the threat posed to the body. The adrenal gland reduces urine production by secreting mineralocorticoids, which work to conserve sodium ions throughout the body.

2. Glucocorticoids, produced in high concentrations during stressful situations, trigger the following reactions:

- They accelerate protein metabolism and convert amino acids into glucose, enabling the body to generate significant energy for an extended period from the direct use of glucose.

- It stimulates the isolation of structural proteins and causes the liver to reduce these amino acids, which can reconstitute the enzymes necessary to stimulate chemical activities, increase cell growth, or convert them into glucose.

- It makes blood vessels more sensitive to stimuli that cause them to constrict. This reaction eliminates the drop in arterial blood pressure caused by bleeding.

- It inhibits the formation of fibrils responsible for the development of connective tissue in cells. It removes fibrils damaged by chemical compounds that help trigger the stress response.

3- TRH stimulates the anterior lobe of the pituitary gland to secrete TSH, which stimulates the thyroid gland to secrete thyroxine, which increases the breakdown of fats and the conversion of glycogen to glucose.

4- GH-RH stimulates the secretion of STH. The regulation between STH and TSH increases metabolism and thus provides the body with increased energy.

Hans Selye (1975) also pointed out the effects of psychological stress on the immune system, as he demonstrated through an experimental situation that acute stress leads to atrophy of the thymus gland and lymph nodes (Boudarene: 2005)

After an extended period of stress, the body goes into the final stage of GAS, known as the exhaustion stage. At this stage, the body has depleted its energy resources by continually trying but failing to recover from the initial alarm reaction stage. (Lana,2023)

One of the main causes of exhaustion is the loss of potassium ions. Glucocorticoids stimulate the kidneys to replenish sodium ions, altering the concentration of both potassium and hydrogen ions and releasing them into the urine. Since potassium, the main cation in cells, is responsible for concentrating water in the cytoplasm, cells that lose large amounts of potassium become less efficient and eventually begin to die. This condition is known as exhaustion and results from the failure to quickly reverse this process (Gerard & Gabowski & Parent: 1995). Exhaustion also results in the cessation of vital organs and death due to the decrease in glucocorticoids in the adrenal cortex. In this case, blood glucose levels drop suddenly, and cells are unable to receive nutrients.

III. Definitions and Concepts of insulin resistance

Before talking about insulin resistance, we must talk about insulin. Insulin is a hormone secreted by the pancreas that stimulates the body's cells -muscle, fat and liver cells- to receive this sugar and convert it into energy. In the event of insulin resistance, the cells do not react and do not receive sugar, which leads to an increase in blood sugar levels. Over time, your pancreas continues to try to regulate your blood sugar and produce more insulin until the pancreas is damaged and can no longer produce as much insulin. As a result, blood sugar levels rise to the point of developing diabetes.

Insulin resistance is a condition in which the body produces insulin but does not use it properly. And Insulin resistance is defined where a normal or elevated insulin level produces an attenuated biological response (Gisela, 2005)

Popular definitions of insulin resistance are with reference to the effects of insulin deficiency on glucose metabolism to cause diabetes. Recently there has been a shift from this traditional “glucocentric” view to an increasingly “lipocentric” viewpoint. Lipids accumulate within myocytes and hepatocytes in insulin resistance (Ogbu and Emmanuel, 2024)

Insulin resistance syndrome refers to the cluster of abnormalities and related physical outcomes that occur more commonly in insulin resistant individuals. Given tissue differences in insulin dependence and sensitivity, manifestations of the insulin resistance syndrome are likely to reflect the composite effects of excess insulin and variable resistance to its actions. (Gisela, 2005)

Anyone can develop insulin resistance. But people who are overweight are at greater risk than the general population. The risk is increased in individuals with a family history of type 2 diabetes, individuals over 45 years of age, individuals of African, Latino, or Native American descent, smokers, and those taking certain medications such as steroids, antipsychotics, and HIV medications. Other medical conditions associated with insulin resistance include obstructive sleep apnea, fatty liver disease, polycystic ovary syndrome, Cushing syndrome, and lipodystrophy syndromes, which are conditions that cause abnormal fat loss. So, having too much or not enough fat tissue in the body can be linked to insulin resistance

One of the main causes underlying the development of insulin resistance syndrome is the persistent elevation of insulin levels in the bloodstream—both in excessive amounts and over extended periods of time. This chronic hyperinsulinemia may eventually lead to pancreatic β -cell dysfunction and impaired insulin secretion (Corkey, 2012). Among the key factors contributing to elevated insulin levels in the blood are:

- Consumption of high-sugar (carbohydrate-rich) foods.
- Frequent meals throughout the day.
- Elevated levels of the stress hormone cortisol. (Liu et al., 2016)
- Pancreatic tumors and other related conditions.
- Long-term use of high doses of corticosteroids. (van Raalte et al., 2009)
- Presence of chronic low-grade inflammation.
- Increased levels of free fatty acids in the bloodstream, which may impair cellular insulin responsiveness.
- Excessive intake of added fructose—commonly found in processed foods—as opposed to the naturally occurring fructose in fruits. (Stanhope et al., 2009)

- The difference between insulin resistance and diabetes

Type 2 diabetes is the most common form of diabetes (accounting for 90–95% of cases). It is a chronic metabolic disorder characterized by persistently elevated blood glucose levels due to insulin resistance and a relative deficiency in insulin secretion by the pancreas.

Type 2 diabetes develops as a result of insulin resistance through the following pathological stages:

Stage 1- Insulin Resistance: It begins in the liver, muscles, and adipose tissue, where these tissues become less responsive to insulin despite its elevated levels. In response, the pancreas compensates by increasing insulin secretion. This leads to:

- Continued glucose production by the liver despite high insulin levels, resulting in elevated fasting blood glucose.
- Decreased ability of muscle cells to absorb glucose.
- Increased breakdown of fat tissue, releasing free fatty acids that further worsen insulin resistance and promote fat accumulation in the liver and pancreas.

Stage 2- β -cell Dysfunction: The pancreatic β -cells become chronically overworked, leading to a gradual decline in their ability to secrete insulin. This results in progressively higher blood glucose levels, first manifesting as prediabetes, and eventually progressing to type 2 diabetes. (Cerf, 2013).

In summary, during insulin resistance, the liver, muscles, and fat cells respond poorly to insulin, preventing glucose from entering the cells efficiently. Consequently, glucose accumulates in the bloodstream. The pancreas tries to compensate by producing large amounts of insulin, leading to chronic hyperinsulinemia. Over time, this burden exhausts the pancreas, diminishing its capacity to produce insulin, and resulting in type 2 diabetes.

Thus, insulin resistance refers to the impaired response of muscle, fat, and liver cells to insulin, making it difficult for them to absorb glucose from the blood. Diabetes, on the other hand, is a chronic disease that occurs either when the pancreas fails to produce enough insulin (as in type 1 diabetes) or when the body cannot effectively use the insulin it produces (as in type 2 diabetes due to insulin resistance). (Kahn et al., 2014)

It is worth noting that some symptoms associated with insulin resistance were previously considered idiopathic, such as the development of skin tags (especially in the neck area) and the appearance of dark, velvety patches of skin (acanthosis nigricans) around the neck. These signs may indicate an increased risk of developing type 2 diabetes due to insulin resistance.

IV. Symptoms and Complications of insulin resistance

insulin resistance often develops gradually and may not cause any noticeable symptoms in the individual. As a result, a person may suffer from this metabolic condition for several years without being aware of it.

Symptoms of insulin resistance that some people may notice include:

- **Obesity:**

Weight gain without clear causes, especially an increase in waist circumference, which is approximately 90 cm in women and approximately 100 cm in men. An increase in waist circumference indicates an increase in abdominal fat known as visceral fat, which is associated in most cases with the body's resistance to insulin.

Insulin is the primary hormone responsible for fat storage. It promotes lipogenesis in liver cells and adipose tissue, and inhibits the release of free fatty acids from triglycerides (TGs) in adipose and muscle tissues. This has a profound effect on lipid metabolism. Fat accumulation in muscle and liver cells has been observed in: Individuals with type 2 diabetes, First-degree relatives of patients with type 2 diabetes who are not yet diabetic (a high-risk group), People with impaired glucose tolerance (IGT), And overweight individuals. These groups are considered at elevated risk of developing insulin resistance. (Ogbu et al., 2024)

- **Persistent Hunger Shortly After Meals and Cravings for Sweets:**

Insulin resistance leads to elevated levels of insulin in the bloodstream, which in turn stimulates appetite and increases cravings for sugar-rich foods. This interaction between insulin and glucose contributes to persistent feelings of hunger and a compulsive desire for sweets. Additionally, insulin resistance is associated with fluctuating energy levels, which often results in fatigue and an increased urge to eat as a means of compensating for the perceived lack of energy.

- **Sleepiness, Irritability, and Mood Swings:**

Insulin resistance affects brain function, leading to mood fluctuations and persistent fatigue. This neurological impact contributes to elevated stress levels, irritability, and reduced sleep quality, all of which further increase feelings of exhaustion and nervousness. Moreover, insulin resistance may trigger sleep disturbances, such as insomnia or fragmented sleep, which can exacerbate both irritability and fatigue.

- **Fatty Liver (Hepatic Steatosis):**

Under normal physiological conditions, insulin suppresses fat breakdown (lipolysis) in adipose tissue, reduces glucose production in the liver, and regulates lipid synthesis in a balanced manner.

However, in the context of insulin resistance, cells become unresponsive to insulin's regulatory signals. This leads to a disruption in lipid and glucose homeostasis within the liver, resulting in fat accumulation and the development of non-alcoholic fatty liver disease.

- **Frequent Urination:**

Elevated blood glucose levels due to insulin resistance impair kidney function. When glucose concentration exceeds a certain threshold (renal threshold), the kidneys begin to excrete glucose in the urine. This glucose draws water along with it via osmotic diuresis, resulting in excessive urination during both day and night. Frequent urination is considered one of the early warning signs of insulin resistance and indicates the need for early medical intervention.

• Polycystic Ovary Syndrome (PCOS) in Women:

Insulin resistance is a contributing factor in the development of polycystic ovary syndrome (PCOS). It leads to elevated androgen levels (male hormones) in the body, which in turn cause:

Irregular menstrual cycles,

Excess hair growth in unusual areas (hirsutism), And acne. (Diamanti-Kandarakis & Dunaif, 2012).

• Low Testosterone in Men:

Insulin resistance negatively affects testosterone levels in men, leading to a reduction in circulating testosterone. This hormonal decline can impair sexual health and reproductive function, and may increase the risk of cardiovascular diseases. (Pitteloud & all, 2005).

• Dark, Velvety Skin Patches (Acanthosis Nigricans):

Acanthosis nigricans is a skin condition characterized by the appearance of dark, thickened, velvety patches in areas such as the neck and underarms. It is considered an early and significant dermatological marker of insulin resistance, and often precedes the onset of type 2 diabetes.

• Suffering from two or more symptoms of metabolic syndrome, which include the following:

- High blood triglycerides of more than 150 mg/dL.
- Low good cholesterol, which is high-density lipoprotein, of less than 50 mg/dL for women and 40 mg/dL for men.
- High blood pressure of more than 130/85 mmHg.
- High fasting blood sugar of more than 100 mg/dL.

• Disturbance of the normal heart rhythm

as some individuals with insulin resistance suffer from a rapid heartbeat, even if they appear healthy. This may occur due to the body's resistance to insulin and a disturbance in the function of the pancreas responsible for producing insulin, which leads to cases of hypoglycemia, the symptoms of which include a rapid heartbeat, fatigue, exhaustion, increased sweating, and sometimes tremors in the extremities, especially the hands.

Complications of insulin resistance

The most common complications include:

- Severe metabolic complications, including hyperglycemia and hypoglycemia.
- Angina.
- Myocardial infarction.
- stroke.
- Severe rise in blood sugar.
- Severely low blood sugar.
- Kidney disease.
- Eye problems.
- Cancer.
- Alzheimer's disease.

V. Stress and insulin resistance

How stress promotes insulin resistance on a cellular level

When a person is exposed to psychological stress—whether acute or chronic—the autonomic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis are activated. This triggers the secretion of stress hormones, primarily cortisol (from the adrenal cortex), as well as adrenaline and noradrenaline (from the adrenal medulla) (Chrousos, 2000).

Elevated cortisol levels during stress play a key role in increasing blood glucose concentrations through the following mechanisms:

- Accelerating protein catabolism and converting amino acids into glucose (gluconeogenesis).
- Inhibiting cellular glucose uptake, while promoting the utilization of fatty acids as an energy source—resulting in elevated blood glucose levels.

With repeated activation of these pathways due to chronic stress, several alterations occur at the cellular level, particularly involving insulin receptors, such as:

- A reduction in the number or sensitivity of insulin receptors.
- Disruption of intracellular signaling pathways (e.g., PI3K/AKT and MAPK), leading to diminished cellular responsiveness to insulin.
- Accumulation of pro-inflammatory cytokines, such as TNF- α and IL-6, which further impair insulin signal transduction (Kyrou & Tsigos, 2009).

Collectively, these changes contribute to impaired insulin signaling, persistent hyperglycemia, and the onset of insulin resistance syndrome.

Chronic stress also promotes the release of pro-inflammatory cytokines from immune cells and adipose tissue, such as:

- ✓ TNF- α (Tumor Necrosis Factor-alpha)
- ✓ IL-6 (Interleukin-6)
- ✓ CRP (C-reactive protein)

These molecules inhibit the normal (tyrosine) phosphorylation of IRS-1 (Insulin Receptor Substrate-1) and instead promote its inhibitory (serine) phosphorylation via activation of the JNK (c-Jun N-terminal kinase) pathway. This biochemical alteration disrupts insulin signal transduction and impairs cellular responsiveness to insulin. (Black, 2006).

The effects of stress on the appetite, cravings, and lifestyle

Stress directly affects key brain regions such as the amygdala, hippocampus, and hypothalamus, leading to several physiological and behavioral changes, including:

- ✓ Increased secretion of ghrelin (the "hunger hormone") and reduced levels of leptin (the "satiety hormone"), which together enhance appetite.
- ✓ Heightened cravings for high-calorie foods, particularly those rich in sugar and fat.
- ✓ A tendency to engage in emotional eating as a coping response to stress, often leading to binge eating behaviors.
- ✓ Reduced self-regulation in dietary choices and eating behavior. (Adam & Epel, 2007).
- ✓ Accumulation of visceral fat, which is more strongly associated with insulin resistance than subcutaneous fat. (Adam & Epel, 2007).
- ✓ Sleep disturbances, circadian rhythm disruption, and reduced physical activity.

Collectively, these stress-induced behavioral patterns contribute to increased visceral adiposity, metabolic imbalance, and a heightened risk of developing insulin resistance.

VI. Conclusion

The concept of stress particularly chronic stress has emerged as one of the most extensively examined constructs across various health domains. Its relationship with numerous variables linked to both mental and physical health has been widely investigated. Contemporary scientific literature indicates that chronic stress is not merely a transient psychological factor, but rather a fundamental determinant in the onset and progression of many physical illnesses. Among the conditions that have recently attracted research attention for their association with chronic stress is insulin resistance.

Over the past two decades, a growing body of evidence has documented the association between chronic stress and insulin resistance within the framework of psychoneuroendocrinology. Chronic stress is now considered a critical biological and psychological factor in the emergence and exacerbation of insulin resistance, which itself represents the central pathway in the development of type 2 diabetes and metabolic syndrome. Recent studies suggest that this relationship is not incidental but causally interconnected, with stress serving as a key explanatory factor in metabolic dysregulation through multiple mechanisms. These mechanisms include hyper activation of the hypothalamic–pituitary–adrenal (HPA) axis and consequent cortisol hypersecretion, increased sympathetic nervous system activity, and chronic low-grade inflammation. Furthermore, research highlights the behavioral consequences of stress—such as sleep disturbances, overeating of calorie-dense foods, and reduced physical activity—which contribute to the accumulation of visceral adiposity and, consequently, the aggravation of insulin resistance.

This contemporary perspective on the reciprocal relationship between stress and insulin resistance underscores the need to move toward an integrative model. Such a model conceptualizes insulin resistance not merely as the outcome of genetic or metabolic factors, but as a multifactorial condition at the intersection of psychological, biological, and behavioral influences. Accordingly, understanding insulin resistance necessitates the adoption of a comprehensive psychoneuroendocrinological approach. This would allow for the integration of psychological and behavioral interventions into prevention and treatment protocols alongside pharmacological and nutritional strategies. Such an integrative framework holds the potential to reduce the burden of metabolic disorders, most notably type 2 diabetes, while reflecting the necessity of a cross-disciplinary perspective that brings together psychology, internal medicine, neuroscience, and immunology.

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