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Association of the Effect of *SLC6A4* Gene Polymorphisms on the Risk of Diabetes

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Abstract

Context: The *SLC6A4* gene encodes the serotonin transporter. Mutations in this gene can lead to various diseases, such as diabetes. Diabetes is one of the most common metabolic disorders with a genetic background. This review study evaluated the role of *SLC6A4* gene polymorphisms in the risk of diabetes.

Evidence Acquisition: In this review article, a literature search was conducted in scientific databases, including Google Scholar and PubMed, to find studies published within 2000 to 2021 on the role of *SLC6A4* gene polymorphisms on the risk of diabetes.

Results: Some genetic and environmental factors are involved in the development of diabetes. Additionally, the association between diabetes and disorder in different genes has been investigated in numerous studies. The discovery of these genetic changes in diabetes might shed light on the functional role of genetic mutations in the development of diabetes.

Conclusions: Further genomic research is needed to determine the possible role of *SLC6A4* gene polymorphisms in diabetes and obesity.

Keywords: *SLC6A4*, Diabetes, Beta Cell, HPA Axis

1. Context

The central nervous system (CNS) function is regulated by several transporters. One of the major transporters in the CNS is the serotonin transporter (SERT or 5-HTT). The SERT plays an important role in stress, mental, and metabolic disorders, such as obesity (1, 2). The human SERT is encoded by the *SLC6A4* gene. This gene has 15 exons and 630 amino acids (3, 4). The polymorphism in this gene causes two short (S) and long (L) alleles. The short type has a negative effect on serotonin uptake and inhibits the gene encoding the SERT (5).

Diabetes is a common metabolic disorder affecting numerous individuals worldwide every year (6). Various factors are involved in the occurrence of this disorder. Reports indicate that proinflammatory cytokines, such as interferon-gamma, interleukin-2, and tumor necrosis factor-alpha (TNF-α), might play a role in diabetes (7). Recent studies show that polymorphisms in some genes, such as glucose-6-phosphate dehydrogenase (*G6PD*) and *SLC6A4*, might be involved in the development of diabetes. Some studies have reported an association between the *SLC6A4* gene and the dysfunction of beta cells (8, 9). The evidence also suggests that polymorphisms in the *SLC6A4* gene can cause diabetes by disrupting the hypothalamic-pituitary-adrenal (HPA) pathway and increasing cortisol (10). Moreover, an increase or decrease in glucose levels is associated with changes in the level of cortisol released in the blood (11). Therefore, the expression of *SLC6A4* and the regulation of SERT activity are important parameters in serotonin function. It seems that *SLC6A4* polymorphisms can affect the nervous system and consequently the endocrine system by affecting the expression of the SERT. Therefore, this study investigated the relationship between *SLC6A4* polymorphisms and increased risk of diabetes.

2. Evidence Acquisition

In this review article, a literature search was conducted in scientific databases, including Google Scholar and PubMed, to find studies published within 2000 to 2021 on the role of *SLC6A4* gene polymorphisms in the risk

of diabetes. For this study, about 200 articles were downloaded from the databases. Then, these papers were reviewed. Finally, 53 articles were considered the references.

3. Results

3.1. Serotonin Transporter Gene (SLC6A4)

In the CNS, the SERT is the biological regulator of the serotonergic system by absorbing serotonin from the synaptic space to presynaptic neurons (1, 2). The SERT plays an important role in the emotional process, stress, and mental and metabolic disorders, such as obesity (3, 4). The SERT is the primary target of therapeutic drugs for various diseases, including depression and stress. Various studies have been performed on the effect of single nucleotide polymorphisms on serotonin transport via transmitters. One of the genes of interest is the SERT, a carrier of family 6, member 4 (*SLC6A4*). Human *SLC6A4* is located on chromosome 17q11.2. This gene contains 15 exons that cover the promoter region with 40 kb. The protein transcription sequence of the SERT gene contains 630 amino acids, with 12 domains passing seven times through the membrane (3, 4). The insertion/deletion polymorphism that occurs in the promoter region associated with the SERT gene results in two major alleles, short (S with 14 replicates) and long (L with 16 replicates). These two allele species control the transcription of the *SLC6A4* gene differently. Type S has a harmful effect on serotonin reuptake through the transporter and inhibits the transcription of the SERT-encoding gene (5). Studies showed that in individuals with short alleles, changes occur in the structure of brain areas, such as the amygdala, cingulate, insula, and prefrontal. These areas are involved in the regulation of the emotional response. Additionally, studies have reported the association between short alleles and reduced substantia grisea volume in areas involved in emotional processing, such as the amygdala and hippocampus. The hypothesis is that short alleles in these brain areas reduce the binding of the serotonin A1 receptor. In this case, individuals with the SS genotype show an anxiety-like state (12).

3.2. Association of SLC6A4 Gene with HPA Axis

Changes in the function of the HPA axis, as the primary stress management system in the body, cause a wide range of stress-related disorders (13). In particular, various molecules, such as hypothalamic-derived neuropeptides, corticotropin-releasing hormone (CRH), and arginine vasopressin, are involved in response to stress, regulating the behavioral response to stress (14). Furthermore, several areas of the brain, such as the hippocampus and amygdala, control the stress response. It has been observed that HPA activity was inhibited by the hippocampus and cingulate cortex; however, cortisol secretion increased by the amygdala and prefrontal cortex (15).

Research shows that various genetic factors affect the HPA axis. The HPA axis can be disrupted in the long run by deoxyribonucleic acid (DNA) methylation. These polymorphisms affect the neurotransmitter systems in the brain. Among the neurotransmitter systems, the serous serotonin system has received much attention. Because the HPA axis is controlled by the serotonergic system, polymorphisms in the SERT genes can affect this axis (16). Based on genetic research, the study of the SERT gene (*SLC6A4*) is an excellent option to show the relationship between DNA methylation and the HPA axis function.

Recent studies have shown a close relationship between the polymorphism of the *SLC6A4* gene and the increased sensitivity of the HPA axis to stress. Carriers containing the homozygous allele S increase cortisol levels (17). Elevation in cortisol levels occurs with an increase in amygdala-insula activity by the allele SS (15). Studies showed that stress alters the expression of the *NR3C1* gene (the gene that expresses the glucocorticoid receptor); cortisol secretion is mediated through polymorphism in the *SLC6A4* gene (18). Therefore, the HPA axis as an important stress controller is influenced by various environmental and genetic factors. Changes in genetic factors can be one of the main reasons for the disorder of this axis and subsequently cause various diseases due to increased cortisol levels in the body. The association of SERTs with the HPA axis is well known. Finally, it can be used as a therapeutic target.

3.3. Association of Diabetes with HPA Axis

Diabetes is a chronic endocrine disorder that affects numerous individuals each year. Many central and endocrine disorders play a role in the development of diabetes. The role of stress in the development of diabetes has been confirmed by some researchers. Stress causes an imbalance in body function, followed by a series of physiological changes through the HPA axis and the sympathetic nervous system (19). The HPA axis includes the hypothalamus, pituitary, and adrenal glands, which play essential roles in energy metabolism, stress responses, and mental function. The HPA axis controls the metabolic process primarily through the secretion of hormones, such as CRH, adrenocorticotropic hormone (ACTH), and

glucocorticoids (GC). Normal GC secretion is essential for the proper functioning of the HPG axis in energy metabolism and homeostasis (20).

As the primary hormone secreted by the pituitary gland, cortisol in the optimal range plays a vital role in various physiological functions and survival. Under stress conditions, when the cortisol level rises due to the increased activity of the HPA axis, it elevates gluconeogenesis in the liver, decreases glucose uptake by adipocytes and skeletal muscle, reduces insulin production by liver beta cells, ad increases adipose tissue lipolysis and insulin resistance. Finally, following these conditions, glucose metabolism is affected (21). In addition, excessive GC secretion reduces peripheral tissue sensitivity to insulin and glucose transport by the glucose transporter type 4 (GLUT4). The GLUT4 plays an important role in glucose transport in mammals, and without the help of this carrier, glucose cannot cross cell membranes freely. By stimulating insulin signaling, glucose is transported into the cell by this carrier. The disruption of the HPA axis can affect glucose transport by GLUT4 carriers in muscle tissue and lead to the development of diabetes by reducing glucose uptake (22).

Studies showed that numerous individuals with visceral obesity and insulin resistance suffer from a wide range of psychological disorders, including depression and stress. Furthermore, in obese patients with chronic stress, the circadian rhythm of cortisol decreases. In other words, natural physiology is disrupted in individuals who are affected by severe stress due to the loss of homeostasis. These biological changes in the body can affect the HPA axis. Eventually, the signals that enter the peripheral tissues through this axis are not accurately received by the organelles, and the body's natural system is disrupted. In regulating the body's metabolism, signals are sent from the liver and musculoskeletal system to the CNS. The reception and interpretation of these messages correctly play an important role in physiological responses. Any factor, such as stress, that disrupts the regular connection between the HPA axis and the metabolic pathway can cause a variety of diseases, including diabetes (10)

3.4. Association of SLC6A4 Gene with Diabetes

The CNS plays an important role in regulating glucose homeostasis. One of the neurotransmitters in the CNS is serotonin, which is involved in regulating energy balance through the modulation of the neuropeptide system and environmental mechanisms activity (23). Serotonin is a multifunctional molecule. Most studies focused on the role of serotonin in the etiopathogenesis of depression and mental health. Recently, there has been evidence of serotonin's role in obesity and metabolic disorders. Serotonin is also essential for proper brain development in the fetus (24).

The SERT plays a vital role in inactivating serotonin transport after release in the synaptic cleft. Research shows that serotonin activity is regulated by 5-HTT. The SERT is dependent on sodium, which is responsible for regulating the entire serotonergic system and its receptors. Therefore, by active transport, serotonin enters the nerve cells, enterochromaffin cells, platelets, and other cells. In this way, it determines the extent and duration of the cell signaling response to serotonin (23, 25).

Serotonergic system genes are a good option for study due to their function in the brain. It has been confirmed that the serotonergic system is involved in regulating nutrition and glucose homeostasis. Human SERT is encoded by the SERT gene (*SLC6A4*). A possible link between this gene and type 2 diabetes has been reported in diabetic animals. A study suggests that changes in the expression of the monoamine transporter gene in the brain might contribute to the development of chronic diabetes in mice (24). Studies showed a close relationship between the homozygous allele S and diabetes. It has been observed that the SS genotype is predominant in diabetic patients (26). Another study reported an association between SERT with glucose metabolism, body mass index, and type 2 diabetes. Studies on female subjects have shown that polymorphisms in the *SLC6A4* gene increase their fasting glucose (25). A study showed the role of the *SLC6A4* gene in insulin secretion in patients with polycystic ovary syndrome. Polymorphism in SERT alters insulin secretion in these individuals (27). The discovery of these genetic changes in diabetes reveals the functional role of genetic changes in the development of the disease. Therefore, further genomic research is needed to determine the possible role of polymorphisms in the *SLC6A4* gene in diabetes and obesity. It is crucial for pharmacological interventions.

3.5. SLC6A4 Gene Polymorphism and Inflammatory Factors

Polymorphisms in genetic factors can affect the concentration of proinflammatory cytokines. Studies showed that polymorphism in the *SL6A4* gene is associated with an increase in plasma interleukin-6 (IL-6) levels (28). Additionally, changes in the plasma levels of TNF-α are observed in patients with a violation of the *SL6A4* gene. The results of studies showed that genetic changes in the SERT cause impaired inflammatory/immune system

function in rats. The hippocampus is the area in the CNS most vulnerable to the adverse effects of inflammatory mediators. Moreover, individuals who carry the allele SS have increased plasma levels of cytokines (29). Different brain areas, including the limbic and sympathetic systems, control the stress response. Furthermore, the serotogenic pathway plays a role in regulating the HPA axis. The serotonergic pathway stimulates the release of cortisol from the adrenal cortex by stimulating the HPA axis and releasing CRH or ACTH. When the HPA axis is affected by various inflammatory cytokines, including TNF-α, IL-1, and IL-6, the function of this axis is disrupted, and CRH secretion from the hypothalamus is stimulated. Increased cortisol secretion is associated with numerous serotonin-related pathological conditions. Studies showed that under conditions of stress and high cortisol, changes in the SERT gene occur in rodents and humans (30). Therefore, an increase in the levels of inflammatory cytokines can affect the serotogenic pathway and lead to a defect in the function of the SERT gene. Defects in this gene can impair cortisol secretion from the adrenals by affecting the HPA axis. Eventually, an increase in plasma cortisol levels disrupts the function of beta cells in the pancreas in the production and secretion of insulin, leading to the progression of diabetes.

3.6. Action of SLC6A4 Gene Polymorphism through Inflammatory Factors on Diabetes

Cytokines are divided into three classes of small soluble or membrane-bound proteins or glycoprotein signaling molecules with a molecular weight within 8 to 40,000 Da. These proteins are synthesized in almost all nucleated cells. Cells respond to an increase in these factors under certain conditions. To date, more than 200 types of cytokines, such as interleukins, growth factors, chemokines, interferons, and hematopoietins, have been identified (31). Studies showed that numerous proinflammatory adipokines, such as IL-β1, IL-6, IL-8, and TNF-α, are involved in the etiology of diabetes (32).

3.6.1. Interleukin-1 (IL-1)

The physiological and pathophysiological function of IL-1 has been extensively investigated (33). The main biological role of IL-1 has been described in many tissues, such as beta cells. The IL-1 plays an important role in cell growth, tissue repair, and chronic inflammatory diseases. Additionally, IL-1b is involved in the destruction of Langerhans islet beta cells in diabetes. Studies showed an increase in *IL-1b* gene expression in the pancreatic tissue of a diabetic rat model. Moreover, in vitro studies reported that at high glucose concentrations, *IL-1* gene expression is increased in beta cells (34). A study showed a link between the mechanism of action of IL-β1 and the pathogenesis and progression of type 2 diabetes. In patients with diabetes, the use of the IL-β1 antagonist improves the secretory function of beta cells and reduces inflammatory biomarkers (35). Furthermore, IL-1, as a primary mediator of innate immunity, is involved in B-cell dysfunction and death. The IL-1 inhibitors can be considered therapeutic targets in metabolic disorders by reducing inflammation and B cell apoptosis (36). Cytokines and their receptors are expressed in different areas of the CNS. Under stress and pathophysiological conditions, the expression level of cytokines in the paraventricular nucleus of the hypothalamus increases (37). In addition, studies have been performed on the effects of cytokines on HPA axis function, particularly the proinflammatory factor IL-b1. The IL-b1 stimulates hypothalamic parietal neurons, which affect CRH cell secretion in rats. The IL-b1 is involved in the activation of the stress-induced HPA axis. Therefore, interleukins can induce the expression and secretion of CRH at the hypothalamic level and the secretion of ACTH in the pituitary gland (38).

3.6.2. Interleukin-6 (IL-6)

The IL-6 is a 25 kDa glycopeptide. It is composed of 184 amino acids (39). This inflammatory factor is one of the critical cytokines synthesized by most cells, such as B lymphocytes, T lymphocytes, macrophages, dendritic cells, monocytes, mast cells, fibroblasts, and adipocytes cells, in response to tissue damage and infections. Prostaglandins and adipokines might be involved in stimulating IL-6 secretion (40). The IL-6 is known as a pleiotropic cytokine. Its pleiotropic nature is determined by several genes regulated by interleukins. After the inflammatory factor IL-6 is secreted, it binds to the IL-6 receptor in the target cells. By initiating intracellular signaling, it activates several cell subsets, such as mitogen-activated protein kinase (MAPK) and the JAK/STAT pathway. Moreover, it transcribes several downstream genes associated with cellular signaling processes (41). Therefore, IL-6 with several signaling pathways can be involved in various diseases, including diabetes.

The IL-6 has been linked to several inflammatory and autoimmune diseases, such as rheumatoid arthritis and diabetes. Diabetes is a metabolic disorder associated with decreased insulin, beta cell dysfunction, and obesity. It has been observed that IL-6 expression increased

in obese individuals (42). Visceral obesity can cause low-grade chronic inflammation in individuals. Low-grade inflammation is associated with elevated inflammatory cytokine IL-6, which is implicated in diabetes. Studies also showed that impaired IL-6 signaling function is closely related to insulin resistance, contributing to the progression of diabetes. Insulin resistance disrupts the function of beta cells in insulin production. Under conditions of metabolic stress, such as elevated blood glucose levels, IL-6 levels increase both in the bloodstream and in the islets of Langerhans; if continued, it disrupts the secretion of glucose-stimulated insulin from beta cells (43).

Stress is a significant factor in the production of proinflammatory cytokines, such as IL-6. Nevertheless, increased inflammatory factors are also involved in inducing stress and activating the HPA axis and cortisol production. The direct effects of cytokines, such as IL-6, on HPA axis stimulation are well known; therefore, cytokines secreted by lymphocytes and macrophages are likely to be involved in stimulating pituitary secretion (44). A study reported a link between increased plasma cortisol, insulin resistance, and decreased β-cell function. Inflammatory factors inhibit insulin secretion from β-cell by increasing cortisol levels, eventually disrupting glucose metabolism and contributing to diabetes (45).

3.6.3. Tumor Necrosis Factor-Alpha (TNF-α)

The TNF-α, as the primary regulator of the inflammatory response, affects different cell types involved in the pathogenesis of some inflammatory diseases. The TNF-α is composed of 157 amino acids and is produced by active macrophages, T lymphocytes, and natural killer cells (46). When TNF-α is released by cells, it can interact with the tumor necrosis factor-1 receptor (TNF-R1) and play an important role in apoptosis by activating nuclear factor kappa B and stimulating the activation pathway caspases. In addition, the TNF-TNF-R1 complex activates downstream signaling pathways, such as MAPK, p38 MAPK, extracellular regulated kinase, and c-Jun activating kinase (47). The TNF-α can be directly involved in the pathogenesis of type 2 diabetes and obesity by affecting insulin signaling. The role of this cytokine has been reported in weight loss, hypermetabolism, and energy consumption (48).

Previous studies showed that TNF-α disrupts β-cell function in rodents and humans. The action of TNF-α in local inflammatory responses is mediated by specific membrane receptors, TNF-R1, and TNF-R2, which activate the mechanisms of apoptosis. Moreover, TNF-α induces insulin resistance by inhibiting MAPK activity. Ultimately, a decrease in insulin secretion makes Langerhans islet β-cells vulnerable to damage caused by inflammatory factors and harms the proliferation rate of these cells (49). Another study showed that TNF-α in adipocytes reduces the secretion of adiponectin, which induces insulin resistance. In addition, TNF damages fat cells and liver cells by activating protein-related protein kinases, such as c-Jun N-terminal kinases 1 and serine phosphorylation. Therefore, the use of TNF-α antagonists can be effective in the treatment of inflammatory diseases (50).

The HPA axis is a regulatory system for the body's response to acute and chronic stress. Long-term stress can cause a weak cortisol response to stress. It, in turn, leads to insulin resistance, obesity, and diabetes. In addition, there is a close relationship between acute and chronic stress, inflammation, and adipose tissue. The evidence suggests that the dysfunction of the HPA axis contributes to obesity, inflammation, and type 2 diabetes (51). Furthermore, studies showed that stress with endothelial dysfunction causes changes in the levels of proinflammatory cytokines, such as TNFα, which are associated with inflammatory diseases. Numerous cytokines, such as TNF, are potent stimuli of the HPA axis. This factor is considered a key mediator in HPA gene expression and peptide release (52).

4. Conclusions

The CNS plays an important role in regulating glucose secretion. Serotonin is one of the brain neurotransmitters involved in regulating energy balance. The SERT is encoded by the *SLC6A4* gene. The *SLC6A4* gene is located on chromosome 17. This gene contains 16 exons and 630 amino acids. Mutations in this gene cause two short (S) alleles and long (L) alleles. The allele (S) inhibits the transcription of the SERT coding gene. Various genetic factors affect the HPA axis. This axis can be controlled by the serotonergic system. Therefore, the polymorphism in the gene encoding the SERT affects the function of the HPA axis. Carriers containing allele (S) increase cortisol levels by disrupting the HPA axis. In turn, an increase in cortisol levels leads to increased glucose levels, decreased insulin production, increased lipolysis, and insulin resistance. It ultimately affects glucose metabolism. Moreover, an association between homozygous allele (S) and diabetes was reported. Polymorphism in the *SLC6A4* gene causes an increase in fasting glucose levels. In addition, it has been observed that there is a close relationship between increases in the levels of inflammatory factors, such as IL-6, IL-1, and TNF-α, with mutations in the *SLC6A4* gene.

Individuals with homozygous S alleles have high levels of cytokines in their serum. Therefore, an increase in the levels of inflammatory factors might play a role in the polymorphism of the *SLC6A4* gene. A defect in the *SLC6A4* gene disrupts the serotrogenic pathway, which can affect the HPA axis and increase cortisol levels. An increase in cortisol levels disrupts the function of beta cells, thereby impairing insulin secretion. It eventually leads to the progression of diabetes.

Footnotes

Authors' Contribution: All the authors contributed equally to this article.

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