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Relationship between SREBF-1 Polymorphism and Insulin Resistance in Polycystic Ovary Syndrome Women

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ABSTRACT

Aims It was reported that there was a significant relationship between 54G/C SREBF1 and diabetes. There may be a relation between SREBF-1 polymorphism and insulin resistance in women with PCOS, but this relation is unknown. This study investigated the relationship between SREBF-1 polymorphism and insulin resistance in polycystic ovary syndrome women.

Materials & Methods Two hundred subjects were studied; 100 polycystic ovary syndrome subjects (case group) and 100 healthy subjects (control group). Blood samples were taken, demographic characteristics were requested, and genomic DNA was extracted. The RFLP-PCR method was used to determine the mutations of 54G/C SREBF1. Following laboratory investigation, the data were investigated using SPSS 23 software. The mutant alleles rate was determined by analysis of variance.

Findings The genotypic frequency of GG and CC was significantly higher in patients than in the control group. In contrast, the frequency of heterozygosity was significantly higher in the control group than in the PCOS group. Allelic frequency was 78.00 for the G allele and 22.00 for the C allele in the patient group. In the healthy group, it was 75% for the G allele and 25% for the C allele. The results showed that homozygote genotypes had higher glucose and insulin resistance sensitivity.

Conclusion The 54G/C polymorphism of SREBF-1 plays a significant role in polycystic ovary syndrome and is closely related to glucose and insulin resistance. Thus, G/C genotype frequency could be considered a biomarker for the detection of PCOS.

Keywords Insulin Resistant; Polycystic Ovary Syndrome; Polymorphism; SREBF-1

CITATION LINKS

[1] Diagnosing and treating the causes of women's polycystic ovary syndrome... [2] The quality of life of menopausal women with polycystic... [3] The double-edged sword of PCOS and gender: Exploring gender-diverse experiences... [4] The story of polycystic ovarian syndrome: A challenging disorder with numerous... [5] Cardio-metabolic disease and polycystic ovarian syndrome (PCOS)... [6] Association of insulin resistance and elevated androgen levels with polycystic ovarian syndrome (PCOS)... [7] Hyperandrogenemia and insulin resistance: The chief culprit of polycystic... [8] Polycystic ovarian syndrome: Correlation between... [9] Polycystic ovary syndrome in insulin-resistant adolescents with obesity: The role of nutrition therapy... [10] Resistance to the insulin and elevated level of androgen: A major cause... [11] γ-Linolenic acid ameliorates DHEA induced pro-inflammatory response in polycystic ovary syndrome via... [12] Mutations in SREBF1, encoding sterol regulatory element binding transcription factor 1, cause... [13] The bHLH-zip transcription factor SREBP regulates triterpenoid and lipid metabolisms... [14] Cytoplasmic vacuolation with endoplasmic reticulum stress directs sorafenib induced non-apoptotic cell death... [15] Can non-coding NR5A1 gene variants explain phenotypes... [16] The genetics of polycystic... [17] Genetics of polycystic ovary... [18] SREBP-1, a basic-helix-loop-helix-leucine zipper protein that controls transcription of the low... [19] Correlation between thrombophilia and recurrent pregnancy loss in patients with... [20] The promoter-1031 (T/C) polymorphism in tumor necrosis factor-alpha... [21] 54G/C polymorphism of SREBF-1 gene is associated... [22] Association study of+ 45G15G (T/G) and+ 276 (G/T) polymorphisms in the adiponectin... [23] Association study between polycystic ovarian syndrome and the susceptibility... [24] The association between polymorphism of INSR and polycystic ovary... [25] Sterol regulatory element binding transcription factor 1 expression... [26] Polymorphisms in the gene encoding sterol regulatory element-binding... [27] Genetic control of de novo lipogenesis... [28] The SREBF-1 locus is associated with type 2 diabetes and plasma adiponectin...

Introduction

Polycystic ovary syndrome (PCOS) is a set of symptoms and diseases in which women have high amounts of androgens or male hormones [1]. This disease has many symptoms, including painful menstruation or no menstrual symptoms, acne, hairy body, skin disorders, mood problems, type 2 diabetes, heart failure, infertility, and endometriosis cancer [2, 3]. Polycystic ovary syndrome disease is an autosomal dominant genetic disease with a high penetrance coefficient, but its occurrence varies in different women, and there is a probability that 50% of the children born will have symptoms of the disease [4]. The negative and extensive effects of this syndrome on the physiology and metabolism of the body lead to a metabolic disorder with visible abnormalities such as high blood insulin, insulin resistance, abdominal obesity, and disorders related to blood fat, which, in the long term, its prevalence rate increases [5, 6]. Insulin resistance is an important abnormality in patients with polycystic ovaries due to the connection between inflammatory and insulin signaling pathways [7, 8]. Insulin resistance may increase steroidogenesis and LH release in individuals with polycystic ovaries through hyperinsulinemia [9]. Studies have shown that hyperinsulinemia caused by insulin resistance and hyperandrogenism have mutual causes [10]. Insulin resistance is an important abnormality in patients with polycystic ovaries due to the connection between inflammatory and insulin signaling pathways [7].

PCOS is a polygenic disease that is affected by several genes, but the genes involved in this disease have not been precisely identified, but the results of some studies indicate that different polymorphisms of the SREBF1 gene, which lead to the production of a protein linked to Regulation of sterol gene expression can play an important role in this disease [11]. The protein bound to the regulatory component of sterol gene expression is a transcription factor that binds to the gene sequence of the regulatory component of sterol gene expression [12]. In mammals, this protein is expressed by genes called transcription factor genes connected to the regulatory components of the sterol gene [13]. Inactive SERBs proteins bind to the nuclear envelope and endoplasmic reticulum, and in cells with low serum levels of sterol, enter the water-soluble N-terminal domain cleft inside the cell nucleus [14]. In fact, in this case, the activated SREBPs are connected to a specific region of the genome sequence and affect the upstream region of the said gene, which is responsible for the production of the enzyme involved in sterol production [15].

Several polymorphisms have been identified and introduced in relation to this gene, of which the C/G 54 polymorphism is one of the most important. There may be a relation between SREBF-1 polymorphism and insulin resistance in women with PCOS, but this relation is unknown. This study investigated the relationship between SREBF-1 polymorphism and insulin resistance in women with polycystic ovary syndrome.

Materials and Methods

This case-control study was conducted on women with PCOS who were referred to clinical centers in Iran during the 2021-2023 years. To determine the appropriate number of samples, the sample volume calculation software was used, using the coefficients e, r, and z with a confidence interval of 95%. 150 patients with polycystic ovary syndrome were selected during the diagnosis. The total number of samples was 150 people for the control and 150 people for the case.

First, a consent letter was obtained from the subjects, and then venous blood sampling was performed; 5ml of blood was taken from each subject and poured into vials containing EDTA as an anticoagulant, and then the vials It was gently shaken to mix and prevent the formation of blood clots. Finally, the samples were stored in the freezer. Demographic data were collected from patients. Blood samples were used to investigate polymorphism status in women with PCOS. The rest was used to investigate insulin resistance with the help of specific kits. Blood glucose between 140mg/dl and 199mg/dl is pre-diabetes, and a blood glucose level of 200mg/dl or higher is considered diabetes. The HOMA index was used to investigate insulin resistance, and a value higher than 2.38 was considered insulin resistant.

Polymerase Chain Reaction (PCR) was used to investigate polymorphism. The 54(G/C) of SREBF-1 primers were used (F: TGAGGCTCCTGTGCTACTTTGCC and R: GGACAGAGCTGGGAGGTGAGAAG). The final volume was 34µl, including Beta PCR mix (30µl), 1µl of forward primer, 1µl of reverse primer, 0.5µl of DNA Polymerase Taq, and 1.50µl of DNA Pattern. After performing the PCR reactions, the resulting products were electrophoresed on 0.2% agarose gel, then stained and imaged. After ensuring the functionality of the PCR products, the products of SREBF-1 polymorphic site 54(G/C) were cut using XmnI enzyme, and the mutation frequency was analyzed using the expected fragments. In the case of G nucleotide, the enzyme acts and cuts, and the sizes of 165 and 211 base pairs of nucleotides were observed. Therefore, the size of fragments in the C/C mode is 376 nucleotide base pairs; in the G/C mode, the size of the fragments was 211, 165, and 376. The size of fragments in the GG state will be 165 and 211 base pairs of nucleotides.

The Kruskal-Wallis test was used to compare between groups. Analysis of variance method was used to compare the mean number of mutant alleles

in the studied population. After completing the laboratory work, the expected and observed frequencies were calculated using the Hardy-Weinberg law and entered into the SPSS 23 software.

Findings

There was no significant difference (p>0.05) between the mean age of the control (38.00±3.04; 28 to 44 years) and polycystic ovary syndrome (38.01±4.00; 29 to 45 years). Also, there was no significant difference (p>0.05) between the body mass index of the control (28.10±4.09; 21.20 to 37.65) and polycystic ovary syndrome (27.56±5.04; 24.17 to 38.18).

The genotypic frequency of GG and CC was significantly higher in patients than in the control group, while the frequency of heterozygosity was significantly higher in the control group than in the PCOS group. Allelic frequency was 78.00 for the G allele and 22.00 for the C allele in the patient group. In the healthy group, it was 75% for the G allele and 25% for the C allele (Table 1).

Table 1. Genotypic frequency of 54(G/C) SREBF-1 polymorphism in healthy group (n=100) and patient group (n=100)

Genotypes	Patient	Control	p-Value	OR	C.I. 95.00%
GG	62%	54%	0.002	0.97	0.55-1.52
GC	32%	43%	0.001	1.05	0.69-2.10
CC	5%	3%	0.001	0.69	0.35-1.35

In healthy subjects, there was no insulin resistance and no high glucose. Homozygote genotypes had higher sensitivity to higher glucose. Thus, GG (45 cases; 72%) and CC (2 cases; 40%) are risky factors for higher glucose, and GC (10 cases; 30%) is a protective genotype (p=0.001). The results showed similar results for insulin resistance. Insulin resistance was significantly higher in GG (46 cases; 74.2%) and CC (4 cases; 80%) compared with the GC (8 cases; 25%) genotype (p=0.001).

Discussion

Polycystic ovary syndrome is a reproductive disorder that is characterized by various symptoms. The cause of the disease is not well known. Several hypotheses have been proposed to explain the cause of this disease. The genetic disorder that supports polycystic ovary syndrome is that different members of the same family may have differences in this respect, but about half of the girls in the same family are evaluated for serum testosterone concentration. However, the presence of abnormal genes in women with polycystic ovary syndrome has been suggested, and attempts have been made to find the polymorphisms that cause it. The main genes involved in steroidogenesis, effects of steroid hormones, regulation of gonadotropin release, insulin secretion and action, and adipose tissue metabolism are usually extensively evaluated [16, 17]. The results of some studies indicate that different polymorphisms of the SREBF1 gene, which leads to the production of a protein connected to the regulatory component of sterol gene expression, can play an important role in this disease. The protein bound to the regulatory component of sterol gene expression is a transcription factor that binds to the gene sequence of the sterol gene expression regulatory component. In mammals, this protein is expressed by genes called transcription factor genes connected to the regulatory components of the sterol gene [18]. Inactive SERB proteins bind to the nuclear envelope and endoplasmic reticulum and, in cells with low serum levels of sterol, to the water-soluble N-terminal domain cleft located inside the cell nucleus. The results of this study showed that there is a relationship between SREBF1 gene polymorphism and SNP 54G/C in polycystic ovary syndrome patients. The present study's findings may be useful for early disease diagnosis and genetic treatment of patients with polycystic ovary syndrome. Studies have identified several genes related to polycystic ovary syndrome, especially those involved in metabolism, inflammation, and insulin signaling [19, 20]. According to the search, only one study in the world has discussed the relationship between polycystic ovary syndrome and SREBF1 gene polymorphism, and their results agree with the present study's findings. Li *et al.* [21] investigated the frequency of the polymorphism and its role in PCOS disease and concluded a significant relationship between the disease and 54C/G polymorphism. In fact, if the frequency of this polymorphism is high in people, especially women, the possibility of diseases such as polycystic ovary syndrome increases. In another study, Lee *et al.* [22] showed that the expression of SREBP-1 is increased in endometrial cancer cells and hyperplasia. Although other studies have not addressed the 54C/G polymorphism of the SREBP-1 gene and its relationship with polycystic ovary syndrome, a relationship between other polymorphisms and polycystic ovary syndrome has been reported. Ha *et al.* [23] investigated the pathogenesis of polycystic ovary syndrome and the environmental and genetic factors involved in its development and showed that different gene polymorphisms are involved in causing this disease and can lead to different pathological conditions. Chung *et al.* [24] investigated the relationship between genetic indices and the disease and evaluated the obtained data using meta-analysis. They concluded a significant relationship between polymorphism of the mentioned gene and polycystic ovary syndrome; these genetic indices are one of the determining factors in suffering from such diseases.

The results showed a significant relationship between high glucose and insulin resistance with polymorphism. The role of SREBF-1 in type 2 diabetes mellitus has been reported, but its

relationship with polycystic ovary syndrome as a diabetes-related disease has not yet been elucidated [25, 26]. Transgenic analysis of mice interferes with the role of SREBF-1 in the expression of genes involved in the metabolism of fatty acids and glucose [27]. In another study, the relationship between SREBF-1, obesity, and type 2 diabetes was reported in English and French populations [28]. Overall, the results of this study accept that there is a difference between the genotypes of both populations, and this shows that there is a significant difference between the SREBF-1 polymorphisms.

Conclusion

54G/C polymorphism of SREBF-1 plays a significant role in PCOS and is closely related to glucose and insulin resistance. It could be stated that G/C genotype frequency could be considered a biomarker for the detection of PCOS.

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