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Review the Association of Ala513Pro and Gly972Arg *IRS-1* Gene Polymorphism with Gestational Diabetes Mellitus in South of Iran

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Abstract

Introduction: Gestational diabetes mellitus is a multi-factor disease. Several genes are shown to be associated with diabetes mellitus. Among them, *IRS-1* gene is located on chromosome No.2 which is an endogen substrate for insulin receptor. *IRS-1* gene has an important role in insulin pathway signaling. Aim of this study was to review the association of Ala513Pro and Gly972Arg *IRS-1* gene polymorphism with gestational diabetes mellitus in south of Iran.

Methods: 200 subjects with gestational diabetes mellitus and 200 healthy subjects as control group were enrolled in the study. DNA was extracted from their blood and polymorphism of G, C and T allele were studied. It was aimed to investigate whether genotype is associated with clinical and biochemical variables such as family history, fasting blood sugar, blood lipid and body mass index. Independent sample t- test, chi- square test, logistic regression and Hardy- Weinberg equilibrium tests were used to analyze data ($p \leq 0.05$).

Results: The finding from the Polymorphism Gly972Arg study show that individuals with CC, CT genotypes were associated with an increased risk of the disease (%95CI: 0.02-0.44, OR=0.1, P<0.001), (%95CI:2-58.43, OR=9.2, P<0.01). There was no allele and genotypic variation in Polymorphism Ala513Pro Polymorphism.

Conclusion: Based on the obtained results, Ala 513Pro polymorphism of the *IRS-1* gene was not correlated, but Gly 972 Arg polymorphism related with gestational diabetes mellitus in population of south Iran.

Keywords: Gestational Diabetes, Polymorphism, Iran

Introduction

Diabetes is a group of metabolic disorders in the metabolism of carbohydrates. Some people may experience severe and fatal periodic attacks of hyperglycemic (such as ketoacidosis or hyperosmolar coma (1). Maintain euglycemia by increasing insulin secretion and gestational diabetes occurs in women, whose body can't make enough insulin. Actually gestational diabetes occurs when a pregnant woman does not release enough insulin or respond to insulin is not enough; as a result, the patient is unable to have normal glucose status (2). After the termination of pregnancy, in a person with GDM (Gestational diabetes mellitus) probability increases of it in the next pregnancy catching type 1 or type 2 (Mostly type II) along with other cardiovascular risks like dyslipidemia, blood pressure, abdominal obesity and metabolic syndrome. Patients with GDM should be evaluated in terms of diabetes at 6 to 12 weeks after delivery, and if they do not have diabetes, be re-evaluated at least every three years (3). Gestational diabetes also has some risks to the fetus, including macrosomia, hypoglycemia, jaundice and increased incidence of fetal death in pregnancy. The prevalence of gestational diabetes in America is between 1 to 3%, in Asian countries is 10.9% and in Europe have

been reported 5.2% (2). Diabetes is a multifactorial disease that genetic defects are involved in the pathogenesis of type II diabetes. In addition, the incidence of type II diabetes in an obese child of a parent with diabetes than obese person who has no family history of diabetes is 10 times higher; however, the manner of inheritance of the disease is not yet clear (4, 5). Many studies in this case have identified several genes associated with type II diabetes. However, despite considerable research to identify the genetic basis of type II diabetes mellitus, genetic factors known to date, less than 5% of people with type II diabetes were allocated. The genes that cause common types of diabetes type 2 are still unknown and some genes that have been identified, have an effect on insulin secretion and are involved in insulin function or body weight regulation (6, 7). Several genetic polymorphisms and their effect on insulin activity are detected, including *IRS-1* gene polymorphisms that are a signaling protein in humans and encoded by the gene *IRS-1*. This gene is located on chromosome 2q36, and encodes one of proteins of IRS family. Insulin is an important determinant of early growth and plays a prominent role in maintaining glucose homeostasis. IRS-1, plays a critical role in insulin signaling and its control has an important place in the development of insulin resistance. One of the polymorphisms of this gene is alanine with proline amino acid substitution at codon 513 (Ala513Pro) and other polymorphisms of this gene is glycine with arginine amino acid substitution at codon 972 (Gly972Arg) that associated with a high incidence of gestational diabetes due to insulin resistance, and impaired insulin secretion (8, 9). Insulin receptor substrate (IRS) proteins that are an important ligand in insulin response of human cells are a family of compatible proteins (adapter). Insulin Receptor Substrate-1 (IRS-1), has an important role in signal transduction of insulin and IGF-1 (insulin- like growth factor-1) to the PI3K / AKT kinase and ERKMAP intracellular pathways (10). In this study, Ala513Pro and Gly972Arg polymorphism of the gene IRS-1 in patients with gestational diabetes was evaluated and compared with the control group.

Methods

In this study, 200 women diagnosed with GDM and 200 healthy pregnant women as controls were chosen and referred to a central laboratory in Minab, Shariati Hospital in Bandar Abbas, Katamolanbia hospital in Jask, and Hafez Hospital in Shiraz for taking blood samples. Basic information including age, height, weight, family history, parity, history of abortion and still birth of all subjects were obtained by questionnaire. Written informed consent was obtained from all subjects. For measure the research variables, 5 CC blood gathered from antecubital vein DNA extraction was done by DNA extraction kits of Yekta Tajhiz Azma Company, and was kept at -20 °***C***. The results of Ala513Pro and Gly972Arg gene polymorphisms in patients and control group were compared. The materials needed for the PCR reaction in order to duplication of the IRS-1 gene including 11 λ H2O, 0.5 λ Forward primer, 0.5 λ Reverse primers, 1λ DNA, 12.5 λ Master Mix with a final volume of 25.5 ml. In order to determine the IRS-1 genotype, Ade1 and SMAI restriction enzyme were used. The resulting genotype was observed after digestion and Polyacrylamide gel electrophoresis (2%). Data were recorded in SPSS software. Independent sample t- test, chi- square test, logistic regression and Hardy- Weinberg equilibrium were used ($p \leq 0.05$).

Results

Clinical and biochemical characteristics of the individuals are shown in Table 1, 2, and 3.

The results of independent sample t- test in Table 2 showed that the levels of FBS (p=0.001), GTT1 (p=0.001), GTT2 (p=0.001), GTT3 (p=0.001), TG (p=0.001), Chol (p=0.001), HDL (p=0.001), LDL (p=0.001),

BMI (p=0.001) and age (p=0.01) in patient group were significantly higher than control group. The finding from the polymorphism Gly972Arg study show that individuals with CC, CT genotypes were associated with an increased risk of the disease (%95CI: 0.02-0.44, OR=0.1), (%95CI:2-58.43, OR=9.2). There was no allele and genotypic variation in polymorphism Ala513Pro polymorphism.

Table 1. The results of logistic regression test for compare the family history and previous gestation between patient and control groups

History	Patient (%)	Control (%)	P value	OR (%95CI)
Family History	52 (26)	22 (11)	0.001	(1.6-4.9) 2.8
Previous Gestation	82 (41)	21 (10.5)	0.001	(3.6-10.7) 6

Table 2. The results of independent sample t- test for compare the biochemical and clinical characteristics in patient and control groups

Variable	Patient	Control	P value
FBS (mg/dL)	111.47±15.659	47.81±7.081	0.001
GTT1 (mg/dL)	234.15±22.485	123.43±15.501	0.001
GTT2 (mg/dL)	194.22±27.754	97.88±12.733	0.001
GTT3 (mg/dL)	174.96±22.776	92.20±15.917	0.001
TG (mg/dL)	234.71±42.231	218.49±51.295	0.001
Chol (mg/dL)	198.99±23.926	186.13±24.509	0.001
HDL (mg/dL)	42.5±10.775	46.60±10.540	0.001
LDL (mg/dL)	109.55±22.353	95.83±16.706	0.001
BMI (kg/m2)	33.55±1.947	29.62±2.628	0.001
Age (years)	30.7±4.8	27.8±6.0	0.01

* FBS: fasting blood sugar. GTT1: one-hour glucose tolerance test. GTT2: tow-hour glucose tolerance test. GTT3: three-hour glucose tolerance test. TG: triglyceride. Chol: cholesterol. HDL: high density lipoprotein. LDL: low density lipoprotein. BMI: body mass index

Table 3. The results of logistic regression test for association study and genotype distribution of genotype in patient and control groups

Genotype	Patient (%)	Control (%)	OR (%95CI)	P value
CC(G972A)	181 (90.5)	198 (99)	0.1 (0.02-0.44)	0.001
CT(G972A)	17 (8.5)	2 (1)	9.2 (2-58.43)	0.004
TT(G972A)	2 (1)	0	8.7 (3.35-59.43)	0.001
C(G972A)	379 (94.8)	398 (99.5)	0.09 (0.01-0.4)	0.005
T(G972A)	21 (5.2)	2 (0.5)	11.03 (2.48-68.5)	0.005
GG(A513P)	198 (99)	200 (100)	-	>0.05
CG(A513P)	2 (1)	0	-	>0.05
CC(A513P)	0	0	-	-

Discussion

Gestational diabetes is carbohydrate intolerance that its intensity is variable with and for the first time during pregnancy begins or diagnosed. Its incidence in several populations is different (2). Several genes have been identified in relation to diabetes and changes in certain genes increase the risk of

this disease.These genes can be connected with insulin resistance, reduction in production of insulin or risk of obesity. In insulin resistant patients reduce the sensitivity of fat cells to insulin hormone it increases the fatty acids free of the blood, which is one of the most common symptoms of type 2 diabetes and gradually increase insulin resistance and in activity of pancreatic beta cells (11, 12). Many studies have been done on the genotype of this gene but have not been obtained similar results from these studies. In a study that Hart *et al.* was conducted on patients with type 2 diabetes concluded that polymorphisms of *IRS-1* gene is associated with type 2 diabetes (13). In another study that Almind *et al.* was conducted on patients with type 2 diabetes, they reported that polymorphisms of this gene in patients were three times higher than the control group (8). While in Arikoglu *et al.* study, they did not find any correlation between polymorphisms of *IRS-1* gene (Gly972Arg and Ala513Pro polymorphism) and type 2 diabetes (14). In another study that Bodhini *et al.* was conducted on patients with type 2 diabetes. They did not find any correlation between polymorphisms of *IRS-1* gene and type 2 diabetes (15). In this study Ala513Pro/Gly972Arg, polymorphisms of the *IRS-1* gene between patients with GDM and woman without GDM in control group were compared and found that Ala513Pro polymorphisms of *IRS-1* gene is not connected with gestational diabetes but Gly972Arg, polymorphisms this gene is associated with GDM. Furthermore, the prevalence of these polymorphisms in patients according to age, family history, blood lipids, blood sugar and body mass index were checked out and found that, there is a direct relationship between the BMI and gestational diabetes so people who are overweight are more likely to develop this disease.

Conclusion

This study showed that increases in blood lipids, increase the risk of gestational diabetes. Also increase in FBS affects in gestational diabetes and in women over 25 years the risk of GDM is more. In our study it was found that family history is one of the causes of gestational diabetes in patients compared with the control group.

Ethical issues

Not applicable.

Authors' contributions

All authors equally contributed to the writing and revision of this paper.

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