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POLYMORPHISM OF THE FABP 2 GENE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS ASSOCIATED WITH CHRONIC HEART FAILURE

[1]Yusupova Sh.K.,[2]Abdurazakova D.S., [3]Umurzakova R.Z., [4]Mukhamedova V.M.
[1]Head of the Department of Hospital Therapy and Endocrinology, Andijan State Medical Institute, Andijan,Uzbekistan.
[2]Candidate of Medical Sciences, Assistant of the Department of Hospital Therapy and Endocrinology, Andijan State Medical Institute, Andijan,Uzbekistan.
[3]Candidate of Medical Sciences, Associate Professor of the Department of Hospital Therapy and Endocrinology, Andijan State Medical Institute, Andijan,Uzbekistan.
[4]Assistant of the Department of Hospital Therapy and Endocrinology - Andijan State Medical Institute, Andijan,Uzbekistan.

Abstract: The aim of the studywas to study the FABP 2 gene polymorphism as a prognosis for the development of cardiovascular complications of type 2 diabetes mellitus.To achieve this goal , a genetic study was conducted in 103 patients diagnosed with type 2 diabetes with and without CHF, as well as patients with CHF without type 2 diabetes treated in the endocrinology and cardiology departments of the Andijan State Medical Institute clinics, which made up the main group.

The patients were divided into 3 groups:
Group 1 - patients with type 2 diabetes + CHF - 42 patients,
group 2 - patients with type 2 diabetes without CHF - 35 patients,
Group 3 - patients with CHF without type 2 diabetes - 26 patients

The control group consisted of 20 healthy individuals of the corresponding average age (10 men and 10 women).

Disease diagnoses were established in accordance with the latest clinical guidelines.

Isolation of DNA from peripheral blood was carried out using a commercial kit of reagents " AmpliPrime RIBO- prep " (OOO " Interlabservis ", Russia), according to the manufacturer's instructions.Comparative analysis of Ala distribution indicators and Thralleles of the FABP 2 rs1799883 gene in the combined and control groups showed no significant differences: 73.8% and 26.2% versus 84.6% and 15.4%, respectively. By frequencies allelespolymorphism rs1799883 of the *FABP 2 gene* , statistically significant differences were revealedbetweengroups,in the presence of a wild allele Alars1799883 of the FABP 2 gene showed a protective effect on the development of both type 2 DM and CHF.

However, the proportion of the unfavorable allele Thr in the main group significantly prevailed relative to the control group. The odds ratio showed that the chance of finding a functional unfavorable allele Thrin respondents with DM2 it is OR =2.0 compared with the control (χ^2 =7.3; p=0.001; OR =2.0; 95% CI :1.20-3.19).

Asignificant relationship was found between the carriage of an unfavorable allelic 54 Thr variant of the FABP 2 gene , associated with increased fat metabolism in the body and the risk of developing DM2, but without CHF. The risk of developing DM2 with this allelic variant is significantly increased by more than 1.9 times (OR =1.9; $\chi 2^{=}$ 3.8; p=0.05), on the contrary, the wild genotypic variantAla 54 of the FABP 2 gene is associated with a reduced risk of T2DM.

Key words: type 2 diabetes mellitus, chronic heart failure, FABP 2 gene polymorphism

Introduction

According to the International Diabetes Federation(IDFdiabetesAtlas 8th _edition),There were about 425 million cases of diabetes among adults aged 20–79 years in 2017 . It is expected that by 2045 thesefigures will increase to 629 million people, which equals 9.9%of the population who will live with diabetes (by ageinterval20–79years). In addition, in2017G.inworldamongpersonsinage20–99yearsnear5milliondeathswere linkedwithdiabetes[1].

Coronary heart disease (CHD) clusters in families, indicating that hereditary factors play a significant role in the etiology of this disease [8,9]. Gene defects leading to decreased insulin sensitivity might contribute to CHD because prospective population-based studies have indicated an association of hyperinsulinemia with CHD [10]. The fatty acid-binding protein 2 (FABP2) gene encodes an intestinal fatty acid-binding protein that is expressed only in the columnar absorptive epithelial cells of the small intestinal villus [11]. Defects in the FABP2 gene could affect the binding capacity of the FABP2 protein, increase fatty acid absorption, and lead to enhanced fatty acid oxidation and an impairment in insulin action. In fact, the polymorphism Ala-»Thr in codon 54 of the FABP2 gene has been shown to be associated with insulin resistance in nondiabetic Pima Indians[12].

According to regional endocrinological dispensaries, in 2020, 277,926 patients with diabetes mellitus (DM) were registered in the Republic of Uzbekistan , of which 18,178 type 1 diabetes, 259,748 type 2 diabetes patients. In 2021, 310,006 patients are already registered with the Republic of Uzbekistan. It should be noted that the true number of diabetic patients exceeds the registered one by 10 times, while over the past 18 years the number of

diabetic patients in Uzbekistan has increased by 2.4 times (according to the Ministry of Health of the Republic of Uzbekistan).

As is known, the online catalog of human genes and genetic diseasesOMIM(OnlineMendelianInheritanceinman)at searched for the keyword " diabetes " provides more than 965 abstracts[3]. It abstract show ongenes, So and on phenotypes. AT based at a HuGEN a vigatorcontaineddata on 3710 genes tested for association with type 2 diabetes[4]. However, despite the wide range of information, there is no qualitative breakthrough in understanding. The literature describes external factors and genetic markers leading to development SD2. Majority genes, in which localized these polymorphisms, affects on insulin secretion, although the precise molecular mechanisms remainin significant degrees unknown[5].

Among them, the FABP2 gene (fatty acid binding protein 2, 4q28-4q31) is considered as a candidate gene for DM and resistancetoinsulinencodedtheproteininvolvedinabsorptionandfatty acid metabolism. The authors emphasize that data on the relationship of polymorphismrs1799883geneFABP2WithSD2 are inconsistent. [6].

All of the above emphasizes the relevance of this study and served as its reason.

The aim of the study was to study the FABP 2 gene polymorphism as a prognosis for the development of cardiovascular complications of type 2 diabetes mellitus .

Material and research methods

To achieve this goal , a genetic study was conducted in 103 patients diagnosed with type 2 diabetes with and without CHF, as well as patients with CHF without type 2 diabetes treated in the endocrinology and cardiology departments of the Andijan State Medical Institute clinics, which made up the main group.

The patients were divided into 3 groups:

Group 1 - patients with type 2 diabetes + CHF - 42 patients,

group 2 - patients with type 2 diabetes without CHF - 35 patients,

Group 3 - patients with CHF without type 2 diabetes - 26 patients

The control group consisted of 101 healthy individuals of the corresponding average age.

Disease diagnoses were established in accordance with the latest clinical guidelines for DM and CHF.

Isolation of DNA from peripheral blood was carried out using a commercial kit of reagents " AmpliPrime RIBO- prep " (OOO " Interlabservis ", Russia), according to the manufacturer's instructions.

Testing of FABP2 rs 1799883 polymorphism was carried out by allele-specific PCR in Real - Time format on a Rotor - Gene instrument .Q (Quagen, Germany) using a commercial test kit from Sintol LLC (Russia) in accordance with the manufacturer's instructions.

OpenEpi application package .V.9.2 .

The distribution of alleles and genotypes corresponded to the Hardy- Weinberg distribution law (RHV). To describe the relative risk of developing the disease, the odds ratio (OR) was calculated. O R >1 was considered as a positive association (predisposition) of an allele or genotype with a disease , and O R <1 ($p< 0.05$) as a negative one.

Results and Discussion

Comparative Analysis of Ala Distribution Indicators and Thralleles of the FABP2 rs 1799883 gene in the main and control groups showed no significant differences: 73.8% and 26.2% versus 84.6% and 15.4%, respectively. (Table 1). Byfrequenciesallelespolymorphism rs1799883 of the FABP2 gene ,statistically significant differences were revealedbetweengroups,in the presence of a wild allele Ala rs1799883 of the FABP2 gene showed a protective effect on the development of both type 2 diabetes and CHF. However, the proportion of the unfavorable allele Thr in the main group significantly prevailed relative to the control group. The odds ratio showed that the chance of finding a functional unfavorable allele Thrin respondents with DM2 it is OR =2.0 compared with the control (χ^2 =7.3; p=0.001; OR =2.0; 95% CI :1.20-3.19). This OR value allows us to consider the carriage of this allelic variant as a high risk factor for the development of pathologies in the main group. (Table 1).

Table 1.

Distribution frequency of alleles and genotypes of the Ala 54 Thr polymorphism of the FABP 2 gene rs1799883in the combined and control groups.

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	p	OR	95%CI
	Main group		Control group					
	n	%	n	%				
Ala	152	73.8	171	84.6	7.3	0.001	0.5	0.31 - 0.83
Thr	54	26.2	31	15.4	7.3	0.001	2.0	1.20 - 3.19
Ala / Ala	59	57.3	74	73.3	5.7	0.02	0.5	0.27 - 0.88
Ala / Thr	34	33.0	23	22.8	2.6	0.10	1.7	0.90 - 3.10
Thr / Thr	ten	9.7	four	3.9	2.6	0.11	2.6	0.82 - 8.30

When comparing the main group and the control group by frequency distribution of genotypes polymorphismAla 54 Thr of the FABP 2 rs1799883 gene was also identifiedstatisticallysignificant differences. Inthe main group of patients, the frequency of occurrence of a favorable Ala / Ala genotype (57.3% vs. 73.3%; χ^2 =5.7; p=0.02; OR =0.5; 95% CI : 0.27-0.88) was significantmore,howingroupcontrol, which indicates the manifestation of the protective effect of this genotype in relation to the formation of both type 2 DM and CHF. RiskformationSD2 types and CHF in 17 times higher _atcarriers of an unfavorable genotype of the genotypeAla / Thrgene FABP 2 rs1799883(33.0% vs. 22.8%; $\chi 2^{=}$ 2.6; p=0.1; OR =1.7; 95% CI :0.90-3.10) compared to reference . Analysis of the obtained results established a trend towards an increase in the risk of developing type 2 diabetes and CHF by 2.6 times when the mutant Thr/ Thr genotype is detected.geneFABP 2 (9.7% vs 3.9%; χ^2 =2.6; p=0.1; OR =2.6; 95% CI : 0.82-8.30) . (Table 1).

When analyzing the distribution of alleles of the studied marker of the gene FABP 2 revealed significant differences between the group of type 2 DM with CHF and the control group. So,carrying a favorable allele Alaand associated wild genotypeAla / Alarenderedprotective effect on the risk of developing type 2 diabetes in patients with CHF (70.2% vs 84.6%; χ^2 =7.8; p=0.001; OR =0.4; 95% CI : 0.24-0.78 and 52.4% vs 73.3%; χ^2 =7.8 ; p=0.002; OR =0.4; 95% CI :0.19-0.84, respectively) . (Table 2). In turn, the carriage of an unfavorable allele Thrgene FABP 2increased the risk of developingType 2 diabetes in patients with CHF2.3 times (29.8% vs. 15.4%; χ^2 =7.8; p=0.001; OR =2.3; 95% CI : 1.29-4.24).

Table 2.
The frequency of distribution of alleles and genotypes of the Ala 54 Thr polymorphism of the FABP 2 gene rs799883in the group of patientsType 2 diabetes with CHF and control .

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	p	OR	95%CI
	SD+CHF		Control group					
	n	%	n	%				
Ala	59	70.2	171	84.6	7.8	0.001	0.4	0.24 - 0.78
Thr	25	29.8	31	15.4	7.8	0.001	2.3	1.29 - 4.24
Ala / Ala	22	52.4	74	73.3	5.9	0.02	0.4	0.19 - 0.84
Ala / Thr	fiftee n	35.7	23	22.8	2.5	0.11	1.9	0.86 - 4.10
Thr / Thr	5	11.9	four	3.9	3.2	0.08	3.3	0.89 -12.09

Statistical data have shown that when an unfavorable Ala / Thr genotype is detected of the FABP 2 gene , there was a tendency to increase the risk of developing type 2 diabetes in patients with CHF by 1.9 times (35.2 % vs. (Table 2). In turn, the carriage of the mutant Thr/ Thr genotypeincreased the risk of developingType 2 diabetes in patients with CHF by 3.3 times (11.9% versus 3.9%; $\chi 2^{=}$ 3.2; p=0.008; OR =3.3; 95% CI : 0.89-12.09, respectively) .

When analyzing the polymorphism of alleles and genotypes of Ala 54 Thr of the FABP 2 rs1799883 gene in the group of type 2 DM without CHF and control , the presence of a favorable allele Ala had a protective effect, and upon detection of a mutant allele Thrthe risk of developing type 2 diabetes increased by 1.9 times compared to control. Analysis of frequency distribution of unfavorable genotypes Ala / Thr and Thr / Thr showed a tendency to increase the risk of type 2 diabetes by 1.8 and 2.3 times, respectively. (Table 3).

Conclusions

1) In the presence of a wild allele Alars1799883 of the FABP 2 gene showed a protective effect on the development of both type 2 DM and CHF.

2) Carrying an unfavorable allele Thrin respondents with DM2 as a high risk factor for the development of pathologies in the main group.

3) RiskformationSDType 2 and CHFin 17timesaboveatcarriers of an unfavorable genotype of the genotypeAla / Thrgene FABP2 rs 1799883

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