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Original article

A54T polymorphism in fatty acid binding protein 2 gene is associated in Type 2 Diabetes Mellitus in adult subjects

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a chronic, non-communicable and complex, metabolic disease caused by resistance to insulin. The role of *FABP2* in T2DM has been confirmed via genomic studies. Genetic studies related to Ala54Thr (A54T) polymorphism in *FABP2* in the Pakistani population are lacking. The objective of the present study was to analyze the prevalence of A54T polymorphism among those diagnosed with T2DM in the Pakistani population. Clinical and genotype data were statistically analyzed. Baseline and demographic characteristics of T2DM cases and controls were evaluated. Genotype analysis indicated a significant association between T2DM cases and the Thr genotype, Thr allele, and genetic models ($p < 0.05$), compared with controls. T2DM was significantly associated with Ala54Thr polymorphism in *FABP2* in the Pakistani population. The T2DM risk in the studied population was assessed via genotype analysis and diagnostic criteria. T2DM was significantly associated with Ala54Thr polymorphism in FABP2 in the Pakistani population.

1. Introduction

Diabetes mellitus comprises a group of metabolic disorders which is defined by abnormal glucose levels related to insulin action, insulin secretion, or a combination thereof (Tang et al., 2019). Diabetes is associated with an increased risk for cardiovascular disease as well as for the resulting morbidity and mortality. The global prevalence of diabetes has been progressively increasing for the last 2–3 decades (Allen and Vessey, 2004). Presently, diabetes is the fastest growing, debilitating disease worldwide. According to WHO estimates, globally, 422 million adults have either type 1 diabetes or Type 2 Diabetes Mellitus (T2DM) (Caroline, 2003). T2DM is defined as a group of multiple metabolic disorders with numerous etiologies characterized by insulin resistance at the onset (Tang et al., 2019; Mohsin et al., 2007). T2DM is documented as a metabolic, non-communicable disease associated with the endocrine system (Zhang et al., 2019). Presently, lifestyle modification via physical exercise, dietary changes and limited pharmaceutical intervention is recommended for management of T2DM (Kerrison et al., 2017; Ribeiroet al., 2019). T2DM has also been described as a public health issue caused by inadequate insulin secretion (Karimian et al., 2019). A well-documented risk factor associated with T2DM is obesity, a very common global issue afflicting approximately 312 million people worldwide (Bego et al., 2019). T2DM is also characterized by a high level of interaction with environmental and genetic factors (Zhou et al., 2019). Pakistan, which is a South Asian country with a population of 207.7 million, covers an extended area of 0.8 million km^2 (Aamir et al., 2019). A majority of the Pakistani population is rural. However, in urban areas, exposure to pollution may lead to diabetes and metabolic disorders (Meo et al., 2016). According to the International Diabetes Federation (IDF), global prevalence of T2DM is expected to rise to 642 million cases by 2040. Additionally, by the end of 2024, the prevalence of diabetes in Pakistan is expected to reach 11.5 million cases. Globally, approximately 200 million diabetic subjects go undiagnosed, raising the possibility of future

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complications such as diabetic neuropathy, nephropathy, retinopathy, and stroke (Mohammad and Nanji, 2018).

The human data base, which is based on global and national human genome studies, has precisely documented the prevalence of single nucleotide polymorphisms (SNPs) associated with specific diseases. Genetic linkage analysis, case-control and associated studies have proved that SNPs are stably inherited through generations. Genetic polymorphism has become a useful tool for investigating human diseases via genetic research in a variety of fields, such as population, agriculture and human, molecular, and forensic genetics (Reis et al., 2016). Genetic studies have been conducted to evaluate the association between SNPs and the risk for developing T2DM and other diabetic diseases. Specific SNPs are used to study precise combinations of 90% of the coding/non-coding sections of genes as also to elucidate the pathophysiology of human diseases regulated by human DNA via proteins (Khan et al., 2019). Genome-wide association studies (GWAS) have documented multiple genes and SNPs associated with T2DM in the human population. Xue et al. (2018) conducted meta-analyses and GWAS studies in a population of 16 million and confirmed 139 variants of European ancestry. Intestinal *FABP2* is one of the genetic markers associated with the T2DM disease pathway (Alharbi et al., 2014). Apart from GWAS, meta-analysis studies have positively confirmed Alanine-54-Threonine (Ala54Thr) polymorphism in *FABP2*. Amino acid substitution has an effect on lipid metabolism and plays an important role in fatty acid (hydrophobic) transport from the cell membrane to the endoplasmic reticulum (Khattab et al., 2017). Only a limited number of case-control studies on genetic polymorphism have been reported in the Pakistani population. Ala54Thr polymorphism in *FABP2* has not been studied in any of the human diseases in Pakistan. Therefore, the current study investigated the genetic basis of Ala54Thr in *FABP2* in individuals diagnosed with T2DM in the Pakistani population.

2. Methods

2.1. Inclusion of T2DM and non-T2DM subjects

A sample of 1100 subjects was recruited from Allied hospitals in Faisalabad, Pakistan, for this study, which was designed as a case-control study, wherein the number of T2DM cases (n = 550) was equal to that of the controls (n = 550). Inclusion and exclusion criteria were determined according to those described in a previously published article (Khan et al., 2014). All 1100 subjects signed consent forms and provided detailed information requested in a questionnaire. Anthropometric, biochemical, clinical, and demographic details of all participants were recorded. Ethical approval was obtained from the hospital (AH 014/2017).

2.2. Questionnaire details

Participants were requested to provide additional information regarding their age, diagnosis, linked diseases, specific surgeries, occupation, and lifestyle details such as smoking, diet, sleep, and physical activity. Anthropometric details, such as the body mass index (BMI) were recorded. Information regarding education, socioeconomic status, and occupation were also collected. Family histories were documented.

2.3. DNA analysis

Genomic DNA was isolated from all 1100 subjects and quantification was carried out using a NanoDrop spectrophotometer (Hitachi). Using probes for rs1799883 polymorphism, qPCR was performed for T2DM cases as well as for controls according to method described in a previously published article (Alharbi et al., 2014).

2.4. Statistical analysis

SPSS software (Version 19.0, USA) was utilized for statistical analysis. For continuous variables t-tests were used to evaluate differences between T2DM cases and controls. Clinical characteristics were expressed as mean ± standard deviation. Deviation from the Hardy Weinberg equilibrium (HWE) was used to differentiate between genotypes. Allele and genotype frequencies were calculated. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Patient clinical details

Baseline details of T2DM cases and control subjects are shown (Table 1). The mean age of T2DM cases was 59.88 ± 13.34, while that in the control subjects was 58.67 ± 11.87. Gender distribution of both T2DM cases and controls (62.6% males and 37.7% females) was equal. In the T2DM cases, those with school education approximated 73.8%, whereas in the controls, those with school education represented 58.6% and those with college education represented 40.5%. The prevalence of smoking and consanguinity was higher in the controls compared with T2DM cases ($p > 0.05$). Obesity, waist size, and a family history of T2DM was found to be higher in T2DM cases when compared with those of the control subjects ($p < 0.05$).

3.2. Demographic details

All participants were non-vegetarian ($p = 0.99$). High fat milk was regularly used by 84.4% of T2DM cases and 70.4% of controls. Approximately 20% of T2DM subjects exercised regularly, whereas 24.4% of the control subjects exercised regularly. More T2DM patients had been diagnosed with heart disease, hypertension and liver disease than the controls ($p < 0.0001$). Paralysis and kidney diseases could be analyzed only in T2DM cases but not in control subjects. A significantly higher prevalence of depression and eye-sight issues was found in T2DM cases ($p < 0.05$). Demographic details are shown (Table 2).

Table 1
Baseline details of study subjects.

Baseline	Cases (n = 550)	Controls (n = 550)	P Value
Age	59.88 ± 13.34	58.67 ± 11.87	0.006
Gender (Male:Female)	343 (62.3%): 207 (37.7%)	343 (62.3%): 207 (37.7%)	0.99
Economic Status (Lower Class)	115 (20.9%)	121 (22%)	0.22
T2DM	550	0	N/A
Mariel Status (Married: Unmarried)	538 (97.8%)	550 (100%)	0.60
Education: None	31 (5.6%)	05 (0.9%)	>0.05
School	406 (73.8%)	322 (58.6%)	>0.05
College/University	113 (20.6%)	223 (40.5%)	>0.05
Consanguinity	149 (27.1%)	168 (30.5%)	>0.05
Smoking	150 (27.3%)	223 (40.6%)	>0.05
Obesity	439 (79.8%)	385 (70%)	<0.05
Waist (30–45 cm)	493 (89.6%)	457 (83.1%)	>0.05
Family History of T2DM	414 (75.3%)	348 (63.3%)	<0.001

t-tests.

Table 2
Demographic characteristics of T2DM study subjects.

Variables	Cases (n = 550)	Controls (n = 550)	P Value
Non-vegetarian	550 (100%)	550 (100%)	0.99
High Fat Milk	464 (84.4%)	387 (70.4%)	<0.05
Regular Exercise	112 (20.4%)	134 (24.4%)	>0.05
Heart Disease	110 (20%)	18 (3.3%)	<0.0001
Hypertension	98 (17.8%)	16 (2.9%)	<0.0001
Liver Disease	58 (10.5%)	4 (0.7%)	<0.0001
Kidney Disease	8 (1.4%)	0 (0%)	N/A
Paralysis	13 (2.4%)	0 (0%)	N/A
Depression	283 (51.5%)	11 (2%)	<0.0001
Eye Sight	312 (56.7%)	234 (42.5%)	<0.002

t-tests.

3.3. Genotype details

HWE did not indicate genotypic deviation between participants. Significant Ala54Thr genotype and allele frequencies in T2DM cases and the controls are shown (Table 3). As shown by the mode of inheritance, mutant allele (p = 0.0001), variant (p = 0.0003), dominant (p = 0.003) and recessive (p = 0.0001) genotypes were shown to be associated with T2DM cases in comparison to control subjects.

4. Discussion

The current study screened T2DM patients exhibiting A54T polymorphism in *FABP2* in the Pakistani population. At present, studies documenting A54T polymorphism in T2DM patients in the Pakistani population are lacking. To our knowledge, the current study is the first to demonstrate significant association between A54T polymorphism and T2DM cases when compared with controls. Our results indicate that, within the Pakistani population, A54T polymorphism in *FABP2* is genetically associated with variant genotypes (p = 0.0003) and mutant alleles (p = 0.0001) as well as with dominant (p = 0.003) and recessive models (p = 0.0001).

Adipose tissue is loosely connected to adipocyte cells in the skin. Hormone sensitive lipase, which is located on the cell-membrane, is an intercellular lipase capable of hydrolyzing lipids, such as triglycerides. The association between various fatty acids and the risk of inconsistent T2DM is well documented (Lankinen et al., 2015). FABP2, a 15 kDa protein, is secreted via epithelial-cells and binds fatty acids (Goncalves et al., 2015). It is located in the 4q28-31 region of the chromosome and has 4 exons and 3 introns. The rs1799883 polymorphism, considered as a missense mutation present in exon-2, results from adenine-guanine substitution. *FABP2* consists of 3382 nucleotides (Exon-700; Intron-2650), and encodes a small-bowel fatty acid which is a member of a protein family that regulates lipid transport and metabolism (Abbas et al., 2017; Han and So, 2019).

Younis et al. (2018) studied 1940 Pakistani subjects diagnosed with diabetic foot ulceration and concluded that peripheral neuropathy was the common causative factor for the development of foot ulcers. This indicates that, in the Pakistani population, any form of diabetes may lead to further complications. Sikhayeva et al. (2017) studied 28 different SNPs associated with T2DM in the Kazakh population and confirmed that *FABP2* was genetically associated with numerous SNPs. Our study also substantiates a study by Shabana et al., which found a significant association between Ala54Thr polymorphism and obesity in the Pakistani population (p = 0.002); (Shabana, 2015). Ala54Thr polymorphism studies have been conducted in relation to many human diseases including T2DM, obesity, metabolic syndrome, hypertension, and stroke (Song et al., 2014; Alharbi et al., 2014). However, only a limited number of meta-analyses have been performed to evaluate the association between T2DM and other diseases and other diseases in the global population (Qiu et al., 2014).

Furthermore, 73.8% of T2DM patients had a high school degree (Fall, 2001). The socioeconomic status of diabetes patients had a highly significant effect on disease affliction (P < 0.05). Prevalence of T2DM within populations appears to vary with socioeconomic status (Vijayakumar et al., 2009). Our study also indicated that the prevalence of diabetes increased rapidly among urban and rural areas (Sowers et al., 2001). The lifestyle of an individual may exert an effect on the incidence of diabetes. As 72% of T2DM patients reported as nonsmokers, it was concluded that smoking was not a risk factor for T2DM. A sedentary lifestyle lacking physical activity may lead to obesity which is a possible risk factor for diabetes. Overweight/obesity, family history, hypertension, and age at onset have been declared as possible risk factors for the increased prevalence of T2DM (Koopman et al., 2005). A previous study concluded that diabetes was a function of a positive family history of diabetes, obesity, and hypertension (Vijayakumar et al., 2009). Diabetes is also associated with a positive family history, which, in turn, may be affected by both maternal and paternal pedigrees (Estacio et al., 2000).

The major limitation of this research was its lack of cross-sectionality, as it only measured the A54T variant

5. Conclusion

It has been concluded, the current study found a significant association between Ala54Thr polymorphism in *FABP2* and T2DM in the Pakistani population. Interestingly, a similar variant was also found to be associated with obesity in the Pakistani population. This study recommends that genetic studies be implemented to investigate Ala54Thr polymorphism in other metabolic diseases in the Pakistani population to rule out diseases associated with *FABP2* genetic polymorphism. However, in order to validate results, further studies should be conducted utilizing large sample sizes.

Table 3
Distribution of Ala54Thr genotype and allele frequencies in T2DM cases.

Genetic Mode of Inheritances	T2DM Cases (n = 550)	Controls (n = 550)	OR (95% CI)	P Value
Alanine	259 (47.1%)	308 (56%)	Reference	–
Alanine54Threonine	185 (33.6%)	182 (33.1%)	1.21 (0.92–1.57)	0.15
Threonine	106 (19.3%)	60 (10.9%)	2.10 (1.47–3.01)	0.0003
Wild allele	703 (0.64)	798 (0.73)	Reference	–
Mutant allele	397 (0.36)	302 (0.27)	1.49 (1.24–1.78)	0.0001
Dominant Model	291 (52.9%)	259 (44%)	1.43 (1.12–1.81)	0.003
Co-dominant Model	365 (66.4%)	368 (66.9%)	1.02 (0.79–1.31)	0.84
Recessive Model	444 (80.7%)	490 (89.1%)	1.95 (1.38–2.74)	0.0001

Allele and genotype frequencies.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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