

Association of Polymorphism in Fatty Acid Desaturase Gene with the Risk of Type 2 Diabetes in Iranian Population

Abstract

Background: The type 2 diabetes is one of the most common autoimmune diseases. Due to a key role in the metabolism of unsaturated fatty acids such as arachidonic acid, one of the most important precursors of immunity mediators, fatty acid desaturase (FADS) genes could have an important impact in the development of type 2 diabetes. **Materials and Methods:** This study aimed to determine the relationship between polymorphisms rs174537 in FADS1 gene and rs174575 in FADS2 gene with type 2 diabetes in Iranian population. After extracting genomic DNA, the locations of mutations and allele types were identified with high-resolution melting (HRM)-polymerase chain reaction method. Then, association between these mutations with metabolic syndrome, dyslipidemia, and type 2 diabetes was investigated using χ^2 correlation coefficients for variables and logistic regression. **Results:** The results showed that among 50 diabetic participants, 68% of patients have the mutant allele for rs174537 in FADS1 gene. This rate is 26% for rs174575 in FADS2 gene. Based on the results, it seems that participants having rs174537 mutant allele are more prone to become diabetic but it has a beneficial effect on total and low-density lipoprotein cholesterol and participants having rs174575 mutant are less prone to become diabetic, and also, it leads to higher triglycerides and body mass index (obesity). **Conclusions:** Detecting FADS1 and FADS2, gene polymorphisms using HRM can be an anticipating tool for making decision on initiating lifestyle modifications to prevent type 2 diabetes.

Keywords: Fatty acid desaturase gene, polymorphism, type 2 diabetic

Introduction

The type 2 diabetes is one of the most common autoimmune diseases. The World Health Organization reported that currently 422 million people are affected by this disease worldwide, making it the first leading cause of death in the world. The development of type 2 diabetes through changes in the lifestyle has increased in the last century.^[1,2] Its prevalence in different generations and different ethnic groups represents environmental, economic, and cultural factors as well as previously approved genetic factors, which play an important role in development of the diseases.^[3,4]

Some factors of fatty acid components in the blood can be a predictor of metabolic syndrome such as linoleic acid (LA), saturated fatty acid (SFA), and polyunsaturated fatty acids (PUFAs).^[5] Many studies have shown that high amounts of W-3 PUFA in the food regimen and also high amounts of phospholipid in cell

membrane, or blood is associated with less risk for type 2 diabetes.^[6-10] SFAs in the human body transformed to unsaturated fatty acids, but due to the lack of $\Delta 12$ desaturase and $\Delta 15$ desaturase enzyme in the biosynthesis of PUFAs, the human body is unable to make fatty acids such as LA and α -LA, and therefore, they counted as essential fatty acids.^[4,11,12]

Fatty acid desaturase 1 (FADS1) and FADS2 gene allele's diversity and the fatty acid composition of diet affect the lipid profile of the body.^[13] Li *et al.*, with high-resolution melting (HRM) analysis techniques, indicated that rs174537 and rs174460 polymorphism in FADS genes can affect the plasma fatty acid concentration and desaturase enzyme activity.^[14] The amount of total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), and triglycerides in childhood influenced by FADS1 and FADS2 genes, resulting in more susceptibility to certain metabolic diseases in adults.^[15]

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The effect of polymorphisms in the FADS gene on the amount of long-chain PUFA (LC-PUFA) in the blood makes it an important factor in the brain development in children and susceptibility to metabolic and neurological diseases. LC-PUFA has a role in the synthesis of eicosanoids and therefore body immunity processes;^[16] it is associated to children's visual, cognitive, and motor functions,^[17,18] psychological disorders and mental health,^[19-21] metabolic syndrome,^[22-24] cardiovascular disease mortality,^[25,26] inflammatory and immunological responses,^[27] and other diseases such as allergies,^[28-30] resulting in its importance on human health.^[31]

Recently, the role of acute inflammatory responses in developing type 2 diabetes is considered. Arachidonic acid and its metabolites are the main molecules that control the immunity mechanisms. LA and α -LA are converted to arachidonic acid by $\Delta 5$ desaturase and $\Delta 6$ desaturase enzymes, which are coded by the FADS1 and FADS2 genes.^[32] According to recent findings, the ability of these enzymes in producing immunity modulating molecules, such as prostaglandin, thromboxane, leukotriene, and lipoxin, in addition to its capability in adjusting receptors involved in immunity processes, describes its function in inflammations, the main causes of type 2 diabetes. These conversions of fatty acids to arachidonic acid show a large variation in relation to individual genetic makeup.^[4,33-37] It has been shown that the activity of delta-5 desaturase inversely and the delta-6 desaturase directly associated to the risk of diabetes.^[38]

The effects of D6D ($\Delta 6$ desaturase) and D5D on glucose metabolism and insulin resistance are changed along with changing in FADS1 and FADS2 gene alleles.^[7,39] The fatty acid components of lipid profile in insulin-resistant participants showed the increased activity in stearoyl-CoA desaturase and D5D and reduced activity in D6D.^[24,40] Recently, association between Single-nucleotide polymorphisms (SNPs) near or within several genes, such as FADS1, and fasting glucose has been shown.^[41,42] Furthermore, two studies have shown that FADS1 gene strongly associated with fasting glucose, fasting insulin, homeostatic model assessment-insulin resistance, and type 2 diabetes in Caucasian populations.^[43,44]

Previous researches revealed the genetic variation in the FADS1 and FADS2 genes and finally the different prevalence of metabolic diseases in different ethnic groups.^[3,4] It has been shown that the changes in desaturase enzymes and fatty acid components of lipid profile are occurred earlier than any metabolic syndrome;^[5] therefore, it provides a good opportunity to prevent metabolic syndrome.

In this study, the prevalence and the relationship between polymorphisms with type 2 diabetes in Iranian population were determined using rs174537 in FADS1 gene and rs174575 in FADS2 gene. Analyzing these changes and

genetic diversity helps us to recognize the risk of diseases and the population at risk in Iranian people and hope to find a better way for reducing burden of disease, maybe by changing lifestyle.

Materials and Methods

This study is a case-control study. The participants obtained from cardiovascular research center, Isfahan, Iran. Written informed consent were obtained from participants, and ethics committees and other relevant national regulatory organizations approved the study. Fifty diabetics and 50 nondiabetic persons were selected as case and control, respectively. As demographic factors, gender, age, weight, height, and abdominal circumference were measured, and body mass index (BMI) and abdominal obesity were calculated. Furthermore, blood samples were taken, and total, LDL, and HDL cholesterol, triglycerides, and serum aminotransferases (aspartate transaminase and alanine transaminase) were measured in blood samples. Systolic and diastolic blood pressures were measured using aneroid sphygmomanometer. After blood collection and separation of leukocytes from other blood components, genomic DNA of the cells was extracted, using Bio Genet DNA extraction kit, made in Korea (GENET BIO, Korea). The used method is the same as described in the kit instructions. Then, FADS1 and FADS2 gene promoters containing rs174537 and rs174575 single-nucleotide polymorphism were amplified using polymerase chain reaction (PCR) method. The primers used for amplification were designed by primer design software, Beacon Designer 7.5 (PREMIER Biosoft International) [Table 1]. Next, real-time PCR-HRM, applied to investigate the certain polymorphisms in FADS genes (Rotor-Gene 6000 HRM, QIAGEN, Co). HRM is a powerful and cost-beneficial method that can identify mutations using DNA strands melting curve, utilizing us to identify mutations associated with many chronic diseases, especially N2DM, a one with a massive burden.

Sequencing was used for identifying unknown mutations in suspected samples that may have unfamiliar patterns. This method is the gold standard to identify suspected unknown mutations. All the procedures were repeated triplicate to minimize the errors. Data were analyzed using descriptive statistics; statistical techniques include fold equation tests and χ^2 correlation coefficients for variables and logistic regression using SPSS statistical package (SPSS, Chicago, IL; Version 18.0) for windows.

Results

From 50 participants with diabetes type 2 and 50 healthy controls, DNA samples were analyzed for FADS1 rs174537 and FADS2 rs174575 polymorphisms. They were 27 males, 23 females in case group, 21 males, and 29 females in healthy control group. There is not significant difference regarding gender and age between case and control groups. The mean age of case and control group was about

Table 1: Sequences of primers used in this study

Gene	Sequence	
	Sense	Antisense
FADS1	F: 5' AGGGGAGAGAGGTGGAGTAGA 3'	R: 5' TGGCTGTGCGTCTGTGATG 3'
FADS2	F: 5' GCAAACTCCTGGCTCCC 3'	R: 5' GCAAATAGACTCATCTCCACTCCTG 3'

FADS: Fatty acid desaturase

15 years. The mean height and weight are approximately equal between two groups, resulting in slightly equal BMI. According to the definition of abdominal obesity, with equal wrist circumference, there are no differences in abdominal obesity between two groups [Table 2].

As shown in Table 3, in FADS1 rs174537, the allele frequencies of T and G in the study population were 137 (68.5%) and 63 (31.5%), respectively. The mutant allele was significantly more frequent in the diabetic participants in comparison to healthy controls (39% vs. 24%, $P = 0.022$) [Table 3]. The frequencies of wild-type, mutant homozygote and heterozygote genotypes were 45 (45%), 8 (8%), and 47 (47%), respectively. The genotypes with mutant allele were significantly more frequent among diabetic cases than control participants (34% vs. 21%, $P = 0.009$) [Table 3].

In FADS2 rs174575, the allele frequencies of G and C in the study population were 168 (84%) and 32 (16%), respectively. The mutant allele was inversely more frequent in healthy controls in comparison to the diabetic participants, but the difference was not significant (18% vs. 14%, $P = 0.443$) [Table 3]. The frequencies of wild-type, mutant homozygote and heterozygote genotypes were 69 (69%), 1 (1%), and 30 (30%), respectively. The genotypes with mutant allele were more frequent among control participants than diabetic cases (36% vs. 26%, $P = 0.284$) [Table 3].

There is an inverse correlation (correlation coefficient = -0.219 , $P = 0.028$) between two mutations, meaning that it is likely to have wild-type alleles for rs174537 and mutant allele for rs174575, both protective genotypes. There are 19 participants meeting this condition which 7 (37%) of them are diabetic and 12 (63%) of them are nondiabetic.

In addition, there is extremely weak correlation between age and Rs174537 mutation (correlation coefficient = 0.024) and also, between age and Rs174575 mutation (correlation coefficient = 0.076). Correlations between gender and Rs174537 mutation (correlation coefficient = 0.012) and Rs174575 mutation (correlation coefficient = -0.032) are not significant. Thus, mutations are well distributed between ages and genders.

In the evaluation of FADS1 polymorphism, in comparison between participants having wild-type alleles and participants having mutant alleles, total cholesterol and LDL cholesterol were significantly higher in participants with

Table 2: Baseline characteristics

Demographic factor	Case	Control
Gender (%)		
Male	27 (27)	21 (21)
Female	23 (23)	29 (29)
Age	14.84±2.376415	14.8±2.579353
Weight	50.74±18.033767	56.82±21.881583
Height	155.102041±12.834272	155.96±21.357941
Wrist circumference	71.775510±15.711282	71.22±11.016296
BMI ¹	20.891630±5.956494	21.721395±5.150052

Difference between two groups in sex, age, weight, height, wrist circumference, and BMI is not significant. ¹BMI: Body mass index

wild-type alleles. However, triglycerides and HDL along with liver biomarkers did not show a significant difference. Abdominal obesity and BMI are not significantly different between two groups.

In the evaluation of FADS2 polymorphism, only triglycerides levels are significantly higher in participants with mutant allele. Considering blood pressures higher than 135/85 as hypertension, there is no significant difference between participants having Rs174537 mutation with wild-type alleles or between participants having Rs174575 mutation with wild-type alleles [Table 4].

By defining dyslipidemia and metabolic syndrome, there are 3 persons with metabolic syndrome in participants with wild-type alleles and 10 persons in participants with mutant alleles. There are 26 persons with dyslipidemia in participants with wild-type alleles and 32 persons in participants with mutant alleles. However, there are no significant differences between two groups regarding these criteria. Classifying blood pressures to normal, prehypertension, and hypertension stage 1 and stage 2 was not resulted in significant differences between two groups [Table 5].

Discussion

Rs174537 polymorphism in FADS1 gene and Rs174575 polymorphism in FADS2 gene are well distributed in both genders and different ages. In this study, there is not any evidence supporting that it occurs more frequent in older ages. According to recent studies, these polymorphisms are affected by race and ethnicity. In the current research, we conducted analysis on Iranian population and the results are consistent with global results.

Table 3: Allele and genotype distribution of Rs174537 in fatty acid desaturase 1 and Rs174575 in fatty acid desaturase 2 genes

Genes and Alleles	Case (%)	Control (%)	P	OR (95% CI)
Rs174537 in FADS 1 gene				
Alleles				
T	61 (61)	76 (76)	0.022	0.150 (0.022-0.278)
G	39 (39)	24 (24)		
Genotypes				
Homozygote (TT)	16 (32)	29 (58)	0.017	0.300 (0.056-0.544)
Heterozygote (TG)	29 (58)	18 (36)		
Homozygote (GG)	5 (10)	3 (6)		
Genotypes				
Wild type (TT)	16 (32)	29 (58)	0.009	0.260 (0.067-0.453)
With mutant allele (TG and GG)	34 (68)	21 (42)		
Rs174575 in FADS2 gene				
Alleles				
G	86 (86)	82 (82)	0.443	-0.150 (-0.022-0.278)
C	14 (14)	18 (18)		
Genotypes				
Homozygote (GG)	37 (74)	32 (62)	0.417	-0.080 (-0.275-0.115)
Heterozygote (GC)	12 (24)	18 (36)		
Homozygote (CC)	1 (2)	0		
Genotypes				
Wild type (GG)	37 (74)	32 (62)	0.284	-0.100 (-0.284-0.084)
With mutant allele (GC and CC)	13 (26)	18 (36)		

OR: Odds ratio, CI: Confidence interval, FADS: Fatty acid desaturase

Rs174537 polymorphism in FADS1 gene has significant association with diabetes type 2, and Rs174575 polymorphism in FADS2 gene is inversely but not significantly associated with diabetes type 2. These results are similar to global results.^[38] The effect of Rs174537 on occurrence of diabetes type 2 is accompanied with many other factors, so patients having Rs174537 mutant allele have only 26% higher chance for getting diabetes type 2. Studies with broad range of participants are necessary to estimate its effectiveness more accurately.

Patients with Rs174537 mutant allele have higher total cholesterol and LDL levels. Its effect can be attributed to desaturase activity of FADS genes. It is consistent

with previous studies.^[13] The effects of FADS gene polymorphism on fatty acid concentration and plasma cholesterol level were identified earlier.^[14,45] Different lipid profiles of affected persons can be the predictor of tendency to be dyslipidemic. However, in case of comparing persons with mutant allele with persons having wild type, the difference is not significant. It is suggested that FADS polymorphisms along with other factors can be a contributing factor for lipid profile dysfunction.

In the recent paper,^[46] it is suggested that it is possible to predict metabolic syndrome from liver enzymes. So as a new research object, effect of FADS genes on serum aminotransferase was assessed that it was not significant. The changes the mutations made do not involve liver function. However, wider researches are needed to evaluate this effect.

Developing diabetes type 2 from FADS gene effect can be described in two ways: one is higher incidence of many metabolic disorders such as insulin resistance^[7,15,39,46] and the second is gene effect on inflammatory molecules such as arachidonic acid.^[4,32] In this study, we assessed the incidence of metabolic syndrome components in mutant participants in comparison to wild-type participants. Metabolic components are affected somehow inversely in two polymorphisms, from which blood pressure is measured higher in Rs174537 wild-type participants (it is *vice versa* in Rs174575, with lower blood pressure in wild-type participants). HDL cholesterol is higher in mutant alleles in Rs174537, but it is higher in wild-type participants in Rs174575. In addition, triglycerides are in the same condition, higher in wilds in Rs174537 and lower in wilds in Rs174575. Abdominal obesity is affected in the same way, where in both polymorphisms wild types have higher amounts. Difference in blood pressure, waist circumference, triglycerides, and HDL cholesterol was not statistically significant. The only component that is really changed is fasting blood sugar. However, it must be noted that all of metabolic syndrome components were higher in patients with mutation in Rs174575 polymorphism except abdominal obesity, but the results for Rs174575 are *vice versa*. The result (regarding metabolic syndrome definition criteria) is that association of metabolic syndrome with having Rs174537 mutation is somehow meaningful ($P = 0.09$) with a narrow distance to be significant, but amazingly, Rs174575 is quite far from being statistically significant. It is consistent with effect of two mutations in developing type 2 diabetes mellitus (T2DM).

Changes in lipid profile can occur earlier to metabolic syndrome and therefore T2DM, so alterations made to lipid profile as a consequence of FADS mutations can be predictor for developing metabolic syndrome later in the life. Changes which, to a high level, can be controlled with good lifestyle interventions and therefore reduce the burden

Table 4: Comparison of blood pressure, total, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, body mass index, and abdominal obesity between wild types and participants with mutant allele

Rs174537 in FADS 1 gene	Wild type (TT)	With mutant allele (TG and GG)	P	Mean difference (95% CI)
Hypertension				
Systolic pressure (mmHg)	116±10	114±15	0.349	2.444 (-2.713-7.602)
Diastolic pressure	74±10	73±11	0.403	1.816 (-2.475-6.107)
Total cholesterol	169±35	154±34	0.041	14.331 (0.566-28.097)
LDL cholesterol	98±20	89±21	0.032	9.012 (0.811-17.213)
HDL cholesterol	39±11	41±13	0.379	-2.168 (-7.038-2.703)
Tg	110±65	104±43	0.567	6.226 (-15.261-27.713)
SGOT (AST)	26±20	24±8	0.557	1.693 (-4.008-7.939)
SGPT (ALT)	20±11	21±11	0.846	-0.420 (-4.689-3.848)
BMI	20.64±5.13	21.84±5.86	0.286	-1.196 (-3.41-1.017)
WHO criteria				
Underweight	9	9	0.469	
Normal weight	24	24		
Overweight	4	7		
Obese	7	15		
CDC criteria				
Underweight	10	11	0.483	
Normal weight	24	24		
Overweight	6	14		
Obese	4	6		
Rs174537 in FADS 1 gene	Wild type (TT) (%)	With mutant allele (TG and GG) (%)	Pearson χ^2	OR (95% CI)
Abdominal obesity*				
Normal	34 (34)	40 (40)	0.748	1.159 (0.47-2.858)
Abdominal obesity	11 (11)	15 (15)		
Rs174575 in FADS2 gene	Wild type (GG)	With mutant allele (GC and CC)	P	Mean difference (95% CI)
Hypertension				
Systolic pressure (mmHg)	114±14	116±11	0.461	-2.071 (-7.628-3.486)
Diastolic pressure	73±12	75±6	0.272	-2.562 (-7.166-2.041)
Total cholesterol	158±34	168±36	0.182	-10.148 (-25.136-4.841)
LDL cholesterol	92±21	95±21	0.400	9.012 (0.811-17.213)
HDL cholesterol	41±12	40±13	0.692	-2.168 (-7.038-2.703)
Tg	99±40	125±74	0.027	6.226 (-15.261-27.713)
SGOT (AST)	21±16	24±9	0.454	
SGPT (ALT)	20±11	20±11	0.953	
BMI	21.54±5.22	20.76±6.26	0.520	-1.196 (-3.41-1.017)
WHO criteria				
Underweight	7	11	0.010	
Normal weight	39	9		
Overweight	7	4		
Obese	16	6		
CDC criteria				
Underweight	9	12	0.024	
Normal weight	38	10		
Overweight	15	5		
Obese	7	3		
Rs174575 in FADS2 gene	Wild type (GG) (%)	With mutant allele (GC and CC) (%)	Pearson χ^2	OR (95% CI)
Abdominal obesity*				
Normal	50 (50)	24 (24)	0.273	0.768 (0.284-2.074)
Abdominal obesity	19 (19)	7 (7)		

*Abdominal obesity is defined according to NHS/NIH criteria (waist circumference of >35 In for women and >40 In for men).

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, Tg: Triglycerides, CI: Confidence interval, OR: Odds ratio, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, FADS: Fatty acid desaturase, WHO: World Health Organization, CDC: Centers for Disease Control and Prevention, BMI: Body mass index, NHS: National health Service, NIH: National Institutes of Health

Table 5: Comparison of metabolic syndrome, dyslipidemia, and blood pressure classes distribution in wild types and participants with mutant allele

Rs174537 in FADS 1 gene	Wild type (TT)	With mutant allele (TG and GG)	P	Mean difference (95% CI)
Blood pressure				
Normal blood pressure	42	49	0.368	-0.061 (-0.194-0.072)
Prehypertension	3	5		
Hypertension Stage 1	0	1		
Hypertension Stage 2	0	0		
Metabolic syndrome	3	10		
Nonmetabolic syndrome	42	45	0.09	0.115 (-0.018-0.249)
Dyslipidemia	26	32	0.968	0.004 (-0.195-0.203)
Nondyslipidemia	19	11		
Rs174575 in FADS2 gene	Wild type (GG)	With mutant allele (GC and CC)	P	Mean difference (95% CI)
Blood pressure				
Normal blood pressure	61	30	0.174	0.098 (-0.044-0.241)
Prehypertension	7	1		
Hypertension Stage 1	1	0		
Hypertension Stage 2	0	0		
Metabolic syndrome	9	4		
Nonmetabolic syndrome	60	17	0.985	-0.001 (-0.147-0.144)
Dyslipidemia	38	20	0.381	0.094 (-0.119-0.308)
Nondyslipidemia	31	11		

FADS: Fatty acid desaturase, CI: Confidence interval

of noncommunicable diseases, especially T2DM, one of the most commons.

Conclusions

Acting before onset is one of the key actions against diabetes. Therefore, detecting FADS1 and FADS2 gene polymorphisms using real-time PCR HRM can be valuable. It helps us to make decision earlier on initiating lifestyle modifications to prevent type 2 diabetes. Further evaluations needed to clarify the potential support it could make for this purpose.

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Conflicts of interest

There are no conflicts of interest.

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