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Association between the Rs7903146 and Rs12255372 Variants of the *TCF7L2* Gene and Metabolic Phenotypes in Pre-Diabetes (Pre-DM) Subjects

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Abstract

Aim: The term "prediabetes" (pre-DM) is used to define individuals with Impaired Fasting Glucose (IFG) and/or Intolerance Glucose Test (IGT). In this study, we analyzed the association between rs12255372 and rs7903146 variants of the *TCF7L2* gene and metabolic phenotypes in pre-DM subjects.

Methods: We included 247 unrelated subjects between 25 to 60 years old, 114 were apparently healthy subjects with glucose levels <100 mg/dl (5.5 mmol/l), and 133 subjects with IFG (fasting glucose >100 mg/dl to <125 mg/dl). Metabolic and anthropometric variables were measured, polymorphisms were genotyped by PCR. Homeostasis model assessment was used to estimate insulin resistance and β-cell function (HOMA-IR, HOMA β-cell function).

Results: The subjects with CT/TT rs7903146 genotypes showed a decrease in weight, BMI, triglycerides, and β-cell function. The pre-DM subjects with these genotypes showed weight and BMI significantly lower than CC genotype. The pre-diabetic subjects with GT and TT rs12255372 genotypes, showed insulin levels, HOMA-IR, and β-cell function significantly decreased (24%, 22%, 31% respectively). BMI (OR=1.26 95% 1.18-1.34, p<0.00001), the age (OR=1.05 95% 1.02-1.08, p=0.0008), and rs7903146 polymorphism (OR=3.11, 95% 1.58-6.1, p=0.0009) are associated with the development of pre-DM. An interaction of rs7903146 was observed when omitting to BMI (OR=1.83, 95% 1.05-3.19, p=0.03). The rs1225372 shows no association with the development of pre-DM

Conclusion: Weight and BMI were lower in pre-DM subjects with CT or TT rs7903146 genotypes. Insulin, HOMA-IR levels, and β-cell function were significantly decreased in pre-diabetic subjects with GT or TT rs12255372 genotypes. BMI, age, and rs7903146 are predictors for development of Pre-DM.

Keywords: Prediabetes; rs7903146; rs12255372; BMI; Metabolic phenotypes

Introduction

Hyperglycemia that does not reach the diagnostic criteria for Diabetes Mellitus (DM) is known as "prediabetes" (pre-DM), and is the term used to include individuals with Impaired Fasting Glucose (IFG) and/or Impaired Glucose Tolerance (IGT), and/or A1C 5.7-6.4% [1]. Prediabetes should not be viewed as a clinical entity but as an increased risk for diabetes and cardiovascular disease [1]. In addition to IFG and IGT, there are other risk factors as first-degree family history, abdominal obesity, dyslipidemia, ethnic group, among others [1,2]. Reports indicate that age-adjusted prevalence of IFG (49.5% and 50.5%), IGT (49.1% and 50.9%), and IFG+IGT (57.3% and 42.7%) are similar in Mexican men and women [3].

Since 2006, specific Single Nucleotide Polymorphisms (SNPs) within the *TCF7L2* gene are known to be associated with increased risk of Type 2 Diabetes (T2DM) [4]. There is evidence in many ethnic groups, that rs12255372 and rs7903146 in *TCF2L7* gene are more strongly associated with T2DM [5]. The analysis of these markers in a sample of controls and patients with T2DM from Mexico City indicates that the rs12255372T allele is associated with diabetes risk [6]. A more recent analysis has shown that eight SNPs and rs7903146 are associated with early-onset T2DM [7]. In Caucasian people, the rs7903146T allele risk was independently associated with increased fasting glucose [8,9]. For the *TCF7L2* and *WFS1* diabetes risk genes, which are associated with impaired incretin signaling, the level of glycemia determines SNP effects on insulin secretion, it indicates the importance of these SNPs during the progression of prediabetes stages toward clinically overt type 2 diabetes [10]. The *TCF7L2* variants rs7903146 and rs12255372 have an effect on the risk of T2DM, at least in part, by modifying the effect of incretins on insulin secretion [11,12]. Other Reports show that the rs7903146 variant increases the risk of IGT/T2DM in obese adolescents and middle-aged subjects by impairing β-cell function [13,14]. Both *TCF7L2* rs7903146 and rs12255372 variants increase the risk of diabetes among subjects with impaired glucose tolerance also acting on the β-cell function [15]. In individuals with IGT, the variant rs12255372 was significantly associated with decreased insulin secretion and with incident T2DM [16].

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In Mexico, the prevalence of T2DM varies from 8.9% to 25.3 (ENSANUT 2012), in low-income people and for prediabetes 18.9% (13.8-24.0) [17]. However, there are not enough data on factors associated with the development of prediabetes, neither of the metabolic characteristics associated with these polymorphisms. Therefore, the aim of this study was to analyze the association between rs12255372 and rs7903146 variants of the *TCF7L2* gene and metabolic phenotypes in pre-DM subjects.

Subjects

We studied a total of 247 unrelated subjects that were within 25 to 60 years old, in two groups, 114 apparently healthy with glucose levels <100 mg/dl (5.5 mmol/l), and 133 with pre-DM diagnosed according to ADA criteria (fasting glucose levels >100 mg/dl to <126 mg/dl in two subsequent days) [1]. None of the subjects had clinical evidence of heart, liver, renal or other endocrine disease. The subjects were recruited from the city of León in the central region of Mexico by means of home visits and public announcements. Informed consent was obtained from all individual participants included in the study. The study was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki in 1983 and in agreement with the Good Clinical Practice guidelines. The study was approved by the Institutional Ethics Committee of the University of Guanajuato.

Material and Methods

Anthropometric and metabolic measurements

All participants were interviewed to obtain clinical data and T2DM family history. Weight, height, waist and hip circumferences were obtained with indoor clothing and without shoes. BMI (weight (kg)/height (M^2)) and Waist/Hip Ratio (WHR) were calculated. Blood samples were drawn after 12 h fasting in order to measure serum glucose, and lipids profile using enzymatic methods with a chemistry analyzer (Auto KEM II, Kontrollab, Italy). Insulin serum concentrations were measured by radioimmunoassay with a commercial kit (MILLIPORE Research Charles, Missouri USA). Insulin Resistance (IR) and β-cell function were assessed with the Homeostatic Model Assessment (HOMA) [18].

Genotyping of rs7903146 and rs12255372 variants

Genomic DNA was obtained from peripheral blood leukocytes using standard methods and stored at -20ºC until batch genotyping. The rs7903146 polymorphism was genotyped using the PCR-RFLP method. The region was amplified with the following primers 5'-TTAGAGAGCTAAGCACTTTTTAGGTA-'3 (forward) and 5'-ACTAAGTTACTTGCCTTCCCTG-'3 (reverse), and for genotyping of rs12255372 polymorphism, we used the following primers 5'-CCCAGGAATATCCAGGCAAGGAT-'3 (forward) and 5'-CAAATGGAGGCTG- AATCTGGCA-'3 (reverse). The PCR reaction was carried out using 50 ng DNA, 2.0 mM $MgCl_2$, 0.5 mM dNTPs (Invitrogen), 10 µMol primers and 2 U Taq polymerase (Platinum Invitrogen) for both polymorphisms. The amplification program consisted in: one cycle of 94ºC for 3 min, 35 cycles of 94ºC for 30 sec, 60ºC for rs12255372 in a Thermal cycler Gene Amp PCR System 2700 (Applied Biosystems, Life Technologies Corporation, Singapore). The PCR products for the genotyping of rs7903146 were digested with RsaI restriction enzyme (New England Biolabs Ipswich, MA, USA) that generated two fragments 91 and 22 bp for C allele and one fragment 113 pb for T allele [6]. The Fok I restriction enzyme (New England Biolabs Ipswich, MA, USA) that was used to typing rs12255372 variants generated two fragments 94 and 24 pb for G allele and one fragment 118 pb for T allele [6]. We carried out genotype replications in 25% of the DNA samples obtaining a 99% rate of a coincidence for both SNPs.

Table 1: Metabolic characteristic of the two groups.

	Healthy subjects N=114	Pre-diabetes subjects N=133	t ó Z	p
Age (years)	38 ± 10	45 ± 11	-4.87	<0.0002
Gender M/F	40/74	26/107		
Family history of DM	40%	56%	3.84	0.05
Weight (Kg)	66.7 ± 16	80 ± 16	-6.44	<0.00001
BMI (Kg/mt^2)	25.8 ± 5	32.5 ± 5.6	-9.69	<0.00001
Waist/Hip ratio	0.91 ± 0.079	0.93 ± 0.078	-1.01	NS
Glucose (mg/dl)	85 ± 8	109 ± 6	-25.8	<0.00001
T cholesterol (mg/dl)	178(152-196)	184(162-204)	-1.34	NS
Triglycerides (mg/dl)	115(91-54)	141(104-214)	-3.44	0.0005
HDL-c (mg/dl)	55(46-62)	47(38-53)	4.91	0.000001
LDL-c (mg/dl)	92(77-115)	103(/86-122)	-1.64	NS
Systolic Blood Pressure (mmHg)	112 ± 10	119 ± 9	-5.63	<0.00001
Diastolic Blood Pressure (mmHg)	75 ± 8	85 ± 10	-8.6	<0.00001
Insulin µUI/ml	13.6(4.7-23)	18(12-25)	-3.97	0.00006
HOMA-RI	2.7(0.95-4.9)	4.8(3-6.9)	-6.0	<0.00001
B-cell Function	210(87-379)	141 (88-198)	3.0	0.002

BMI: Body Mass Index; HDL-c: High Density Lipoprotein Cholesterol; LDL-c: Low Density Lipoprotein Cholesterol; HOMA-IR and B-cell Function, Homeostasis model assessment (HOMA). Mean ± SD, median (25-75 quartiles); t test for independent samples value; Z Mann & Whitney U test value; NS = No Significant.

Table 2: Genotype and allelic frequencies of rs7903146 and 12255372 in two groups.

SNP		Genotype	Healthy subjects n = 114	Prediabetes subjects n = 133	X^2_y	P
***TCF7L2* rs7903146**	C/T	CC	77 (0.675)	75 (0.565)	4.84	0.08
		CT	35 (0.307)	50 (0.375)		
		TT	2(0.0175)	8 (0.06)		
	Allele C		0.829	0.75	1.48	NS
	Allele T		0.171	0.25		
***TCF7L2* rs12255372**	G/T	GG	78 (0.684)	86 (0.647)	6.17	0.05
		GT	36 (0.316)	40 (0.30)		
		TT	0	7 (0.053)		
	Allele G		0.842	0.80	0.30	NS
	Allele T		0.158	0.20		

Frequency (percent); $X^2_{y=}$ Yates corrected X^2

Statistical analysis

Data for anthropometric and metabolic characteristics of the volunteers were expressed as the mean ± SD or median (25-75 quartiles). Differences between groups were examined using the t-test for independent samples, Mann & Whitney U test, ANOVA or

Kruskal-Wallis test. Risk factors associated with pre-Diabetes were analyzed with the logistic regression analysis. The Analyses were conducted using a statistical package (Statistica 7.0, Statsoft Inc., Tulsa, OK, USA).

Results

The total group included 66 men and 181 women with an average age of 42 ± 11 years, 114 healthy subjects, and 133 pre-diabetic subjects. The weight, BMI, age, blood pressure, triglycerides, insulin, and HOMA-IR were significantly higher, but HDL-c and β-cell function lower in pre-DM subjects than in healthy subjects (Table 1). There are no differences in the allelic and genotypic frequencies of rs7903146 between healthy and pre-DM groups (Table 2). A marginal difference in genotypic frequencies of rs12255372 *TCF7L2* between healthy and pre-DM subjects was observed (p=0.05) (Table 2). The distribution of genotype frequencies of both polymorphisms is in the agreement of the Hardy-Weinberg distribution.

In the analysis of metabolic characteristics by rs7903146 genotypes in the whole group, we found weight, BMI, triglycerides levels, and β-cell function, decreased (16.6%), but increased serum glucose in subjects with CT and TT genotypes (Table 3). When comparing the healthy vs pre-DM subjects by rs7903146 genotypes, weight and BMI were significantly lower in pre-DM subjects with CT/TT genotypes. In the insulin levels and β-cell function, there are decreases no significant (22% and 16.6% respectively). In the analysis of rs12255372 genotypes, all subjects with GT and TT genotypes showed insulin levels, HOMA-IR and β-cell function significant lower than GG wild type (23.6%, 25%, 26.9% respectively) (Table 4). In addition, comparing healthy and pre-DM subjects by rs12255372 genotypes, serum insulin levels, HOMA-IR, and β-cell function were significantly decreased in pre-DM subjects with GT and TT genotypes (26%, 22%, and 31% respectively).

In the logistic regression analysis using BMI, the age, and rs7903146 polymorphism (under dominant model) as regressors observed association of BMI (OR=1.26 95% 1.18-1.34, p<0.00001), age (OR=1.05 95% 1.02-1.08, p=0.0008), and rs7903146 (OR=3.11, 95% 1.58-6.1, p=0.0009) with the development of pre-DM. When BMI is omitted of the model logistic regression, a decrease of the risk conferred for rs7903146 (OR=1.83, 95% 1.05-3.19, p=0.03) was observed, however, the risk confers no change on the age. The rs1225372 shows no association with the development of pre-DM using the same logistic regression. In another model including only the age (OR=1.11 95% 1.06-1.16, p=0.0000004), and positive family history of DM (OR=2.19 95% 1.09-4.36, p=0.024) also showed to be a predisposing factor of pre-DM.

Discussion

In this work, we analyzed the association between rs12255372 and rs7903146 variants of the *TCF7L2* gene with the development of pre-DM and its metabolic phenotypes in healthy and pre-diabetic subjects. Pre-DM is an obvious risk factor for both T2DM and cardiovascular disease [1]. However, there are no specific symptoms of pre-DM, and its clinical course is variable. Also, because there is not a worldwide consensus on diagnostic criteria, there are inadequacies in defining it as a single disease. Nevertheless, it has been considered that the prevalence of pre-DM is higher than that for T2DM, and

Table 3: Metabolic characteristic of the rs7903146 genotype in whole group.

	N=152 CC	N=95 CT /TT	t ó Z	p
Weight (Kg)	75.8 ± 19	71± 14	2.08	0.038
BMI (Kg/mt^2)	30 ± 6.6	28.4 ± 5.6	1.95	0.052
Glucose (mg/dl)	97 ± 13	100 ± 13	-1.98	0.048
T cholesterol (mg/dl)	180 ± 33	181 ± 34	-0.0814	NS
Triglycerides (mg/dl)	136 (103-192)	115(92-153)	2.28	0.02
HDL-c (mg/dl)	52 ± 34	51 ± 9	0.251	NS
LDL-c (mg/dl)	102 ± 31	101 ± 32	0.068	NS
Systolic blood pressure (mmHg)	116 ± 10	116 ± 9	0.142	NS
Diastolic blood pressure (mmHg)	81 ± 11	80 ± 10	0.136	NS
Insulin µUI/ml	17.4 (9-25)	14 (7-23)	1.586	NS
HOMA-IR	4.2 (2.2-6.2)	3.6(1.8-5.9)	1.140	NS
B-cell function	168 (103-297)	140 (73-226)	2.399	0.016

BMI: Body Mass Index; HDL-c: High Density Lipoprotein cholesterol; LDL-c: Low Density Lipoprotein cholesterol; HOMA-IR and B-cell Function, Homeostasis model Assessment (HOMA). Mean ± SD, median (25-75 quartiles); t test for independent samples value; Z Mann & Whitney U test value; NS = No Significant

Table 4: Metabolic characteristic of the genotype rs12255372 in whole group.

	N =165 GG	N = 82 GT/TT	t ó Z	P
Weight (Kg)	75 ± 18	72 ± 16	1.00	NS
BMI (Kg/mt^2)	29.7 ± 6.4	28.8 ± 6	1.053	NS
Glucose (mg/dl)	97 ± 14	100 ±14	-1.332	NS
T cholesterol (mg/dl)	181 ± 34	179 ± 33	-0.591	NS
Triglycerides (mg/dl)	131 (104-172)	120 (92-174)	1.43	NS
HDL-c (mg/dl)	52 ± 33	52 ± 11	-0.053	NS
LDL-c (mg/dl)	104 ± 31	98 ± 32	1.317	NS
Systolic blood Pressure (mmHg)	116 ± 10	117 ± 11	-0.467	NS
Diastolic blood pressure (mmHg)	81 ± 11	80 ± 20	0.387	NS
Insulin µUI/ml	17.8 (9-26)	13.6 (7.2-22)	2.42	0.015
HOMA-IR	4.4 (2.2-6.3)	3.3 (1.7-5.3)	2.15	0.031
B-cell function	171 (104-294)	125 (78-217)	2.78	0.005

BMI: Body Mass Index; WC; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; HOMA-IR: Homeostasis Model Assessment Insulin Resistance and B-cell Function. Mean ± SD, median (25-75 quartiles); t test for independent samples; Mann & Whitney U test; NS = No Significant

there are many epidemiological characteristics involved in different regions and races [19]. We replicated the association of age, obesity, high triglycerides, and low HDL-cholesterol, but not of hypertension [20,21]. Although none of the pre-DM subjects had hypertension, they had a higher systolic and diastolic blood pressure than healthy subjects. We found the β-cell function decreased and insulin resistance increased in the pre-DM subjects, as previously described [22]. Other investigators propose that subjects with IGT and IFG/IGT have a significantly greater reduction in insulin secretion than subjects with IFG [23], and that the pathogenesis of IFG is more closely associated with insulin resistance, and the pathogenesis of IGT is more closely associated with impaired insulin secretion [24].

In our work the subjects with CT/TT rs7903146 genotypes

showed higher glucose concentrations, but lower weight, BMI, triglycerides and β-cell function than the subjects with CC genotypes. Similar results have been reported in European populations [8,14,25], specifically, it has been reported that subjects with rs7903146 risk allele showed lower BMI, waist circumference, total body fat and body weight [14]. However, we observed no significant lower insulin levels and β-cell function (22%, and 16.6%, respectively) in pre-diabetic subjects with the risk T allele rs7903146, probably as a result of the number of pre-diabetic subjects with genotypes CT/TT. The *TCF7L2* gene harbors common genetic variants with the strongest effect on T2DM risk, yet described, one of them is the SNP rs7903146 [26]. Impaired *in vivo* [27] and *in vitro* insulin secretion has been shown in risk T allele carriers of rs7903146 [28,29]. Interestingly, the subjects with risk T-allele are characterized by elevated plasma proinsulin levels and an increased proinsulin-to-insulin ratio suggestive of perturbed proinsulin processing [30] and show a higher degree of open chromatin in pancreatic islets [31].

Also, the allele T of *TCF7L2* rs7903146 also has been identified as a significant risk factor to impaired proinsulin conversion [32], and IFG risk in a cohort of Caucasian subjects [9]. In our study, the BMI, age, and rs7903146 polymorphism are predictors of the development of pre-DM. An interaction between allele risk rs7903146T and metabolic factor as BMI was observed, since the BMI of the logistic regression model was omitted, the risk conferred for rs7903146 decreased. The previous report showed that the association between rs7903146 and IFG risk was stronger in Caucasian with obesity [9].

The rs12255372 genotypes have been associated with impaired insulin secretion, impaired fasting glucose, and impaired glucose tolerance [15,16,33]. In our study, the pre-diabetic subjects with GT or TT genotypes showed significantly lower insulin levels, and β-cell function (26%, 31% respectively) than the GG wild type. The data suggest that the risk variant of rs12255372 polymorphism may have similar effects on insulin secretion as it has shown in the subjects with risk T allele rs7903146 previously described [28,29]. This work describes the phenotypes of subjects with rs7903146 and rs12255372 genotypes, but only the rs7903146 shows to be an associated factor to development to pre-DM, which may be explained by the sample size, and it requires additional confirmation.

This is the first report analyzing the relationship of *TCF7L2* rs7903146 and rs12255372 with impaired insulin secretion and β-cell function in pre-DM Mexican population. Our Mestizo population resulted from the recent admixture of European, Amerindian and African populations, in estimated average proportions of ~50, ~45, and ~5% respectively [34]. Therefore, it is likely that the genetic variants common in Europeans are part of the genetic background of the pre-DM subjects of our study, as reported for T2DM [7].

Recently, the molecular mechanisms by which TCF7L2 regulates glucose metabolism were described. The TCF7L2 functions as a master regulator of insulin production and processing, which have been established identifying TCF7L2-target genes and the downstream regulatory network responsible for its effect on insulin secretion. *ISL1* is a direct target of TCF7L2, for regulating proinsulin production and processing via regulation of *PCSK1, PCSK2, SLC30A8, MAFA, PDX1,* and *NKX6.1*. These multiple targets in key pathways may explain why *TCF7L2* has emerged as the gene showing the strongest association with T2DM among common variants [28].

Conclusion

The subjects with CT or TT genotypes of rs7903146 showed weight, BMI, triglycerides, and insulin levels significantly decreased. The pre-diabetic subjects with these genotypes also showed a significant decrease in weight, BMI. The subjects with GT or TT rs12255372 genotypes, including pre-diabetic subjects showed a significant decrease in insulin content, HOMA-IR, and β-cell function (24%, 22%, 31% respectively). In this study, we described the phenotypic features of the subjects with rs7903146 and rs12255372 polymorphisms in healthy and pre-diabetic subjects. The BMI, the age, and rs7903146 polymorphism (under dominant model) are strong predictors for the development of pre-DM.

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