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Transcription Factor 7-Like 2 (TCF7L2) Polymorphism and Hyperglycemia in an Adult Italian Population-Based Cohort

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OBJECTIVE — To assess whether TCF7L2 polymorphism has a role in the deterioration of glycemic control.

RESEARCH DESIGN AND METHODS — Metabolic variables were evaluated at baseline and after 6-year follow-up in 1,877 Caucasians from a population-based cohort.

RESULTS — At baseline, T-allele carriers showed significantly lower BMI and homeostasis model assessment for β-cell function (HOMA-B) values and higher fasting glycemia and diabetes prevalence. At follow-up, fasting glucose and HOMA-B index were increased and reduced, respectively, in carriers of the T-allele. Incident impaired fasting glucose (IFG) and incident diabetes were 5.7, 10.7, 16.9% and 1.6, 1.7, 3.0% in the CC, CT, and TT genotypes, respectively. In a multiple logistic regression model, the association between incident IFG and the T-allele was significant (odds ratio [OR] 2.08 [95% CI 1.35–3.20] and 3.56 [2.11–5.98] in CT and TT genotypes, respectively).

CONCLUSIONS — The T-allele of TCF7L2 rs7903146 polymorphism was independently associated with increasing fasting glucose values toward hyperglycemia in the follow-up.

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Among the variety of TCF7L2 polymorphisms correlating with type 2 diabetes, the single nucleotide polymorphism (SNP) rs7903146 has shown the strongest association with the disease (1). We investigated the association of the SNP rs7903146 with type 2 diabetes or 2 impaired fasting glucose (IFG) or 3 the metabolic syndrome (MS) in an adult Italian population-based cohort both cross-sectionally and after 6-year follow-up.

RESEARCH DESIGN AND METHODS — All 1,877 Caucasians aged 45–64 years and representative of the province of Asti (Italy) were invited to participate in a metabolic survey in 2001–2003; 1,658 (88.3%) agreed to participate in a metabolic survey in 2001–2003; 1,480/1,658 (89.3%) were eligible after excluding those who died (n = 61) and those whose blood samples were not available for genotyping (n = 117). Mean follow-up was 6.1 ± 0.34 years. At baseline, 25.1% of patients were on anti-hypertensive treatment and 4.7% were on hypoglycemic drugs.

Characteristics at baseline and follow-up of subjects grouped by genotypes are presented in Table 1. The rs7903146 genotypic distribution was in Hardy-Weinberg equilibrium. At baseline, carriers of the T-allele showed significantly higher values of fasting glucose and lower BMI and HOMA-B index in a regression model (Table 1). Prevalence of diabetes was significantly higher in subjects carrying the minor T-allele in a multiple logistic regression model, while no significant differences were detected for prevalence of IFG and MS.

At follow-up, fasting glucose and HOMA-B values were increased and reduced, respectively, in T-allele carriers. In these patients, prevalence of IFG, diabetes, and MS were significantly higher in a multiple logistic regression model in both CT and TT genotypes (OR 1.78 [95% CI 1.06–2.99] and 3.10 [1.63–5.91] for diabetes; 1.81 [1.31–2.51] and 3.10 [1.63–5.91] for IFG; 1.34 [1.02–1.75] and 1.79 [1.22–2.64] for MS in CT and TT genotypes, respectively). The association between T-allele and MS was exclusively and used in all analyses. Multiple regression analyses (for continuous variables) or multiple logistic regression analyses (for dichotomous variables) were used to evaluate the associations between each variable and the presence of the CT or TT genotypes (introduced in the model as dummy variables) after adjustments for age, sex, familial diabetes, BMI, and waist circumference. The capacity of the TT genotype for predicting incident IFG and diabetes was examined by calculating the receiver operating characteristics (ROC) curves and the area under the curve (AUC).

RESULTS — From January to November 2008, patients were contacted for a follow-up visit: 1,480/1,658 (89.3%) were evaluated after excluding those who died (n = 61) and those whose blood samples were not available for genotyping (n = 117). Mean follow-up was 6.1 ± 0.34 years. At baseline, 25.1% of patients were on anti-hypertensive treatment and 4.7% were on hypoglycemic drugs.

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due to the higher prevalence of hyperglycemia in these subjects.

Incident diabetes was almost double in homozygous for the T-allele, but the association was not significant due to the low case number. Incident IFG was two- to threefold higher in the heterozygous and homozygous T-carriers, respectively (OR 2.08 [95% CI 1.35–3.20] and 3.56 [2.11–5.98] in CT and TT genotypes, respectively). Adjustments for smoking habits, lipid parameters, or HOMA-B values did not significantly affect the results. The AUCs of the ROC curves for the TT genotype were 0.56 for incident IFG and 0.54 for incident diabetes.

**CONCLUSIONS** — The major findings of the present study are: 1) a high prevalence of the defective T-allele in an Italian population-based cohort; 2) a significant association between the T-allele and hyperglycemia and β-cell dysfunction at baseline and follow-up; 3) a two- to threefold higher risk of incident IFG in the T-allele carriers at follow-up; and 4) an increased prevalence of MS in the T-allele carriers.

The minor T-allele is significantly associated with reduced HOMA-B levels, suggesting that the polymorphism could affect the ability of the β-cells to secrete insulin. These data indicate that SNP rs7903146 polymorphism may modulate the degree of insulin secretion to offset the prevailing level of insulin resistance without being a cause of insulin resistance. SNP rs7903146 acts like other TCF7L2 polymorphisms, such as rs12255372 (6).

The prevalence of MS in subjects carrying the TT genotype was about twofold higher at follow-up when compared with the prevalence at baseline. This increment was almost exclusively due to the significantly higher prevalence of hyperglycemia in this subgroup. The AUC values are similar to those reported in literature dealing with one single SNP (11).

Our study confirms an effect of the widely replicated TCF7L2 rs7903146 polymorphism on hyperglycemia in an adult Italian population-based cohort both in cross-sectional and longitudinal evaluation. The independent association of TCF7L2 polymorphism with increasing fasting glucose values in the follow-up may represent a marker for higher metabolic risk, which is useful for developing
more closely tailored lifestyle preventive approaches as we have recently reported (12).

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References