Association of the G276T polymorphism of the adiponectin gene with ischemic heart disease and end-stage renal disease in patients with type 2 diabetes

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Background

• Adiponectin, a hormone expressed by adipocytes, has insulin-enhancing and anti-atherogenic effects.

• Epidemiologic studies have shown lower levels of adiponectin in subjects with different aspects of the metabolic syndrome and ischemic heart disease (IHD) compared to normal controls.

• The intronic variant *rs1501299* (G276T, G allele) at the adiponectin gene is associated with ischemic heart disease (IHD) in Western populations.

• Studies assessing adiponectin as a candidate gene for diabetic nephropathy (DN) have not been done, although high levels of adiponectin predicts end-stage renal disease.

• It has been also shown that the T allele is associated with greater levels of adiponectin than the G allele.

Hypothesis

•In Brazilian subjects, the *rs1501299* (G276T, G allele) of the *adiponectin* gene is associated with IHD and DN.

Subjects and Methods

Subjects

• Data from 1072 Brazilian subjects with type 2 diabetes were assessed from a multicentric study designed to understand the pathogenesis of micro- and macrovascular complications of diabetes in 4 tertiary hospitals of Rio Grande do Sul.
• Diabetes was diagnosed based on fasting plasma glucose and/or 2-h plasma glucose after a 75g oral glucose load according to the American Diabetes Association Criteria or the requirement of diabetes medications.
• Type 2 diabetes was defined based on the World Health Organization (WHO) criteria (age ≥35 years and absence of insulin requirement in the first 5 years after diagnosis).

Design

The frequency of the variant was determined and related to cross-sectional data.

• Cross-sectional evaluation: In 1072 subjects, differences in clinical (age, sex, hypertension, smoking habit, family history of IHD, anthropometrics) and laboratory characteristics (glycemic control, lipid profile, renal function) were assessed and examined by genotype.
• IHD evaluation: IHD was diagnosed by the presence of angina or possible infarct (World Health Organization Cardiovascular Questionnaire), and/or perfusion abnormalities upon myocardial perfusion scintigraphy.
•Nephropaty evaluation: Patients were grouped according to the 24-h urinary albumin excretion (UAE) in normoalbuminuric (UAE<20 µg/min), microalbuminuric (UAE 20–199 µg/min), macroalbuminuric (UAE>200 µg/min) and those with end-stage renal disease (ESRD; dialysis group). Glomerular filtration rate (eGFR) was estimated by the MDRD equation.

Statistical Analysis

• Data expressed as percentage, mean±SD, median (25-75 percentile).
• ANOVA or χ^2 tests for comparison of clinical and laboratory data.
• Multiple logistic regression analysis to assess the relationship between genotypes and the variable of interest while adjusting for potential confounders.
• Logarithmic transformation for the dependent variable if not normally distributed
• The genotypic distribution at *rs1501299* were in Hardy-Weinberg equilibrium (P= 0.290).

Question 1

Do baseline clinical and laboratory characteristics differ in individuals with the G276T variant of the adiponectin gene?

Results

	G/G (n=540)	G/T (n=416)	T/T (n=116)	P
Male (%)	48,1	44,7	44,8	0,534
Age (years)	58,6 ± 10,3	59,1 ± 10,5	61,3 ± 10,7	0,485
Diabetes duration (years)	10,0 (5,0-18,0)	12,0 (6,0-18,0)	12,0 (5,0-20,0)	0,242
Ethnicity (white, %)	76,9	72,8	70,9	0,247
Hypertension (%)	68,7	71,3	66,3	0,570
Smoking habit (%)	18,9	15,0	26,0	0,112
Family history of IHD (%)	22,4	18,9	20,8	0,535
Body mass index (kg/m²)	29,0 ± 5,2	28,6 ± 5,2	28,7 ± 5,2	0,898
Waist to hip ratio	0,95 ± 0,07	0,94 ± 0,08	0,93 ± 0,08	0,498
A1c (%)	6,8 ± 2,0	6,7 ± 1,9	6,9 ± 2,1	0,781
Plasma creatinine (mg/dl)	1,0 (0,8-1,4)	1,0 (0,8-1,4)	1,0 (0,8-2,1)	0,310
Total cholesterol (mg/dl)	208,6 ± 49,6	207,9 ± 50,6	203,4 ± 46,5	0,924
LDL cholesterol (mg/dl)	130,6 ± 43,7	128,3 ± 45,2	133,4 ± 48,6	0,335
HDL cholesterol (mg/dl)	44,7 ± 13,4	45,5 ± 12,6	44,8 ± 12,04	0,503
Triglycerides (mg/dl)	158,0 (108,0-230,0)	149,0 (103,5-207,0)	155,0 (95,0-225,0)	0,292

Data expressed as percentage, mean±SD or median (P25-75)

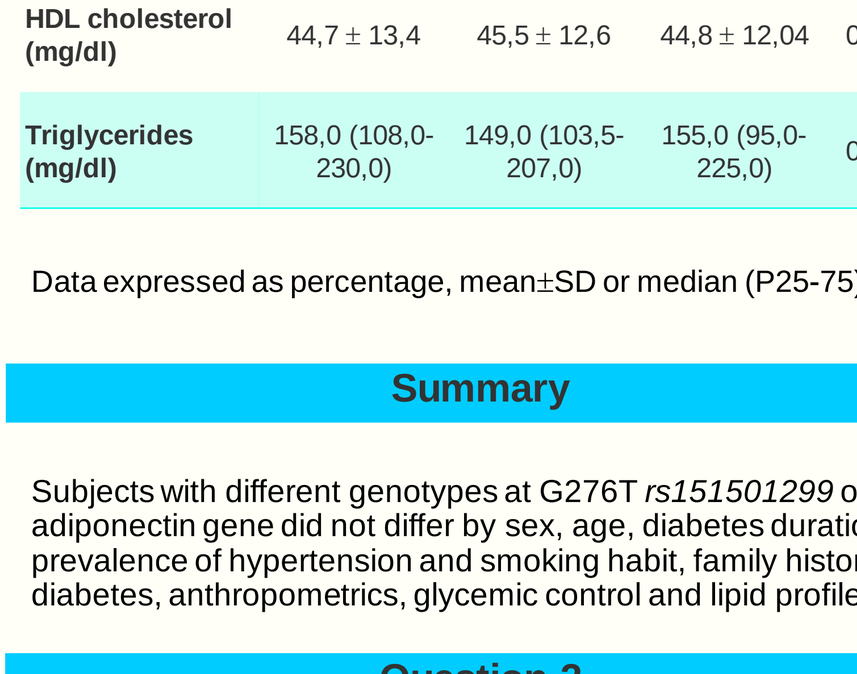
Summary

Subjects with different genotypes at G276T *rs151501299* of the adiponectin gene did not differ by sex, age, diabetes duration, prevalence of hypertension and smoking habit, family history of diabetes, anthropometrics, glycemic control and lipid profile.

Question 2

Is the G276T polymorphism of the *adiponectin* gene associated with diabetic nephropaty?

Results



Summary

Homozygous subjects for the T allele had a greater risk for ESRD than those with the G allele comparing the genotypes.

Question 3

Is the association between the G276T polymorphism of the adiponectin gene with DN exist after adjustments for risk factors in a multinomial regression model?

Results

Independent Variables	OR	CI95%		P
Age	**1,03**	**1,00**	**1,06**	**0,008**
Sex (Male)	**3,27**	**1,98**	**5,40**	**0,001**
Hypertension (Yes)	**5,81**	**2,79**	**12,04**	**0,001**
Adipo 276 (TT)	**2,53**	**1,09**	**5,84**	**0,029**
Ethnicity (White)	**1,21**	**0,94**	**1,57**	**0,130**

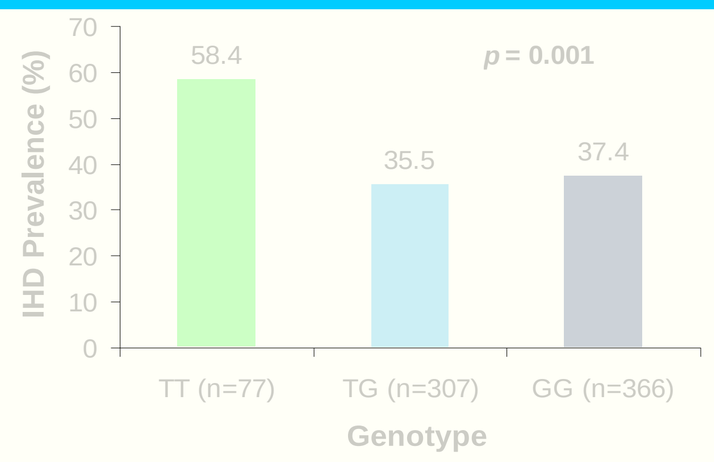
Summary

Homozygous subjects for the T allele had 2.5 times the risk for DN than subjects with the G allelle after adjustments for risk factors.

Question 4

Is the G276T polymorphism of the *adiponectin* gene associated with IHD?

Results



Summary

Homozygous subjects for the T allele had a greater risk for IHD than those with the G allele comparing the genotypes.

Question 5

Is the association between the G276T polymorphism of the adiponectin gene with IHD exist after adjustments for risk factors for cardiovascular diseases in a multiple logistic regression model?

Results

Independent Variable	OR	CI 95%	*p*
Genotype (TT vs GT/GG)	**1,795**	**1,011-3,186**	**0,046**
Sex (Male)	**0,958**	**0,660-1,391**	**0,822**
Age	**1,010**	**0,992-1,029**	**0,266**
Hypertension	**1,241**	**0,842-1,829**	**0,275**
Smoking habit	**1,564**	**0,982-2,489**	**0,060**
A1c	**1,064**	**0,966-1,172**	**0,205**
Creatinine	**1,135**	**1,016-1,269**	**0,269**

Summary

Homozygous subjects for the T allele had almost 2 times the risk for IHD than subjects with the G allele while adjusting for classical risk factors for cardiovascular diseases.

Conclusion

Different from other Western populations, Brazilian diabetic subjects homozygous for the T allele had a greater prevalence of IHD and ESRD than subjects with the G allele. The mechanisms that might explain this association is not known. However, different genetic background and lifestyle might interact resulting in a different modulation of gene expression and adiponectin production in those who have this polymorphic variant and may be related with our findings.