REVIEW ARTICLE

Adiponectin gene polymorphisms and susceptibility to atherosclerosis: A meta-analysis

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Previous studies have inspected the associations between Adiponectin (ADIPOQ) 276G/T polymorphisms and atherosclerosis, but the results are inconclusive. The aim of this study was to explore the relationship between polymorphism +276 G > T (rs1501299) in ADIPOQ and atherosclerosis. A widespread search was directed to identify all studies on the association of ADIPOQ 276G/T polymorphism with atherosclerosis risk. The fixed effect pooled measures according to odds ratio (OR) and 95% confidence interval (CI) were calculated in the meta-analysis. Heterogeneity among studies was evaluated using *Q* test and the I^2. Publication bias was estimated using modified Egger's linear regression test and Fuunel plot. Nine studies regarding the associations between the ADIPOQ 276G/T polymorphism and atherosclerosis risk were enrolled in this meta-analysis, including 1959 cases and 3739 controls. The 276G/T polymorphism was not significantly associated with atherosclerosis, yielding pooled ORs of 0.925 (95% CI: 0.728-1.178) and 0.921 (95% CI: 0.804-1.054), for TT versus GG, and TG versus GG, respectively. Significant between-study heterogeneity was not found in our meta-analysis. Furthermore there was no evidence of publication bias in the meta-analysis. The present meta-analysis showed that there is no association between ADIPOQ 276G/T polymorphism and atherosclerosis. High quality studies are still needed to add for more investigation of the association between ADIPOQ 276G/T polymorphisms and atherosclerosis

Key words: Adiponectin, atherosclerosis, gene, meta-analysis, polymorphism

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INTRODUCTION

Adiponectin is a 244-amino-acid-long polypeptide, which in humans is encoded by the ADIPOQ gene.[1] It modulates several metabolic processes, including glucose regulation and fatty acid catabolism.[2] Adiponectin is mainly synthesized and secreted by adipose tissue.[2] However, some studies suggest that it is also synthesized by cardiomyocytes, skeletal muscle and osteoblasts.[3] The synthesis of adiponectin by adipocytes is complex, and involves transcriptionally regulated machinery as well as a number of post-transcriptional mechanisms.[2] Adiponectin expression is subject to regulation by different factors comprising TNF-α, interleukin-6 and possibly also by insulin.[4]

Adiponectin has several known vasculoprotective effects. Previous studies have indicated that adiponectin has anti-inflammatory, anti-atherogenic, and antidiabetic properties.[5] However, the significance of adiponectin as a risk predictor of atherosclerosis is less certain. While an inverse relationship between plasma adiponectin levels and subclinical atherosclerosis, has been observed in several studies,[6-8] two recent studies have shown no significant association between baseline adiponectin levels and intima-media thickness (IMT) values.[9-10] Furthermore, a meta-analysis including 1313 cases and 2954 controls revealed that a higher adiponectin concentration had no protective effect on coronary heart disease.[11] These findings have raised questions about the role of adiponectin in the pathogenesis of atherosclerosis.

It has been proposed that adiponectin plasma levels are highly heritable. This fact is tempting to the search for the effect of genetic variations in the human genome on variations in plasma adiponectin levels and consequently atherosclerosis.[12-14] The ADIPOQ gene is located on chromosome 3q27 and contains three exons and two introns spanning a 17-kb region.[13] A number of polymorphisms in the ADIPOQ gene have been analyzed demonstrating associations with the Metabolic syndrome, type 2 diabetes and a more pronounced atherogenic lipoprotein phenotype.[15]

Most of the published studies have determined the association of C.45T >G (rs2241766) and the +276G >T (rs1501299) polymorphisms in the ADIPOQ gene with risk factors of atherosclerosis.[11,13,16]

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For +45T/G variant, the study by Pischon *et al*. showed no association with adiponectin level, however, there was significant association between +276G/T variant, and the adiponectin level.[17] A recent meta-analysis on the association of adiponectin polymorphisms (+45T/G, +276G/T) with coronary atherosclerosis in the Chinese Han population suggested that +276G/T, but not +45T/G polymorphism was associated with decreased risk of coronary artery disease.[18] It has been shown that the 276G/T polymorphism in intron 2 is associated with obesity, insulin resistance and the type 2 diabetes as risk factors of atherosclerosis.[19] Moreover, several studies have reported the associations between ADIPOQ 45T/G and 276G/T polymorphisms and atherosclerosis, but the results are inconclusive.[20]

So, in order to derive more precise estimates of the associations, a meta-analysis and HuGE review were performed to investigate the associations between ADIPOQ 276G/T polymorphisms and atherosclerosis.

MATERIALS AND METHODS

Search strategy

A search of the online databases (HUGE, PUPMED, ISI and EMBASE) without any time constraints was performed using key words "adiponectin single-nucleotide polymorphism (SNP) +276" "atherosclerosis" "Coronary artery disease" limited to studies carried out in humans. We also found references lists of identified published papers for additional relevant studies. Inclusion criteria to be included in meta-analysis were: Original article, case-control and cohort studies, adult human population and coronary atherosclerosis as the main event. No language restrictions were imposed. After subsequent screening, 21 studies were identified for recruitment in the light of the inclusion criteria.

Eligibility criteria

The 21 epidemiologic studies considered for inclusion in this meta-analysis on the association between coronary atherosclerosis and adiponectin SNP +276 gene.[10,14,21-39] The features were confirmed through review of medical records. All subjects were selected randomly without sex restriction. Studies were excluded if they did not provide data that allowed calculation of standard errors for effect estimates and if the estimates had not been reported. When there were multiple publications from the same population, only data from the most recent report were included. We excluded three studies[21,23,31] because of the study population which has not been done on adults and six studies[10,26,28,30,33,39] that reported only correlation between risk factors of coronary atherosclerosis and adiponectin SNP +276 gene and a study[29] without crude data that had not been reported the standard errors for the estimations and three other studies which was not case-control or cohort schemes[25,32,14] and finally a study[27] that had investigated polymorphisms other than SNP +276. The seven epidemiologic studies considered for inclusion in this meta-analysis were two case-control studies,[24,35] four cohort studies[22,27,34,38] and a study containing two parts, according to both case-control and cohort designs[37] on the association between coronary atherosclerosis and adiponectin SNP +276 gene. Also the paper number[38] includes two cohort studies on the two random populations from Swiss and Germany.

Data extraction

For each publication included, we extracted data on first author's name, year of publication, country, study design, numbers of cases and controls, age, sex, type of coronary artery disease, risk estimates, and corresponding CIs. Information on study design, participant characteristics, measurement of fractures, adjustment for potential confounders, and estimates of association was extracted independently by two reviewers (M. M. and SH. H. J.). Discrepancies were resolved through discussion.

Statistical analysis

An unadjusted odds ratio (OR) corresponding to a 95% CI of each study (case-control studies) was first calculated in a 2 × 2 table. These studies provided primarily three genotypes, and all possible comparisons of these genotype groups were performed using allelic comparisons. We pooled these data in order to compare the special genotype groups. The Z-test was used to assess the significance of the pooled OR, and a $P < 0.05$ was considered significant. Summary OR estimates with their corresponding 95% CIs were derived by the method of DerSimonian and Liard[40] using both fixed and random effect models. A heterogeneity check was calculated based on Cochran's Q statistic and the inconsistency index (I^2).[41] $P > 0.10$ and $I^2 < 25\%$ denoted that heterogeneity did not exist between the studies.[42] If there was no heterogeneity, the overall gene effect was evaluated by fixed effects model, or else by the random-effects model. Funnel plots and the Egger's linear regression test were used to provide diagnosis of potential publication bias ($P < 0.05$) indicated statistically significant publication bias.[43] All statistical tests were performed using Comprehensive Meta-Analysis Version 2, and all P values are two-tailed.

RESULTS

Study characteristics

Seven independent papers containing nine studies met the predefined inclusion criteria. The seven epidemiologic studies considered for inclusion in this meta-analysis were two case-control studies,[24,35] four cohort studies[22,27,34,38] and a study containing two parts, according to both case-control and cohort designs[37] on the association between coronary atherosclerosis and adiponectin SNP +276 gene. Also the paper number[38] includes two cohort studies on the two random populations from two independent populations. Four studies were conducted in the Europe,[27,35,37,38] two

in Asia,[22,35] and one in Africa.[24] The characteristics of all studies included in meta-analysis are presented in Table 1. In the meta-analysis of coronary atherosclerosis and ADIPOQ 276T/G, we included both the three case-control studies[24,35,37] and the five cohort studies (22, 27, 35, 38, 39 [part 1] and 39 [part 2]). These nine studies comprised 5698 participants and 1251 incident cases of coronary and 708 cases of carotid atherosclerosis.

Main results, subgroup analyses

Nine case-control and cohort studies which investigated the association the ADIPOQ 276T/G polymorphism and susceptibility to coronary atherosclerosis were included in this research [Table l]. Individual study results and overall summary results for the nine studies are presented in Figures 1 and 2. There was no evidence that the TT and TG alleles were associated with susceptibility to coronary artery disease. Fo TT versus GG, and TG versus GG the overall pooled OR was 0.925 (95% CI: 0.728-1.178) and 0.921 (95% CI: 0.804-1.054), respectively using the fixed-effects model. No evidence was found for between-study heterogeneity. The results of heterogeneity test were (I^2 = 43.78%, P = 0.076) and (I^2 = 47.78%, P = 0.060) for TT versus GG, and TG versus GG, respectively.

TT versus GG overall pooled ORs for Asian and European were 0.944 (95% CI: 0.634-1.405) and 1.095 (95% CI: 0.910-1.318), respectively and for TG versus GG were 0.732 (95% CI: 0.590-0.909) and 1.027 (95% CI: 0.733-1.438), respectively. The Begg's funnel plots were symmetrical by visual inspection [Figures 3 and 4], and neither the Begg's test nor the Egger's test suggested publication bias. The P values for

Table 1: Characteristics of different studies included in a meta-analysis of the association between SNP+276 of adiponectin gene and coronary art disease

Source	Year	Gender	Age	Region	Case			Control		
					GG	TG	TT	GG	TG	TT
Katakami *et al*.[2]	2011	M/F	54.9±7.9	Japan	129	71	13	1230	976	218
Boumaiza *et al*.[4]	2011	M/F	60.6±10.6	Tunisia	105	84	23	45	41	18
Rodriguez *et al*.[7]	2010	M/F	45-56	Spain	69	44	6	287	224	44
Kim *et al*.[16]	2008	M/F	61.9±9.3	Korea	197	166	34	154	131	26
Hoefle *et al*.[17]	2007	M	61±10	Austria	22	108	120	10	49	93
Filippi *et al*.[19] (1)	2005	M/F	59.1±9.4	Italy	152	145	28	155	96	19
Filippi *et al*.[19] (2)		M/F	61.7±10.4		135	96	24	111	71	14
Lacqueman *et al*.[20] (3)	2003	M/F	57.7+12	Switzerland	76	27	4	145	34	2
Lacqueman *et al*.[20] (4)		M/F	54±7.8		33	21	1	104	23	7

(1)= A case-control study on 325 cases and 270 controls based on Italian population; (2)= A cohort study on 451 Italian subjects; (3)= Cohorts of 189 French subjects, (4)= Cohort of 288 Swissair subjects; SNP=Single-nucleotide polymorphism; GG=Guanine Guanine; TG=Thymine Guanine; TT=Thymine Thymine

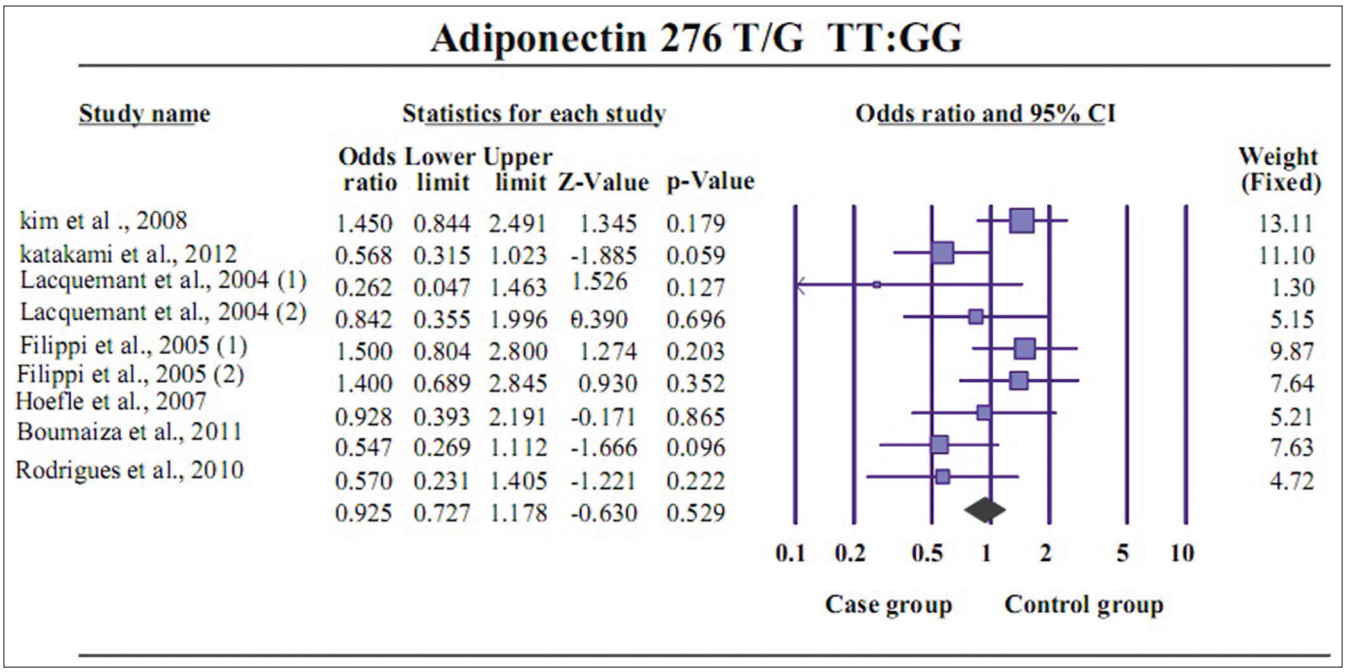

Figure 1: Individual and pooled ORs and 95% CI for SNP + 276 (TT vs.GG) for all studies

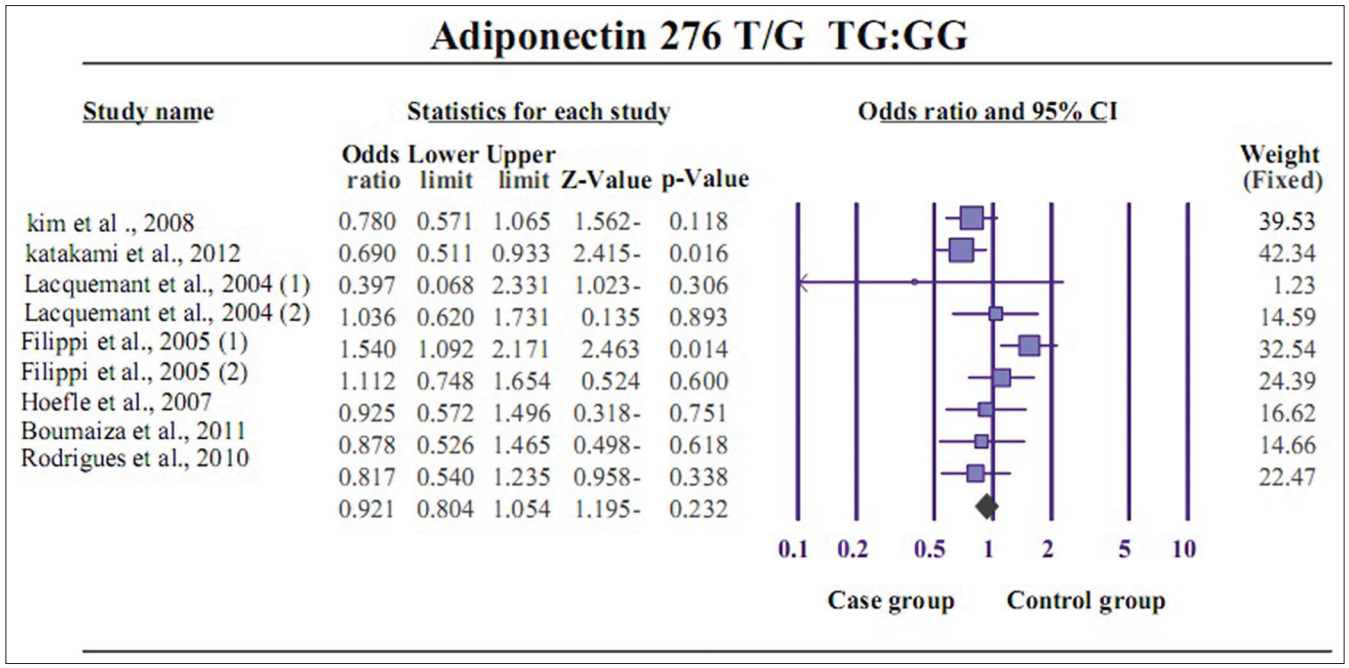

Figure 2: Individual and pooled ORs and 95% CI for SNP + 276 (TG vs.GG) for all studies

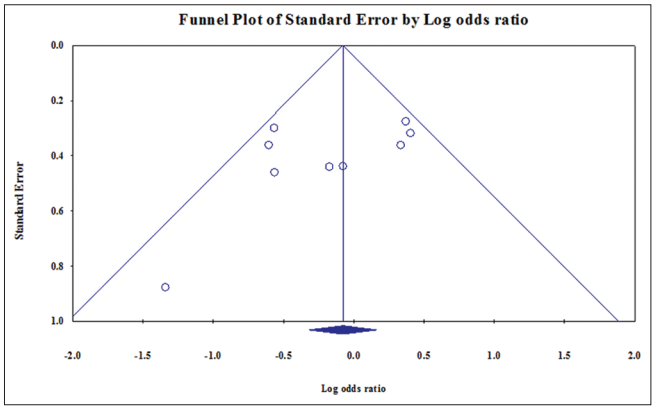

Figure 3: Begg's funnel plot analysis for the comparison of the TT versus GG alleles of SNP + 276. *P* value of Begg's test was 0.14 (continuity corrected)

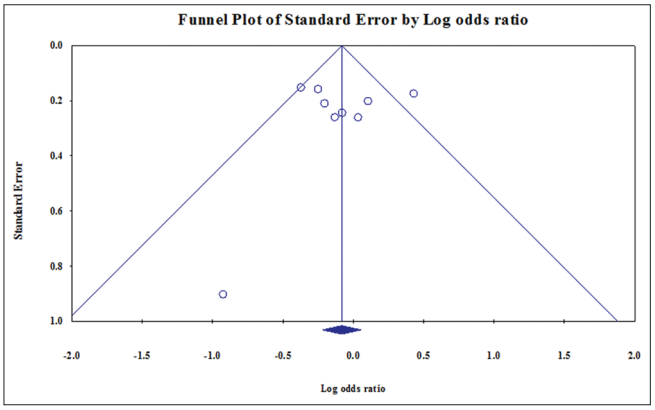

Figure 4: Begg's funnel plot analysis for the comparison of the TG versus GG alleles of SNP + 276. *P* value of Begg's test was 0.75 (continuity corrected)

Egger's test were 0.16 (95% CI: -6.16-1.29) for TT allele and 0.86 (95% CI: -3.97-3.32) for TG allele.

Sensitivity analysis

A sensitivity analysis was done by omitting one study at a time and computing the pooled ORs for the remaining studies. This analysis showed that none of the individual studies influenced the pooled ORs, which ranged from 0.85 (95% CI: 0.76-0.96) to 0.97 (95% CI: 0.88-1.06) for SNP + 276. The sensitivity analysis specified that the results of the meta-analysis were consistent and stable.

DISCUSSION

To the best of our knowledge, this is the first meta-analysis which assessed the associations between +276G/T polymorphism in the adiponectin gene and atherosclerosis. The results indicated that there was no significant association between 276G/T polymorphism and atherosclerosis.

The association between adiponectin and atherosclerosis is a still a matter of debate. Adiponectin has been indicated to play an important role in protecting against atherosclerosis through its anti-inflammatory effects[44] and control of glucose, lipid and energy metabolism.[45] Adiponectin decreases plasma TG and improves glucose metabolism by increasing insulin sensitivity Although an inverse relationship between plasma adiponectin levels and intima-media thickness, a marker for subclinical atherosclerosis, has been reported frequently[20] previous meta-analysis revealed that a higher adiponectin concentration had only a minor protective effect on coronary atherosclerosis.[11]

On the other hand, the relationship between ADIPOQ gene variants and cardiovascular risk has not yet been widely studied, and available data are inconsistent.[20] Most of the published studies have determined the association of + 276G >T or rs1501299 polymorphisms in the ADIPOQ gene with higher adiponectin levels, and lower odds of cardiovascular disease (CVD). However, these studies have demonstrated a positive but small contribution to the variation of plasma adiponectin levels in homozygous mutation carriers.[13]

In agreement to our results a recent meta-analysis showed no significant association of 276G/T polymorphism with atherosclerosis susceptibility.[46]

In Qi *et al*. meta-analysis including 827 CVD cases and 1,887 CVD-free control there was only week association between rs1501299 and CVD risk among diabetic patients.[47] There are two other meta-analysis for rs1501299 and CVD, which also reported the protective effect of rs1501299T allele in type 2 diabetes population.[48,49]

In conclusion, by combining the results of the current, relevant studies, our review suggests that the + 276G >T or rs1501299 polymorphism of ADIPOQ gene is not associated with the risk of atherosclerosis. The potential limitations of our study could be that the eligible studies in our research were mainly from Asia and Europe, and data of other populations, like African, was limited. Furthermore, the results might be distorted by potential weakness and biases of genetic association studies, such as genotyping error, phenotype misclassification, population stratification, gene-gene or gene-environment interactive effect, and selective reporting biases.

Further studies, especially studies conducted among other ethnicities and with larger sample sizes will provide a more comprehensive conclusion that could have significant clinical implications.

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