ADIPOQ and adiponectin: the common ground of hyperglycemia and coronary artery disease?

ADIPOQ e adiponectina: base comum da hiperglicemia e doença arterial coronariana?

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SUMMARY

Plasma adiponectin and the coding gene for adiponectin, *ADIPOQ*, are thought to explain part of the interaction between obesity, insulin resistance, type 2 diabetes (T2DM) and coronary artery disease (CAD). Here, we illustrate the role that adiponectin and *ADIPOQ* variants might play in the modulation of CAD, especially in the occurrence of hyperglycemia. Recent evidence suggests that total and high molecular weight (HMW) adiponectin levels are apparent markers of better cardiovascular prognosis in patients with low risk of CAD. However, in subjects with established or high risk of CAD, these levels are associated with poorer prognosis. We also provide recent evidences relating to the genetic control of total and HMW adiponectin levels, especially evidence regarding *ADIPOQ*. Accumulated data suggest that both adiponectin levels and polymorphisms in the *ADIPOQ* gene are linked to the risk of CAD in patients with hyperglycemia, and that these associations seem to be independent from each other, even if adiponectin levels are partly dependent on *ADIPOQ*. Arq Bras Endocrinol Metab. 2011;55(7):446-54

Keywords

Total adiponectin; HMW adiponectin; *ADIPOQ*; polymorphisms; coronary artery disease; type 2 *diabetes mellitus*

SUMÁRIO

Os níveis plasmáticos de adiponectina e o gene codante desta proteína, *ADIPOQ*, parecem explicar parte da interação de doenças como obesidade, resistência à insulina, diabetes melito tipo 2 (DM2) e doença arterial coronariana (DAC). Apresentamos as evidências do papel tanto dos níveis de adiponectina quanto das variantes no *ADIPOQ* na modulação da DAC, sobretudo na presença de hiperglicemia. Estudos recentes sugerem que níveis de adiponectina total e de alto peso molecular (HMW) são marcadores de bom prognóstico DAC, sobretudo em pacientes de baixo risco cardiovascular, enquanto nos pacientes de alto risco ou com doença já estabelecida podem se associar com pior prognóstico. Apresentamos também as evidências em relação ao possível controle genético dos níveis circulantes de adiponectina, tanto total quanto da isoforma de alto peso molecular, sobretudo em relação ao *ADIPOQ*. A análise global dos dados sugere que tanto os níveis circulantes de adiponectina quanto polimorfismos no gene *ADIPOQ* estão implicados na evolução de DAC em pacientes com hiperglicemia e que essas associações podem existir de forma independente. Arq Bras Endocrinol Metab. 2011;55(7):446-54

Descritores

Adiponectina total; adiponectina de alto peso molecular; *ADIPOQ*; polimorfismo; doença arterial coronariana; diabetes melito tipo 2

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in patients with type 2 *diabetes mellitus* (T2DM) and accounts for up to 80% of deaths in patients with this disorder (1). It is believed that diabetic patients have a 3-fold higher risk

than nondiabetic individuals of developing atherosclerosis and its clinical complications, such as peripheral vascular disease, coronary artery disease (CAD) and stroke (1,2). Classical risk factors for atherosclerosis, such as central obesity, arterial hypertension, and dyslipidemia, frequently coexist with diabetes and contribute to the increased prevalence of CAD. However, T2DM remains an independent risk factor for CVD, even after adjustment for these comorbid conditions (1,3). The mechanistic links between T2DM and atherosclerosis remain largely unclear, but several metabolic dysfunctions associated with T2DM have been proposed to contribute to the acceleration of atherosclerosis (3). In this context, proteins, mainly those secreted by adipose tissue, known as adipokines (for example: adiponectin, leptin, resistin and visfatin/Nampt) and other known secretory products of adipose tissue, could play a role in the interaction of complex diseases and traits such as obesity, insulin resistance, T2DM and CVD (4-6).

Similar to many other highly prevalent diseases, T2DM and CVD are believed to be multifactorial and determined by interactions among numerous environmental factors and predisposing genes. Genome-wide associations studies (GWAS) have identified genes that influence the risk of developing both CVD and T2DM (7). The candidate gene approach has also revealed that variants of some genes that are involved in the pathophysiology T2DM and CVD are actually associated with the prevalence and incidence of these diseases (1,7).

Given that the function of adiponectin apparently modulates the pathophysiology of both T2DM and CVD (5), the coding gene *ADIPOQ* is a good candidate gene that could determine concomitant risk to both diseases (8). The investigation of this hypothesis has generated positive results, as will be discussed in this review. In addition, the area of the genome that harbors *ADIPOQ* has been identified by GWAS to be a susceptibility locus for risk of metabolic syndrome, T2DM and CVD (2). Studies have shown that *ADIPOQ* has some influence on adiponectin levels and plasma isoform levels, which are themselves related to modulation of the risk of developing T2DM and CVD (9).

The aim of this review was to provide an update about the role of the *ADIPOQ* as an independent determinant of CVD, particularly in the occurrence of hyperglycemia. In addition, we discuss recent evidence on the genetic modulation of both total and high molecular weight (HMW) adiponectin levels.

PLASMA ADIPONECTIN AS A CARDIOMETABOLIC MARKER

Experimental data suggest that adiponectin exerts a direct protective effect on the vessels, probably due to its anti-inflammatory and anti-atherosclerotic properties, having multiple favorable effects on glucose and lipid metabolism (2-5,7). Epidemiological studies demonstrate an association between lower adiponectin and the prevalence and incidence of insulin resistance, and T2DM in various populations (10). There are indications that this progression to diabetes associated with low adiponectin levels is modulated by insulin resistance (11,12). A recent meta-analysis emphasized the substantial inverse association between total plasma adiponectin levels and the incidence of T2DM, which was clearly consistent in various populations (10).

Adiponectin has a seemingly salutary influence on some phenotypes clearly associated with CVD, such as blood pressure, inflammation, lipid profile and endothelial dysfunction (5). Independent of its influence in these traditional risk factors, several cross-sectional studies of diverse populations have documented an inverse association between lower plasma levels of total adiponectin and higher prevalence of CAD (13-17). However, other cross-sectional analyses found no association between total adiponectin levels and the prevalence of CAD (18,19,21).

In addition to the cross-sectionals surveys, some large prospective studies evaluated the association between adiponectin levels and incident CAD. Several of these studies indicate an inverse correlation between adiponectin and CVD incidence (Table 1). For instance, a nested case-control study of Caucasian American men (7% T2DM) documented that higher total adiponectin levels were protective for incident CAD (14). Results were maintained in the posterior analysis of the diabetic subgroup (20). Another example of an inverse correlation between adiponectin and incident CAD is the study of older (mean age, 70 years old) Swedish Caucasians (~8% T2DM) in which baseline concentrations of adiponectin were negatively associated with CAD development (18). In a group of Caucasian Dutch women without prevalent CAD at baseline, a higher total adiponectin level was protective against the development of CAD, even after adjustment for the presence of T2DM (22). However, in the same study, the analysis that included all patients with CAD at baseline found that higher total adiponectin

levels were associated with higher mortality. In an older Caucasian Californian population (15% T2DM) (19), male subjects with higher total adiponectin levels were protected from nonfatal CAD, but higher total adiponectin was associated with increased mortality risk. Results were adjusted for glucose levels. A similar result was observed for a European population (31% T2DM) followed up for 5.4 years (15). In this cohort, higher total adiponectin was associated with higher mortality, but this association was not significant in the group that was CAD negative at baseline, even after adjustment for T2DM. Two other studies demonstrated the association of higher total adiponectin levels with worse cardiovascular outcomes in Americans (15% T2DM) (21) and Germans (85%T2DM) (23). However, there are several studies that demonstrated a neutral effect of adiponectin levels on the risk of incident CAD disease. This neutral effect was noted in several populations with different percentages of diabetic patients (15%-75%) among studied patients (13,16,24). Differences in population characteristics, statistical adjustments (especially for the presence of diabetes) and statistical power, or even analytical methods, might explain part of the apparent discrepancies between studies.

Altogether, accumulated evidence suggests that higher plasma adiponectin is a surrogate biological marker for better cardiovascular prognosis, mainly in patients with low risk of CVD. In subjects with high risk of CVD, or in those with established CAD, however, higher total adiponectin level seems to be associated with poorer prognosis (25). A possible explanation is that higher levels of adiponectin may be a physiological response to limit endothelial damage in the very early stage of the atherogenic process. In more advanced disease, however, the compensatory processes, including an increase in adiponectin levels, are often surpassed (25). Additionally, the finding of negative associations may be partly due to the preferential measurement of total adiponectin in the majority of these investigations (26-31).

Are adiponectin isoforms better cardiometabolic markers?

As mentioned above, one of the current hypotheses for the lack of consistent association between adiponectin and better overall and cardiovascular outcomes is that risk is more influenced by isoform distribution than by total adiponectin levels. Adiponectin is present in plasma in at least three homomeric complexes/isoforms, trimer, hexamer (trimer–dimer) and "high molecular weight" HMW. There is growing interest in the role of these isoforms in metabolism and disease, as research suggests that oligomeric state affects the biological activity of adiponectin (26). Lower HMW adiponectin levels have been associated with more prevalent T2DM in Japanese and Italian cohorts, and with a higher incidence of T2DM in an American cohort (26).

The epidemiological evidence of an association between adiponectin isoforms and CVD is still scarce and mostly based on the HMW isoform. A cross-sectional study that evaluated diabetic Japanese subjects demonstrated that lower HMW adiponectin levels were associated with higher prevalence of DAC (27). Severity of CAD risk was inversely associated with HMW adiponectin levels in a German population (17% T2DM) (28). In a Japanese cohort of subjects at higher risk of CVD (40% T2DM), HMW adiponectin was lower in more severe multi-vessel disease, and predicted future events after a follow-up of 7 years (29). However, HMW-adiponectin levels showed no association with secondary cardiovascular events in prospective studies in an European population (17%T2DM) (28), and in one Japanese cohort of subjects with T2DM (31) (Table 1).

Based on current evidence, it is still difficult to ascertain that plasma HMW adiponectin is a better cardiometabolic marker than total adiponectin levels. Additional prospective studies with rigorous adjustments for the traditional cardiovascular risk factors are required to better answer this question.

GENETICS OF ADIPONECTIN LEVELS

Considering that adiponectin levels are highly heritable (30%-70%), extensive research has been undertaken in the past few years to pinpoint which genes influence these levels, including *ADIPOQ* (2,5,32,33). Richards and cols. performed a genome-wide association study (GWAS) utilizing information on population-based European cohorts (total of 14,733 subjects) to identify genetic variants influencing total adiponectin levels, and found 4 single nucleotide polymorphisms (SNPs) at the *ADIPOQ* locus that demonstrated significant associations (34). Another combined analysis of GWA studies in a healthy, Caucasian Austrian population (n = 4,659) singled out the *ADIPOQ* gene region as the only genome-wide significant locus for plasma total adiponectin. In this study, intronic SNP rs17366568 (-8-387G>A) showed the strongest association and explained 3.8% of the variance in total adiponectin levels (35).

Table 1. Prospective studies evaluating the risk of CAD according to total and HMW adiponectin levels

Study	Population	T2DM	Cases	Controls	Baseline	Follow-up	
Pischon e cols.[14]	North American, men, 94% white	7%	266	532	Lower Adn in cases	6y	Higher Adn protective
Schulze e cols.[20]		100%	89	656	No association	6y	Higher Adn protective
Frystyk e cols.[18]	Swedish, white, older men	8.5%	116	716	No association after adjusting HDL	8y	Higher Adn protective
Dekker e cols.[22]	Dutch, white, 46% men	?	Quartiles of Adn 1248 probands		No association better CAD risk profile	15y	In women (no CAD at baseline): higher Adn protective Higher Adn: higher mortality in men: higher Adn less nonfatal CAD
Laughlin e cols.[19]	North American, white 55% men, older	15%	252	1100	Highest Adn quintile lower CAD No association after adjustment for HDL, Tg or metabolic syndrome)	20y	No association in women or fatal CAD higher Adn: higher mortality
Pilz e cols.[15]	European, white 52%-75% men	31%	Quartiles of Adn 3146 probands		Lower Adn in cases	5y	Higher Adn: higher mortality not significant if CAD negative at baseline
Kizer e cols.[21]	North American 20%-60% white, 47% men	15%	604	782	No association	4y	Highest quintile more CAD, especially nonfatal MI and fatal CAD
Schnabel e cols.[23]	German, white, 79% men high risk	85%	760	1130	Similar in SAP or ACS	20y	Upper quartiles of Adn: highest event-rates
Sattar e cols.[13]	Men, British, white	2%	589	1278	No association	16y	no association
Maiolino e cols.[16]	Italian, white, 72% men high CV risk	16%	Low *vs.* high Adn		Lower Adn association with atherosclerosis	4y	no association
Luc e cols.[24]	European, white, men	4%	617	1215	No association with CAD at baseline	10y	no association
Inoue e cols.[29]	Japanese, 70% men	40%	124	45	HMW-Adn lower in CAD and multivessel	7y	Higher HMW-Adn protective
Von Eynatten e cols. [28]	German, white, 85% men CHD patients	17%	95	956	Total and HMW associated to HDL-col, LDL-col and NT-proBNP	4.5y	No association of HMW-Adn
Krzyzanowska e cols.[31]	Japanese, 57% men	100%	61	86	No association with prevalent CVD	1.5y	No association of HMW-Adn

Adn: adiponectin; Controls: no incident or re-incident CAD; Cases: incident or re-incident CAD; ACS: acute coronary syndrome; SA: Stable angina.

The candidate gene approach has also corroborated the association of *ADIPOQ* gene SNPs and adiponectin levels. The SNPs most consistently associated with total adiponectin levels are the variants –11391 G/A (rs17300539) and –11377 C/G (rs266729) located in the promoter region, the synonymous +45 T/G (rs2241766) variant located in exon 2, the +276 G/T (rs1501299) SNP located in intron 2, and the +2019 single nucleotide insertion/deletion polymorphism in the 3´untranslated region (9). However, these are not the only SNPs identified by association studies. For example, Cohen and cols. (36) studied a total of 71 SNPs in *ADIPOQ*, and adiponectin-receptor genes in multiethnic women (n = 1,967). The same SNP rs17366568 identified by Heid and cols. (see above) was the only one significantly associated with serum total adiponectin levels, although only in Caucasian women.

Knowledge about the genetic determinants of adiponectin isoform levels, on the other hand, is still scarce. Menzaghi and cols. studied a family-based sample of 640 nondiabetic white Caucasians from Italy, and showed that all adiponectin isoforms are highly heritable. In addition, this study reported that the association of rs17300539 and rs1501299 with adiponectin levels is due exclusively to an effect on the HMW isoform (37).

Melistas and cols., studying 349 women without diabetes, found that carriers of the most common +45T/+276G (rs2241766/rs1501299) haplotype had

significantly lower total adiponectin levels than non-carriers, even though single SNP analysis had shown no significant associations with circulating adiponectin concentrations. A similar trend was observed for HMW adiponectin, albeit not statistically significant (38).

ALLELIC VARIATIONS IN *ADIPOQ* AND CVD

Genetic factors that influence plasma levels and function of adiponectin are good candidates to account for part of the predisposition to atherosclerosis, especially in diabetic patients (1,3). Interestingly, in some reports, these allelic associations were independent from circulating levels of adiponectin (2,7).

The region of the genome that harbors *ADIPOQ* has been identified by GWAS and by family-based studies to be a susceptibility locus for the risk for the metabolic syndrome, T2DM and CVD (32,39). Furthermore, association studies also corroborate that *ADIPOQ* variants, individually or as haplotypes, are linked to phenotypes such as obesity, high blood pressure, dyslipidemia, T2DM and CVD (8,32,38,40,42,43).

Of interest is the fact that the vast majority of *ADIPOQ* SNPs that have been implicated in these phenotypes are either located in non-coding regions or are synonymous variants, and that the variants associated with alterations in adiponectin levels are not consistently associated with CVD risk. Therefore, the causative role these SNPs play in influencing CVD might be due to a direct effect on adiponectin levels, but more probably by modulation in other systems directly or indirectly involved in CVD in diabetic subjects (37).

There are three SNPs in *ADIPOQ* that have been more extensively studied and show more consistent evidence of association with CAD: rs266729 (-11377C>G), rs2241766 (+45T>G), and rs1501299 (+276G>T). For that reason, they will be approached separately in the following section (Figure 1).

rs266729 (-11377C>G)

SNP rs266729 is located in the promoter region of ADIPOQ, in the first linkage disequilibrium (LD) block, and consists of a C>G substitution in the -11377 position (or -11365, depending on the reference sequence employed). This SNP is in LD with other two polymorphisms in the promoter region (rs16861194 [-11426 A/G] and rs17300539 [-11391 A/G]), and their haplotypes seems to affect promoter activity (39). In cohorts of 162 French and Swiss type 2 diabetic patients and 315 normal controls, Lacquemant and cols. found no association between CVD and rs266729, individually. However, haplotype analyses showed the combination of five SNPs in wild-type alleles (rs266729 -11377C>G, -4041A>C, rs2241766 +45T>G, rs1501299 +276G>T, +349A>G, +2019delA) in the decrease in CAD risk, even after adjustment (OR: 0.5; 95% CI: 0.3–0.7; p= 0.0006) (40).

Qi and cols. (42) studied 239 CVD cases in diabetic American men (defined as new cases of fatal and nonfatal CAD, and fatal and nonfatal stroke) and 640 control subjects. No association between -11377C>G (termed -11365C>G in this study) with CVD was observed, either alone or in haplotype analyses. The addition of plasma adiponectin, lipids, and inflammatory markers to the model did not appreciably change the results, and similar association was observed if the outcome was restricted to CAD, excluding the stroke cases. Soon after that, the same authors published their investigation of associations between these SNPs and adiponectin levels and CVD risk in a cohort of American diabetic women including 285 cases and 704 controls (43). Those GG homozygotes in rs266729 had significantly decreased plasma total adiponectin levels, compared with C-allele carriers, but no association with CVD was demonstrated. In a nested case-control of Caucasian American men, rs266729 polymorphism was not associated with the incidence of MI, although the minor allele was associated with lower incidence of stroke (44), even after adjustment for the presence of T2DM (5% of subjects). Pischon and cols. (45) analyzed rs266729 in two parallel studies of American men and women (on the whole, 8.4% subjects with T2DM). The major C-allele SNP rs266729 was associated with an increased number of coronary artery bypass grafts (CABG) or percutaneous transluminal coronary angioplasties (PTCA), only in men, even after adjustment for T2DM. Also in 2007, Gable and cols. (46) published data on the prospective risk of T2DM and CAD in a Caucasian European population, and found that the minor G allele of rs266729 was associated to an increased risk of MI, but not with an increased risk of T2DM. Chiodini and cols. (47) found no association between rs266729 and the risk of myocardial infarction (MI) and T2DM in 2008 Italian subjects. Persson and cols. (17) studied 244 pairs of Swedish young survivors of MI (age < 60 years old; 10% T2DM) and age-matched normal controls. The minor G allele of rs266729 was associated with lower total adiponectin levels, but not with MI.

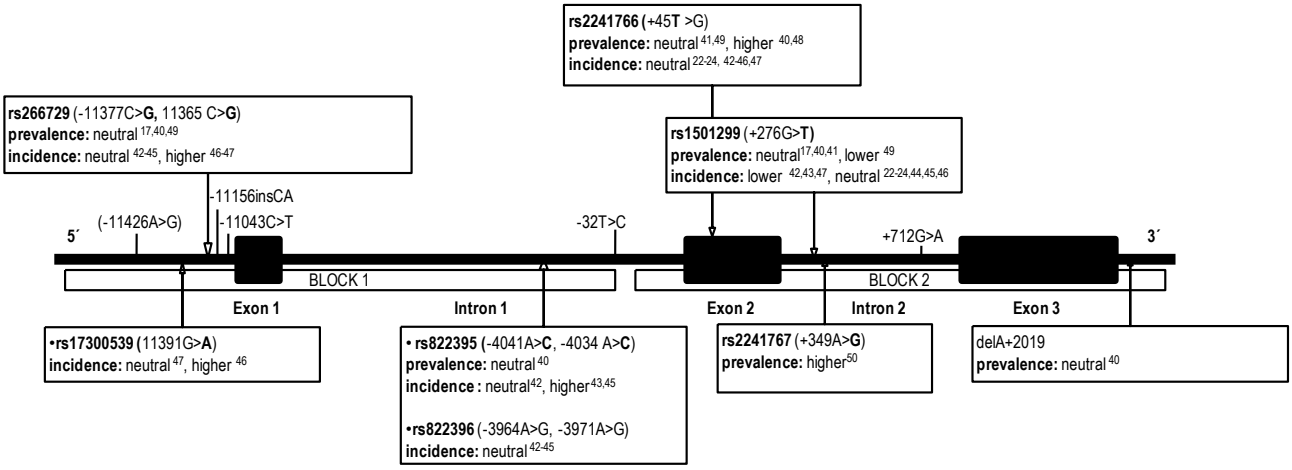

Illustration of the *ADIPOQ* gene comprising 3 exons and 2 introns, focusing on SNPs associated with CAD described in the text, and their relative positions in regard to the two linkage disequilibrium blocks. The associations that refer to the allele are in bold type. The percentage of diabetic patients in each study is described in the text. Two notations are given for rs266729, rs822395 and rs822396 because they have been thus described in the literature.

Figure 1. Variants of ADIPOQ associated with CAD.

Therefore, based on current published evidence, we concluded that the effect rs266729 might have in modulating CAD disease risk is limited or slightly protective, even in T2DM subjects.

rs2241766 (+45T>G)

Among the several common genetic variations of the *ADIPOQ* gene, the rs2241766 in exon 2 has been one of the most extensively studied. This +45T >G base change is a synonymous mutation (GGT → GGG, Gly → Gly), although higher mRNA expression in adipose tissue and higher circulating total adiponectin levels have been observed in G-allele carriers. Besides this potential biological basis for the protective effect of this silent variant, it is located in the second LD block of *ADIPOQ* and might possibly be in LD with the functional and causal polymorphism (32).

A positive association between the major T allele of rs2241766 and CAD was observed in the two cohorts of French and Swiss T2DM patients described above (40), with OR of 2.0 (95% CI: 1.3-3.2; p = 0.02), and this association was independent of other traditional risk factors. No association was observed individually with the other SNPs studied. A similar result was observed for Chinese subjects diagnosed with CAD by coronary angiography (600 patients), compared with 718 non-CAD controls (48). The minor G rs2241766 allele had a protective association with CAD, with an OR 0.75 for each copy, after adjustment for classical risk factors not including diabetes, only adjusted for glucose levels. Moreover, there was an interaction between this SNP and blood pressure and total cholesterol levels. Many other studies found no association between rs2241766 variation and CAD across various populations including different percentages of diabetic subjects (22-24).

Taken together, these studies suggest that the rs2241766 has either no influence on CAD risk or confers greater risk of CAD in some populations.

rs1501299 (+276G>T)

This intronic SNP is unlikely to be itself the functional variant and it is most probably a marker in LD with another functional SNP (32). Lacquemant and cols. found a protective association between +276G>T and CAD only in haplotype analyses, as described above (40).

Bacci and cols. investigated diabetic Italian subjects. Cases consisted of 142 patients with CAD (previous myocardial infarction or stenosis > 50% at coronary angiography). Control subjects (n = 234) were asymptomatic patients with negative resting or exercise ECG and/or coronary stenosis < 50% at angiography. A significant association with CAD was observed in TT homozygotes presenting lower risk of CAD, compared with carriers of other genotypes (OR of 0.13; 95% CI: 0.037-0.46, p = 0.002, after adjusting for potential confounders such as age, sex, duration of diabetes, smoking, HbA1c, lipid levels, systolic and diastolic blood pressure, antihypertensive and antidyslipidemic treatments, insulin therapy, and adiponectin levels) (49).

As described above, a large prospective cohort of diabetic men (42) showed a significant association between TT homozygotes and lower risk of CVD risk, compared with carriers of other genotypes (OR of 0.38; 95% CI: 0.18-0.79, p = 0.009, after appropriate adjustments). The addition of plasma total adiponectin, lipids, and inflammatory markers to the model did not appreciably change the results, even when the outcome was restricted to CAD, excluding stroke cases. No associations were observed with the other SNPs or in haplotype analysis. The study of diabetic women by the same authors (43) found that the haplotypes of 5 common SNPs that possessed the allele T were also associated with significantly lower CVD risk than the haplotype of wild-type alleles (OR of 0.70; 95%CI: 0.50-0.98, p = 0.039). Pischon and cols. demonstrated reduced risk of non-fatal MI or fatal CAD in male carriers of the T allele of rs1501299 in American men and women (8.4% T2DM) (45). Chiodini and cols. (47) found a protective effect of TT homozygosis for +276G>T on myocardial infarction alone (OR = 0.58, p = 0.01), and on MI in association with T2DM (OR = 0.55, p = 0.006) when compared with carriers of the G allele. A meta-analysis of five studies performed with the results of rs1501299 SNP suggested that T-allele homozygosity was associated with an approximate 45% reduction in CVD risk (43).

Therefore, the presence of the T allele of this intronic SNP shows the most consistent association with CVD and is apparently related to a reduction in risk.

Other SNPs

Many other SNPs have been studied less often. The diabetic patients studied by Lacquemant and cols. showed no association between -4041A>C, +349A>G, and +2019delA and CAD or metabolic syndrome components (40). Chiodini and cols. (47) found no association of rs17300539 (-11391G>A) with the risk of myocardial infarction and T2DM in Italian subjects. Ohashi and cols. studied British women (5%T2DM) and observed an increased frequency of the +517T>C (Ile-164Thr) heterozygosity in CAD cases, compared with control British women (2.9% *vs.* 0.8%, p < 0.05) (41).

The rs822395 (-4034A>C) variant was associated with increased cardiovascular risk in a recessive model in American diabetic women (43). Also, in the female subgroup of American subjects, association between rs822395 (-4034A>C) and risk of non-fatal MI or fatal CAD was demonstrated (45). Moreover, GG homozygosity for rs822396 (-3964A>G) was associated with the same outcomes (45).

Wassel and cols. (50) studied the association between 11 *ADIPOQ* SNPs and common and internal carotid intima media thickness (cIMT), and coronary artery calcification (CAC) in 2847 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) (~25% with T2DM). In African Americans, genotypes AG/GG of rs2241767 were associated with 36% greater CAC prevalence and larger common cIMT (P = 0.0043). Genotypes AG/AA of rs1063537 were associated with 35% greater CAC prevalence. In Hispanics, the AA genotype of rs11711353 presented 37% greater CAC prevalence compared with the GG genotype. No SNP was associated with subclinical CVD phenotypes in Chinese or Caucasian participants.

Accumulated data suggest that genetic variants of the *ADIPOQ* might have an influence in the genetic predisposition to CAD in some populations. As mentioned above, some studies demonstrated that allele associations with disease phenotypes seem to be independent of circulating levels of adiponectin, which indicate an independent effect of *ADIPOQ* on CAD risk determination and evolution. Furthermore, evidence of the modulation on CAD risk by *ADIPOQ* are not robust and ubiquitous. Absence of consensus in the various studies could be, in part, due to different study power, design and tested outcomes, and because of genetic differences in the populations studied.

CONCLUSIONS

The causes and mechanisms of the increased cardiovascular risk observed in patients with diabetes are still largely unexplained. The increased risk does not seem to be solely dependent on the effects of hyperglycemia on the vessels (3). It is proposed that a common genetic background shared by disorders of glucose homeostasis and atherosclerosis might heighten the risk of atherosclerosis, even in the absence of hyperglycemia (1,7). Among the candidate genes that could fit this common risk hypothesis is *ADIPOQ*. We emphasize that the available evidence implicates both *ADIPOQ* variants and adiponectin circulating levels in the progression of CAD in patients with hyperglycemia, and that these associations probably exist in an independent manner, even if part of the genetic regulation of circulating adiponectin levels is determined by *ADIPOQ* (2,51).

It is important to take into consideration, when analyzing these studies, that adiponectin levels may reflect a dynamic process. Moreover, adiponectin circulates in a wide range of full-length and globular multimers that need to be properly quantified in future studies.

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