Adiponectin Gene and Cardiovascular Risk in Type 2 Diabetic Patients: A Review of Evidences

ABSTRACT

Diabetic patients have a 3-fold higher risk of developing atherosclerosis and its clinical complications as compared to non-diabetic individuals. Part of the cardiovascular risk associated with diabetes is probably due to genetic determinants influencing both glucose homeostasis and the development of atherosclerosis. However, type 2 diabetes frequently coexists with other cardiovascular risk factors like arterial hypertension, central obesity and dyslipidemia. Genetic variability affecting many areas such as lipid and energy metabolisms, hypertension and haemodynamic mechanisms, blood clotting homeostasis, inflammation, and matrix turnover in the vascular wall will have an impact on the development of macrovascular complications in diabetic patients. Adiponectin is abundantly secreted by adipocytes. It plays important roles in lipid and glucose metabolisms and has direct anti-inflammatory and anti-atherogenic effects. In this review, we summarize recent data from the literature suggesting an implication of allelic variations of the adiponectin gene (*ADIPOQ*) in the genetic determinants of cardiovascular disease in diabetic subjects. **(Arq Bras Endocrinol Metab 2007;51/2:153-159)**

Keywords: Genetics; Adiponectin; Macrovascular disease

RESUMO

O Gene da Adiponectina e o Risco Cardiovascular em Pacientes com Diabetes Tipo 2: Uma Revisão das Evidiencias.
Os pacientes com diabetes apresentam risco três vezes maior de desenvolverem aterosclerose e suas complicações quando comparados a indivíduos sem hiperglicemia. Parte desse risco associado ao diabetes é provavelmente relacionado a determinantes genéticos que influenciam tanto a homeostase glicídica quanto o desenvolvimento da aterosclerose. Entretanto, o diabetes tipo 2 freqüentemente coexiste com outros fatores de risco cardiovascular, tais como hipertensão arterial, obesidade central e dislipidemia. A variabilidade genética interfere em várias áreas tais como o metabolismo lipídico, o metabolismo energético, hipertensão, mecanismos hemodinâmicos, mecanismos de coagulação, inflamação e na formação da matriz na parede vascular, que podem estar envolvidos nas complicações macrovasculares dos pacientes com diabetes. A adiponectina é secretada com abundância pelos adipócitos. Apresenta importante papel no metabolismo lipídico e glicídico, tendo ação direta tanto antiinflamatória quanto anti-aterogênica. Na atual revisão, nós resumimos os dados recentes da literatura que sugerem uma implicação de variantes alélicas do gene da adiponectina (*ADIPOQ*) que podem estar envolvidos na determinação genética da doença cardiovascular em indivíduos com diabetes. **(Arq Bras Endocrinol Metab 2007;51/2:153-159)**

Descritores: Genética; Adiponectina; Doença macrovascular

revisão

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CARDIOVASCULAR DISEASE (CVD) is the leading cause of mortality and morbidity in patients with diabetes. As compared to non-diabetic individuals, diabetic patients have a 3-fold higher risk of developing atherosclerosis and its clinical complications such as stroke, myocardial infarction, and peripheral vascular disease (1). Atherosclerosis is a complex inflammatory disease of large arteries in which the interaction of immune, metabolic and haemodynamic mechanisms results in asymmetric focal thickenings of the intima by the accumulation of lipids, connective-tissue elements, cells and debris (2,3). The atheroma lesion starts with the accumulation and entrapment in the intima matrix of apolipoprotein B-containing lipoproteins, namely VLDL/LDL and Lp(a). These lipoproteins undergo lipid oxidation and other modifications, by interaction with cellular oxidative waste and various enzymes, resulting in LDL particles that have pro-inflammatory properties. They are able to induce the production of adhesion molecules, chemokines, and growth factors by the overlying endothelial cells, which results in the recruitment to the vessel wall of monocytes and lymphocytes. Monocytes proliferate and differentiate into macrophages that take up the modified LDL. These cholesterol-engorged "foam cells" eventually undergo necrosis or apoptosis, contributing their contents to a necrotic core of lipids and cell debris. HDL particles protect against atherosclerosis by inhibiting lipid oxidation of LDL and by promoting cholesterol efflux from macrophages, while lymphocytes contribute to lesion development by the production of cytokines and immunoglobulins. Eventually, smooth muscle cells migrate from the media layer and proliferate. They secrete the collagen that forms a fibrous cap overlying the necrotic core of the lesion. Myocardial infarction and stroke are usually caused by rupture or erosion of the atheroma lesion, leading to the formation of a thrombus that result in acute stenosis of the vessel. Mechanisms of atheroma stability and of the haemostatic cascade are likely to modulate the clinical outcome.

Atherosclerosis-related CVD involves thus a large number of pathophysiological processes in many different cell types and organs (3), and an increasing list of risk factors influenced both by genetic and environmental determinants have been identified (3). Classical risk factors like arterial hypertension, central obesity and dyslipidemia frequently coexist with diabetes and contribute to the increased prevalence of CVD in diabetic patients. However, type 2 diabetes seems to be an independent risk factor for CVD (4). The molecular mechanisms linking type 2 diabetes and accelerated atherosclerosis remain unclear (5). Several metabolic dysfunctions associated with type 2 diabetes have been proposed to play a role in atherosclerosis, including hyperglycaemia, formation of advanced glycation end-products, hyperinsulinemia, endothelial dysfunction, platelet hyperaggregability, coagulation abnormalities, increased oxidative stress and chronic inflammation (5).

Family history is a major risk factor for CVD (6), and both mendelian and complex inheritance are involved in the familial clustering of the trait. Monogenic defects leading to accelerated atherosclerosis have been described (3), but they only account for a small percentage of patients with CVD. In most cases, atherosclerosis is a multifactorial disorder resulting form the simultaneous action of many unfavourable alleles interacting with environmental determinants. Studies in rodents suggest that as many as 100 genes can influence the development of atherosclerotic lesions (3,7).

Several recent studies (8-11), as well as many abstracts presented in Diabetes meetings (12-16), reported associations of variants in the *ADIPOQ* gene encoding adiponectin with CVD in type 2 diabetic patients. These studies differed greatly in sample size, power and tested CVD outcome, and not many fulfilled ideal criteria for the design of association studies (17), notably regarding sample size. Allelic associations of these *ADIPOQ* variants with obesity, insulin resistance and type 2 diabetes have been reported previously in many populations (18-20).

The aim of this review was to evaluate the literature published over 2004–2006 on the role of adiponectin in the genetic determinants of macrovascular complications in diabetic subjects. In the first part of the review, an introduction on the basic mechanisms of action of adiponectin associated with cardiovascular protection will be presented.

ADIPONECTIN IMPLICATION IN THE PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE

Adiponectin is a 244 amino acid protein containing a collagen like fibrous domain and a globular C1q-like C-terminal domain, and which is abundantly secreted by adipocytes. Adiponectin, also previously called Acrp30, apM1, GBP28, or AdipoQ, has structural homology with collagens VIII and X, complement factor C1q, and the TNF family. The protein form the basic unit of a trimer, which self-associates to form hexamers then multimers of high molecular

weight. These heavier forms seem to be the most active ones in relation to insulin sensitivity (21). Moreover, adiponectin circulates as a full-length protein as well as a proteolytic cleavage fragment consisting of the globular C-terminal domain that might have increased potency (22). Two adiponectin receptors named AdipoR1 and AdipoR2 have been identified (23). AdipoR1 is preferentially expressed in muscle as high-affinity receptor for globular adiponectin and low affinity for full-length adiponectin, whereas AdipoR2 is abundantly found in the liver and serves as intermediate-affinity receptors for both forms of adiponectin. The major role of adiponectin in lipid and glucose metabolisms can be explained by activation of AMP-activated protein kinase (AMPK) and stimulation of PPARα, which lead to increased glucose uptake and oxidation of fatty acids in skeletal muscle and decreased hepatic glucose output (24).

Adiponectin has many protective actions in the initiation and progression of atherosclerosis by means of direct anti-inflammatory and anti-atherogenic effects. It modulates the inflammatory response of endothelial cells to oxidized LDL and the activation of monocytes and macrophages by inhibiting TNFα induced monocyte adhesion and the expression of endothelial leukocyte adhesion molecule 1 (E selectin), vascular cell adhesion molecule-1 (VCAM1) and intracellular adhesion molecule-1 (ICAM1) in endothelial cells (25). Adiponectin inhibits the transformation from macrophages to foam cells by decreasing the expression of class-A macrophage scavenger receptor (26) and acyl-coenzyme A cholesterol acyltransferase-1 (ACAT-1) (27). It also inhibits proliferation and migration of smooth muscle cells and stimulates the production of nitric oxide (NO) in endothelial cells. Moreover, serum adiponectin levels are positively associated with both endothelium-dependent and endothelium-independent arterial vasodilatation. Recent results suggest that it also might have direct protective effects against ischemia in the heart. Adiponectin-KO mice submitted to surgical induction of ischemia and reperfusion had increased myocardial infarct size, myocardial apoptosis and TNFα production compared with wild-type mice submitted to the same procedure (28). Administration of adiponectin diminished infarct size, apoptosis and TNFα production in both groups of animal. These effects were mediated in cardiac cells by the activation of AMPK signaling and by cycloxygenase 2 (COX2) dependent production of prostaglandin E2.

ADIPONECTIN LEVELS AND CARDIOVASCULAR DISEASE

Plasma levels of adiponectin are significantly decreased in obese patients, and negatively correlated with BMI (29). Type 2 diabetic patients have lower plasma adiponectin concentrations than non-diabetic subjects, independently of BMI (30). In many studies, plasma levels of adiponectin were found to be lower in patients with coronary artery disease (CAD) than in age and BMI adjusted control subjects. Hypoadiponectinemia defined by the 25th percentile was associated with a 2-fold increase in CAD prevalence in male subjects, after adjustments for other risk factors (31). Even in type 2 diabetic patients, those with CAD have lower adiponectin levels than those without CAD. Although adiponectin levels are increased in type 1 diabetic patients and in patients with end-stage renal disease, hypoadiponectinemia is an independent predictor of cardiovascular events in these patients (32). In a prospective study, men with high plasma adiponectin levels without previous CVD had lower risk of myocardial infarction than those with medium or low levels (33). In type 2 diabetic men from the same cohort, adiponectin was associated with a decreased risk for CAD events (myocardial infarction and coronary artery bypass surgery), this association being mediated in part by effects of adiponectin on HDL cholesterol levels (34). It has also been suggested that low adiponectin levels are related to impaired catabolism of VLDL-apoB particles, which increases the dyslipidemic effect of insulin resistance resulting mainly in increased hepatic production of VLDL-ApoB (35). However, a prospective case-control study failed to demonstrate similar effects on CAD events in women, despite adequate statistical power and though associations with CVD risk factors were found (36). Recently, a large prospective study in men could not confirm the strong associations previously reported between adiponectin levels and CAD (37), and a meta-analysis of seven studies suggested only a moderate association (37). Moreover, in another study in men with CAD, a paradoxical effect was observed, as higher adiponectin levels were an independent predictor of both all-cause mortality and cardiac mortality (38).

ALLELIC VARIATIONS IN THE ADIPONECTIN GENE (ADIPOQ) AND CARDIOVASCULAR DISEASE

An increasing body of data suggests associations of *ADIPOQ* variants with CVD in diabetic patients. Lacquemant and co-workers investigated associations with

CAD of five SNPs (-11377C>G, -4041A>C, +45T>G, +276G>T, +349A>G, +2019delA) in cohorts of French and Swiss type 2 diabetic patients (9). Cases consisted of 162 patients with CAD, defined by transmural myocardial infarction or positive coronary angiography performed because of clinical angina or abnormal resting electrocardiogram. The criteria of positivity for the coronary angiography were not given. Controls consisted of 315 subjects with no history of angina pectoris and a normal resting electrocardiogram. An association between the +45T>G SNP and CAD was observed in both cohorts separately, as well as when the two groups were pooled. GG homozygotes and GT heterozygotes combined presented an increased risk of CAD as compared to TT homozygotes (OR: 2.0; 95% CI: 1.3–3.2; p= 0.02), and this association was independent from other risk-factors such as age, sex, BMI, duration of diabetes, smoking, arterial hypertension, triglycerides and HDL-cholesterol levels. No association was observed individually with the other SNPs. However, haplotype analyses showed the combination of the five SNPs wild-type alleles to decrease CAD risk (OR: 0.5; 95% CI: 0.3–0.7; p= 0.0006). Interestingly, in that study, no association was observed between the SNPs and components of the metabolic syndrome (BMI, blood pressure, HDL-cholesterol and triglycerides).

Bacci and co-workers investigated the possible role of two frequent SNPs (+45T>G and +276G>T) as genetic markers of CAD in a cohort of Italian type 2 diabetic patients (8). Cases consisted of 142 patients with CAD, defined either by previous myocardial infarction or by the presence of a 50% reduction in diameter of at least one major vessel at coronary angiography. Control subjects consisted of 234 patients who had no symptoms and no ECG signs of myocardial ischemia and a normal exercise ECG test and/or coronary stenosis of less than 50% at angiography. In those controls, screening of CAD had been indicated because of the presence of peripheral vascular disease and/or more than two cardiovascular risk factors. A significant association with CAD was observed for the +276G>T SNP, with TT homozygotes presenting a lower risk of CAD as compared to 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). No association with CAD was observed for the +45T>G SNP.

Ohashi and colleagues examined associations of the frequent +45T>G and +276G>T SNPs and of the less frequent +517T>C (Ile164Thr) missense polymorphism with CAD in a cohort of Japanese subjects (10). Cases consisted of 383 patients with CAD, defined by the presence of a 75% stenosis of at least one segment of a major coronary artery confirmed by coronary angiography. The controls consisted of 368 subjects, matched for age and sex with cases, with no history of angina or other atherosclerotic vascular diseases, and normal exercise electrocardiogram stress testing. This study was not restricted to subjects with diabetes, but diabetic subjects represented 48% of cases and 10% of controls. Subjects with CAD had lower plasma levels of adiponectin as compared to controls. The authors observed an increased frequency of Ile-Thr heterozygosity at codon 164 in CAD cases as compared to controls (2.9% vs. 0.8%, p< 0.05). No Thr homozygotes were found. Of note, adiponectin plasma levels in Thr-allele carriers were half as much lower than in wild-type subjects. No differences in the genotype frequencies of the other SNPs were observed between the two groups.

Similar results were observed in larger prospective studies. Associations of five SNPs (-11365C>G, -4034A>C, -3964A>G, +45T>G, +276G>T) with CVD risk were examined in a prospective cohort of diabetic men (11), including 239 CVD cases and 640 control subjects. CVD consisted of new cases of fatal coronary heart disease, nonfatal myocardial infarction, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, fatal stroke, and nonfatal stroke that had occurred between 1986 and 2000. Diagnoses of myocardial infarction were confirmed by reviewing medical records for symptoms plus typical EKG changes, elevated levels of cardiac enzymes and/or autopsy findings. Diagnosis of stroke was confirmed by reviewing medical records and required evidence of a neurological deficit with sudden or rapid onset that persists for more than 24 h or until death. Individuals with CVD were older and more likely to have a history of hypertension or hypercholesterolemia than the control subjects. Mean plasma adiponectin levels were comparable between the two groups. Here again, a significant association with CVD was observed for the +276G>T SNP, with TT homozygotes presenting a lower risk of CVD as compared to carriers of other genotypes (OR of 0.38; 95% CI: 0.18–0.79, p= 0.009, after adjusting for age, BMI, smoking, alcohol consumption, physical activity, aspirin use, HbA1c, and history of hypertension or hypercholesterolemia). The addition of plasma adiponectin, lipids, and inflam-

matory markers to the model did not appreciably change the results, and similar association was observed if the outcome was restricted to CAD, with stroke cases excluded. No associations were observed with the other SNPs or in haplotype analysis.

More recently, the same authors have also investigated associations of these SNPs with adiponectin levels and CVD risk in a cohort of diabetic women (the Nurses' Health Study) including 285 cases and 704 controls (39). CVD was defined as in the previous study, plus cases of sudden death. GG homozygotes for the -11365C>G polymorphism presented significantly decreased plasma adiponectin levels as compared to C-allele carriers. The -4034A>C variant was associated with increased cardiovascular risk under a recessive mode (OR of 1.62 for C-allele homozygosity; 95% CI: 1.07–2.45, p< 0.02). The association did not appreciably change after adjustment for age, BMI, smoking, alcohol consumption, physical activity, HbA1c, history of hypertension and hypercholesterolemia, diabetes duration, and postmenopausal hormone use. The haplotype analysis indicated that a common haplotype possessing the allele T of the +276G>T was associated with a significantly lower CVD risk than the most common haplotype (OR of 0.70; 95%CI: 0.50–0.98, p= 0.039). A meta-analysis of five studies performed with the results of +276G>T variant suggested that T-allele homozygosity was associated with an ~45% reduction in CVD risk (39).

Other studies from China, France, Korea, Poland and the UK were presented in Diabetes meetings and confirmed associations of the -1191G>A, +45T>G and -276G>T SNPs with CAD or CVD in diabetic patients from different populations (12-16,40). These associations with CAD or CVD were also confirmed in cohorts composed for a large part of non-diabetic subjects (41-43).

CONCLUSIONS

This review on the genetics of CVD had a limited scope, focusing only on recently published association studies of the gene encoding adiponectin (*ADIPOQ*) in patients with diabetes. Selected studies with other candidate genes were reviewed elsewhere (44). It is clear from studies in the general population that genetic variability affecting many areas such as lipid and energy metabolisms, hypertension and haemodynamic mechanisms, blood clotting homeostasis, inflammation, and matrix turnover in the vascular wall have an impact on cardiovascular risk (2,3,45). This increasing list of processes, each involving a large number of genes and proteins, illustrates the difficulty of approaching the genetics of CVD. Moreover, the lack of easily accessible intermediate phenotypes for many candidate genes makes more difficult their evaluation.

The causes and mechanisms of the increased cardiovascular risk observed in patients with diabetes are still unclear (5). The genetic factors associated with macrovascular complications of diabetes are deemed to be substantially the same as those associated with atherosclerosis and its clinical complications in non-diabetic subjects. Acceleration of atherosclerosis would be due to processes resulting from insulin deficiency, defective insulin action, and hyperglycaemia or associated metabolic defects. However, it is also possible that part of the cardiovascular risk associated with diabetes is due to genetic determinants influencing both glucose homeostasis and the development of atherosclerosis. There is an increasing body of evidence that this is indeed the case for adiponectin, even if the genetic mechanism behind the associations of these silent or intronic SNPs in the *ADIPOQ* gene with diabetes and/or CVD remains unexplained. Linkage disequilibrium with a functional mutation located elsewhere in the *ADIPOQ* gene is a possible explanation. Different SNPs are associated with different diabetes-related or atherosclerosis-related phenotypes in different populations, suggesting variable degrees of linkage disequilibrium of the SNPs with the putative functional variant. The biology underlying these allelic associations is also currently unknown. A genotype-related effect on serum adiponectin levels is not consistently observed, and in some studies, associations with diabetes or CVD are independent of serum adiponectin levels (8,11,20). It is noteworthy that present adiponectin levels as reported in theses studies might not be good indicators of levels when atherosclerosis started to develop. Variation of adiponectin levels over time with age and the effect of diabetes upon this variation are unknown. Regarding atherosclerosis, it is also unclear whether adiponectin levels in the vascular wall reflects serum concentrations, or if does not, whether there is a genotype-related effect. Moreover, adiponectin circulates in a wide range of full-length and globular multimers that need to be properly quantified. All these questions are waiting for further investigations.

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