Adiponectin gene variants, adiponectin isoforms and cardiometabolic risk in type 2 diabetic patients

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ABSTRACT
Aims/Introduction: The aim of the present study was to examine the associations of rs2241766 (+45T>G), rs1501299 (+276G>T), rs17300539 (−11391G>A) and rs182052 (−10069G>A) in the adiponectin (Ad) gene with adiponectin concentrations, and concomitantly the association of these variants with cardiometabolic risk in type 2 diabetic patients of African ancestry.

Materials and Methods: A cross-sectional study of 200 patients was carried out. Concentrations of total, high (HMW), middle (MMW) and low (LMW) molecular weight adiponectin isoforms were measured. The four polymorphisms were genotyped.

Results: Decreased values were noted for total Ad in overweight, dyslipidemia and coronary artery disease (CAD), for HMW in overweight and dyslipidemia, for MMW in CAD, for LMW in dyslipidemia and CAD, for the percentage HMW/total in overweight, and for MMW:HMW ratio in patients without hypertriglyceridemic waist (HTGW). Significant associations were noted between total Ad, HMW, and HMW/total Ad and rs182052 under an dominant model (P = 0.04, P = 0.03 and P = 0.04, respectively), and between MMW and rs17300539 (P = 0.006). No significant difference in adiponectin concentrations was noted according to rs2241766 and rs1501299 genotypes. Patients carrying the rs2241766 Ga l l e l e (TG+GG) had an increased risk of HTGW (odds ratio [OR] 3.1; P = 0.04) and of CAD (OR 3.3; P = 0.01). The odds of having low total adiponectin concentrations (<25th percentile: 3.49 ng/mL) for carrying the rs182052A allele (AA+GA) was: OR 0.40; P = 0.009. The single-nucleotide polymorphism associated with adiponectin levels was not concomitantly associated with cardiometabolic risk factors.

Conclusions: Adiponectin concentrations and ADIPOQ variants are implicated in the pathophysiological process leading to cardiovascular diseases, but the genetic effects seem to be independent of adiponectin concentrations in our Afro–Caribbean diabetic patients.

INTRODUCTION
Adiponectin (Ad), an adipose tissue-derived peptide, is a determinant of insulin sensitivity that exerts anti-inflammatory and anti-atherogenic effects1. Decreased plasma Ad levels are associated with type 2 diabetes mellitus2 and arteriosclerosis3–5. Ad circulates in human blood in multiple isoforms: high (HMW), middle (MMW) and low (LMW) molecular weight forms6. There is no consensus about the clinical or biological relevance of these forms, although HMW is considered the
main determinant of insulin sensitivity. In addition, in type 2 diabetic patients, agents such as thiazolidinediones or pioglitazone could preferentially modify levels of certain isoforms.

Inconsistent results have been reported on the association between adiponectin concentrations and coronary artery disease (CAD), especially when the multimeric forms were evaluated. Thus, in a recent report, total Ad and LMW levels were not associated with myocardial infarction in non-diabetic men, whereas the MMW:HMW ratio correlated with incident myocardial infarction.

The Ad-encoding gene, ADIPOQ, is located on chromosome 3q27 within a region linked to type 2 diabetes mellitus, metabolic syndrome and CAD. Several single-nucleotide polymorphisms (SNPs) have been identified, and genetic associations have been reported between these SNPs and insulin resistance, type 2 diabetes, and adiponectin levels in cross-sectional or prospective studies and in different populations. Association studies between ADIPOQ SNPs and CAD also provided inconsistent results, but a recent meta-analysis showed that the associations between rs2241766 (+45T>G) and rs1501299 (+276G>T) in the ADIPOQ gene and cardiovascular disease were significant but weak, and that studies are still required to confirm these associations.

In our previous study in Afro-Caribbean patients with type 2 diabetes, rs2241766 was associated with CAD under a dominant model, as in Caucasian patients. Studies on rs17300539 (−11391G>A) and rs182052 (−10069G>A) are scarce, particularly in type 2 diabetes mellitus patients and in individuals of African descent. We made the assumption that there is a concomitant relationship between the following three parameters: (i) ADIPOQ variants; (ii) adiponectin concentrations; and (iii) risk factors; and we aimed in the present study to examine the associations of rs2241766 (+45T>G), rs1501299 (+276G>T), rs17300539 (−11391G>A) and rs182052 (−10069G>A) in the ADIPOQ gene with Ad isoforms, and concomitantly the association of these variants with cardiometabolic risk factors in Caribbean type 2 diabetic patients of African ancestry.

METHODS

In a cross-sectional study carried out in the French West Indies University Hospitals, we studied 200 volunteers with type 2 diabetes from the Departments of Cardiology and Endocrinology. The ethnic origin was defined by whether the patient defined him/herself as Afro-Caribbean. The exclusion criteria included previous history of kidney or inflammatory disease, pregnant women, patients treated with thiazolidinediones or pioglitazone and those of another ethnic background. The protocol was approved by the ethical committee. All participants gave their written informed consent. Data were collected between 2007 and 2009.

The individuals were interviewed by physicians using a standard questionnaire that provided information on age, sex, history of cardiovascular diseases and use of antihypertensive, antidiabetic or lipid-lowering treatments. Height and weight were measured with participants standing without shoes and lightly clothed. Body mass index was calculated as weight divided by height squared (kg/m²). These measurements were made by trained nurses and physicians. Blood pressure was measured according to a standardized protocol with an automatic sphygmomanometer. The retained values were the average of two or more readings. Blood samples were obtained from participants after overnight fasting. Plasma cholesterol and triglyceride concentrations were measured by enzymatic method (Boehringer–Mennheim). All usual blood analyses were carried out with standardized programs.

Circulating total and multimers (HMW, MMM and LMW) Ad concentrations were measured using an enzyme-linked immunosorbent assay kit (ALPCO-Bühlmann, Mulhouse, France). Treatment with two different proteases enabled the selective determination of HMW and HMW plus MMW, in addition to total Ad concentrations. The concentrations of MMW and LMW isoforms were then calculated by subtraction. This method has been validated against western blot analysis, and was used previously. The percentage of HMW adiponectin to total adiponectin (HMW:total Ad) and the MMW:HMW ratio were calculated.

Genotyping

Genomic deoxyribonucleic acid was extracted from peripheral white blood cells by standard methods and stored at −20°C until analysis. Genotyping of the study population was carried out using a TaqMan allelic discrimination assay on an ABI PRISM 7000 sequence detector according to the manufacturer’s instructions (Applied Biosystems, Foster City, CA, USA). The conditions for TaqMan reaction were as follows: 50°C for 2 min, 95°C for 10 min, and 54 cycles of 95°C for 15 s and 60°C for 1 min. This method achieved a successful genotyping rate >95%.

Four SNPs were genotyped rs2241766 (+45T>G), rs1501299 (+276G>T), rs17300539 (−11391G>A) and rs182052 (−10069G>A) of the ADIPOQ gene.

These polymorphisms were chosen because of different arguments from the literature: rs2241766 (+45T>G) and rs1501299 (+276G>T) are the most cited regarding the cardiovascular risk, the rs17300539 (−11391G>A) was highly associated with adiponectin levels, and the rs182052 (−10069G>A) seemed specially associated with diseases in populations of African origin.

Clinical Factors

Obesity was defined as body mass index ≥30 kg/m². Dyslipidemia was defined as having one of the following: high-density lipoprotein cholesterol concentration <1.04 mmol/L in men or <1.29 mmol/L in women, triglyceride concentration ≥1.69 mmol/L, low-density lipoprotein cholesterol concentration ≥3.40 mmol/L, or under lipid-lowering treatment combined with a history of blood lipid abnormality. The “hypertriglyceridemic waist” phenotype (HTGW), was defined as a waist circumference ≥90 cm in men or ≥85 cm in women, along
with a plasma triglyceride concentration \( \geq 2.0 \text{ mmol/L} \) in men or \( \geq 1.5 \text{ mmol/L} \) in women\(^{29,30}\).

Pre-existing CAD was defined on evidence of previous acute myocardial infarction, coronary bypass surgery, coronary angioplasty or documented myocardial ischemia. The latter was established on the basis of a positive stress test (exercise testing, myocardial scintigraphy or stress echography).

### Statistical Methods

The results are expressed as mean ± standard deviation for the continuous variables, and as number (percentage) for the categorical variables. Variables were compared between groups using analysis of covariance. Variables with a skewed distribution (triglycerides and Ad concentrations) were log10 transformed to approach a normal distribution.

We used logistic regression analysis to study the associations between ADIPOQ variants and the following five conditions: overweight, dyslipidemia, HTGW, total Ad concentration <25th percentile (3.49 ng/mL) and pre-existing CAD. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The data were adjusted for age and sex.

The IBM SPSS statistical software package version 19.0 (IBM, Armonk, NY, USA) was used for the data analysis. All \( P \)-values were two-sided, and \( P < 0.05 \) was considered significant.

### RESULTS

The clinical and biological characteristics of the patients are shown in Table 1 for the overall study sample. The sample comprised 81 (40.5%) men. The mean age was 64 ± 12 years. A total of 56% of the patients had dyslipidemia, 82% were overweight, 12% had HTGW and 25% had total Ad levels <25th percentile (3.49 ng/mL). A total of 54 patients (27%) had pre-existing coronary events and among them, 41 (76%) had had a previous acute myocardial infarction.

The levels of total adiponectin and the multimeric forms according to overweight, dyslipidemia, HTGW and pre-existing CAD are presented in Table 2.

Mean total adiponectin levels were the lowest in patients with overweight, dyslipidemia and CAD. This decrease in total Ad was associated with decreased levels of HMW and of the percentage HMW / total in patients with overweight, and with decreased levels of HMW and LMW in patients with dyslipidemia. MMW and LMW were lower in patients with CAD than in the others, but the difference in HMW levels was not statistically significant. The MMW:HMW ratio was higher in patients with HTGW than in the others (\( P = 0.04 \)).

The genotype distributions in the study population was in Hardy–Weinberg equilibrium for rs2241766 (\( P = 0.90 \)), rs1501299 (\( P = 0.90 \)) and rs182052 (\( P = 0.90 \)), but not for rs17300539 (\( P = 0.02 \)).

Regarding the relationship between SNPs and adiponectin concentrations, total Ad, HMW and HMW:total Ad were significantly higher in patients carrying the rare allele rs182052 A (AA+GA) than in those with the GG genotype (Table 3). MMW concentration was lower in carriers of the rare allele of rs17300539 A (AA+GA) than in those with the GG genotype (0.6 ± 0.5 vs 1.3 ± 1.2; \( P = 0.006 \); data not shown). No significant difference in adiponectin concentrations was noted according to rs2241766 and rs1501299 genotypes.

No significant difference in genotype frequencies of the four SNPs studied was noted in patients with and without dyslipidemia or overweight. The frequency of carriers of the minor allele rs2241766 G (TG+GG) was higher in patients with CAD than without (21% vs 8.5%; \( P = 0.01 \)), and in those with HTGW than in the others (25% vs 10%; \( P = 0.04 \); Table 4). For the rs2241766, serum triglycerides concentrations were significantly higher in participants carrying the minor allele GG+TG than in those with the TT genotype (1.7 ± 1.9 vs 1.1 ± 0.7 mmol/L; \( P = 0.01 \); Table 4).

Table 5 shows the adjusted ORs for overweight, dyslipidemia, HTGW, total Ad concentration <3.49 ng/mL (25th percentile) and pre-existing CAD for ADIPOQ variants. The frequent homozygous genotype was considered as the reference group. The rs182052 GG genotype was associated with an increased risk of low total Ad concentration, whereas the ORs were OR 0.4, 95% CI 0.2–0.9; \( P = 0.03 \) for the GA genotype, and OR 0.3, 95% CI 0.1–0.9; \( P = 0.03 \) for the AA genotype. The OR of low total Ad concentration for carrying the minor allele (AA+GA) was OR 0.4, 95% CI 0.2–0.8; \( P = 0.009 \) (data not shown). The rare allele rs2241766 G (GG+TG) was associated with an increased risk of CAD (OR 3.3, 95% CI 1.3–8.5; \( P = 0.01 \)) and of HTGW (OR 3.1, 95% CI 1.1–9.5; \( P = 0.04 \)).

### DISCUSSION

Previous studies have reported associations between genetic variants of adiponectin and diabetes in Africans or African–Americans\(^{18,25,26}\). In the present study of Caribbean patients of African ancestry with type 2 diabetes mellitus, the rs2241766 in
Table 2 | Distribution of total adiponectin and multimeric forms according to overweight, dyslipidemia, hypertglyceridemic waist, and pre-existing coronary artery disease

|                | Overweight | Dyslipidemia | HTGW | CAD |
|----------------|------------|--------------|------|-----|
|                | No         | Yes          | P    | No  | Yes          | P    | No  | Yes          | P    |
| Total Ad (µg/mL) | 33         | 167          | 0.05 | 89  | 111          | 0.04 | 174 | 24           | 0.02 |
| HMW Ad (µg/mL)  | 5.5±0.7    | 2.8±0.3      | 0.03 | 3.4±0.7 | 3.1±0.6       | 0.03 | 3.1±0.7 | 3.2±0.6       | 0.08 |
| MMW Ad (µg/mL)  | 1.7±0.2    | 1.2±0.9      | 0.25 | 1.4±1.0 | 1.2±1.3       | 0.09 | 1.3±1.0 | 1.1±1.3       | 0.37 |
| LMW Ad (µg/mL)  | 2.6±1.7    | 2.7±1.5      | 0.31 | 2.9±1.5 | 2.5±1.5       | 0.02 | 2.6±1.5 | 2.4±1.5       | 0.64 |
| HMW:total Ad    | 0.4±0.2    | 0.3±0.2      | 0.02 | 0.4±0.2 | 0.3±0.2       | 0.13 | 0.3±0.2 | 0.4±0.2       | 0.45 |
| MMW:HMW ratio   | 0.7±0.8    | 1.2±3.3      | 0.34 | 0.8±1.2 | 1.4±3.9       | 0.16 | 1.0±1.2 | 2.4±3.9       | 0.04 |

The data are presented as mean ± standard deviation. Data were analyzed by ANCOVA after adjustment for age and sex. Significant P-values are presented in bold. Ad, adiponectin; HMW, high molecular weight; LMW, low molecular weight; MMW, middle molecular weight.

Table 3 | Distribution of total adiponectin and multimeric forms according to rs182052 genotypes of the ADIPOQ gene

| rs182052 G>A (n = 189) | Genotypes | Dominant model |
|-------------------------|-----------|----------------|
|                         | AA        | GA             | GG | P           | AA/GA v GG | P           |
| Total Ad (µg/mL)        | 32        | 77             | 80 | 0.10       | 0.04       |
| HMW Ad (µg/mL)          | 3.7±0.6   | 3.7±0.6        | 2.6±3.2 | 0.09       | 0.03       |
| MMW Ad (µg/mL)          | 1.2±0.9   | 1.4±1.4        | 1.3±1.0 | 0.81       | 0.62       |
| LMW Ad (µg/mL)          | 2.5±1.0   | 2.9±1.7        | 2.5±1.6 | 0.52       | 0.29       |
| HMW:total Ad            | 0.4±0.2   | 0.4±0.2        | 0.3±0.2 | 0.10       | 0.04       |
| MMW:HMW ratio           | 1.0±0.9   | 1.3±4.6        | 1.1±1.5 | 0.86       | 0.87       |

The data are presented as mean ± standard deviation. Data were analyzed by analysis of covariance after adjustment for age and sex. Significant P-values are presented in bold. Ad, adiponectin; HMW, high molecular weight; LMW, low molecular weight; MMW, middle molecular weight.

Table 4 | Frequencies of carrying the rare allele of rs2241766 in patients with coronary artery disease or hypertglyceridemic waist phenotype and mean triglyceride levels according genotypes

| rs2241766 T>G | CAD | HTGW | Triglycerides |
|---------------|-----|------|---------------|
|               | No  | Yes  | P             | No  | Yes  | P             | mmol/L | P    |
| TT (n = 169)  | 141 | 51   | 0.01          | 89  | 75   | 0.04          | 1.1±0.7 | 0.01 |
| GG/TG (n = 23)| 8.5 | 21.6 |               | 10  | 25   |               | 1.7±1.8 |      |

The data are presented as column percentage for coronary artery disease (CAD) and hypertglyceridemic waist (HTGW) and as mean ± standard deviation for triglyceride levels. Significant P-values are presented in bold.

ADIPOQ was associated with HTGW phenotype and pre-existing CAD. Associations were also noted between rs182052 and adiponectin levels, but this variant was not concomitantly associated with overweight, dyslipidemia, HTGW phenotype or CAD. In addition, the HMW isoform, which is considered the main determinant of insulin sensitivity, was associated with overweight and dyslipidemia, but not with pre-existing CAD, suggesting that all the multimeric forms do not have the same functions for all diseases.

Decreased levels of total Ad, HMW and percentage of HMW adiponectin to total adiponectin (HMW:total Ad) were associated with overweight in the present study population. The complex HMW:total Ad, also called adiponectin sensitivity index, was reported to correlate more strongly with insulin sensitivity than just total adiponectin in patients with type 2 diabetes mellitus31. The adipose tissue is considered as an active organ secreting proteins that have marked effects on cardiovascular disease and type 2 diabetes mellitus32. Adiponectin, secreted by adipose tissue, appears to protect against all stages of atherosclerotic plaque formation and progression, and plaque rupture and thrombosis33. Except for HMW level, the odds of CAD decreased for all Ad forms in the present study. Regarding cardiovascular events, there are conflicting reports. In a cohort of CAD patients, total Ad and its isoforms did not cor-
relate with severity of CAD\textsuperscript{34}. Inoue et al.\textsuperscript{14} suggested that serum HMW adiponectin levels might serve as a predictor of future cardiovascular events in patients with CAD, whereas Baessler et al.\textsuperscript{12} observed, in a prospective study, that neither total Ad nor LMW were significantly different in patients with or without incident myocardial infarction. However, these authors found a decreasing association of the MMW:HMW ratio with incident myocardial infarction\textsuperscript{12}.

The relevance of the different Ad multimers is not fully known, and ethnic variations in adiponectin isoform distribution has been evocated\textsuperscript{17,35}. The clinical importance of measuring, not only the total Ad levels, but the level of each Ad isoform separately\textsuperscript{8} has been highlighted. However, little is known about production and secretion of the different Ad isoforms. According to some authors, MMW and LMW could proceed from sources other than adipose tissue in contrast to HMW that might be secreted primarily by the adipose tissue with differences in adiponectin secretion between subcutaneous and visceral adipose tissue\textsuperscript{36–37}. This could partly explain the observed ethnic differences in the relationship between adiponectin isoforms and risk factors\textsuperscript{17}, as fat distribution also differs between ethnic groups. In the present diabetic patients who had a high prevalence of overweight (81.5%), our results show that HMW is the isoform most broadly related to risk factors. In fact, HMW was not associated with CAD, whereas a strong link was found between LMW and CAD. We also noted a stronger relationship between LMW and dyslipidemia than between HMW and dyslipidemia. The ethnicity of our study population probably had an impact on these relationships. Indeed, in our Afro–Caribbean population, as in other populations of African descent, the abdominal subcutaneous fat is generally more common than the abdominal visceral fat, and could have an impact on the secretion of HMW.

In the present study, the rs2241766 was associated with pre-existing CAD and with HTGW, which is an optimal screening tool to identify subjects with metabolic syndrome and at high risk of cardiovascular disease\textsuperscript{29}. Conversely, the rs1501299, rs17300539 and rs182052 were not significantly associated with CAD. However, some authors reported, in a large cohort of diabetic men, significant associations between ADIPOQ rs1501299, decreased cardiovascular risk and increased plasma Ad level\textsuperscript{38}. In a recent study of type 2 diabetics in a Saudi population, there was no association between this ADIPOQ variant (rs1501299) and CAD risk, but a significant association with rs2241766\textsuperscript{20}. A recent meta-analysis showed that the associations between variants in the ADIPOQ and cardiovascular disease were weak, and highlighted the need to confirm the associations\textsuperscript{34}.

Slightly higher plasma triglyceride and insulin levels were reported in the rs2241766 European G allele carriers\textsuperscript{16}. Triglyceride levels were also the highest in our Afro–Caribbean patients carrying this rs2241766 G allele. Thus, it appears that in addition to the association with CAD, rs2241766 is also associated in our population to major metabolic syndrome features, such as triglyceride levels and HTGW.

Studies analyzing the relationships between rs182052 and cardiometabolic risk factors are scarce. The association found in the present study between rs182052 and adiponectin levels is particularly interesting because, in the literature, associations between this polymorphism and diseases have been described mainly in populations of African ancestry. In a study of African–Americans, rs182052 was associated with type 2 diabetes mellitus under a dominant model, and the presence of the minor allele (A/A or G/A) was associated with earlier onset of type 2 diabetes and diabetic nephropathy\textsuperscript{25}. In the present study, the rs182052 minor allele was associated with a decrease of the odds of low total Ad

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Table 5 | Adjusted odds ratios of overweight, dyslipidemia, hypertriglyceridemic waist, low total adiponectin concentration and pre-existing coronary artery disease in patients with type 2 diabetes for ADIPOQ polymorphisms

| ADIPOQ | N | Overweight | Dyslipidemia | HTGW | Low total Ad levels | CAD |
|--------|---|------------|-------------|------|-------------------|-----|
|        |   | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| rs2241766 | | | | | | |
| TT     | 169 | 1 | 1 | 1 | 1 | 1 |
| GG/TG  | 23  | 0.3 (0.1–0.9) | 1.6 (0.6–4.0) | 0.30 | 3.1 (1.1–9.3) | 0.04 |
|        |     | 0.7 (0.3–2.9) | 0.62 | 3.3 (1.3–8.7) | 0.01 |
| rs1501299 | | | | | | |
| GG     | 72  | 1 | 1 | 1 | 1 | 1 |
| GT     | 93  | 1.4 (0.6–3.6) | 1.0 (0.5–1.9) | 0.92 | 0.4 (0.1–1.2) | 0.10 |
|        |     | 0.6 (0.3–1.2) | 0.16 | 0.7 (0.2–1.4) | 0.32 |
| TT     | 29  | 0.5 (0.2–1.4) | 0.17 | 1.7 (0.7–4.1) | 0.24 |
|        |     | 0.8 (0.2–2.8) | 0.69 | 0.8 (0.3–2.1) | 0.60 |
|        |     | 1.1 (0.4–2.9) | 0.87 |
| rs17300539 | | | | | | |
| GG     | 182 | 1 | 1 | 1 | 1 | 1 |
| GA/AA  | 8   | 1.0 (0.1–9.0) | 0.97 | 1.3 (0.3–5.7) | 0.70 |
|        |     | 1.2 (0.1–10.5) | 0.28 | 1.7 (0.4–8.1) | 0.49 |
|        |     | 1.6 (0.3–7.1) | 0.57 |
| rs182052 | | | | | | |
| GG     | 80  | 1 | 1 | 1 | 1 | 1 |
| GA     | 77  | 1.0 (0.4–2.3) | 0.92 | 1.1 (0.6–2.1) | 0.76 |
|        |     | 2.2 (0.8–5.8) | 0.12 | 0.4 (0.2–0.9) | 0.03 |
|        |     | 1.4 (1.7–3.0) | 0.31 |
| AA     | 32  | 2.1 (0.5–7.9) | 0.26 | 0.9 (0.4–2.1) | 0.54 |
|        |     | 0.7 (0.1–3.5) | 0.65 | 0.3 (0.1–0.3) | 0.03 |
|        |     | 0.5 (0.2–1.6) | 0.27 |

Low total adiponectin (Ad): total Ad concentration <25th percentile (3.49 ng/mL). Odds ratios (OR) and 95% confidence intervals (CI) were adjusted for age and sex. Significant P-values are presented in bold. CAD, coronary artery disease; HTGW, hypertriglyceridemic waist.
leading to cardiovascular diseases in our Afro-morphisms are implicated in the pathophysiological process concentrations. These genetic effects seem to be independent of adiponectin not concomitantly associated with cardiometabolic risk factors. Patients, but the SNP associated with adiponectin levels was port so relationship that may pose a conflict of interest.

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