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High–molecular weight adiponectin is associated with coronary artery angiographic findings in Asian Indians

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Abstract

Asian Indians (AIs) have a higher prevalence and a more aggressive form of coronary artery disease (CAD), and it has been suggested that hypoadiponectinemia may have a role in this accelerated CAD. The present study was undertaken to determine the extent and severity of angiographic findings in 2 groups of CAD patients matched for age and sex, AIs (n = 29) vs whites (n = 30), and to elucidate the potential relationship between adiponectin (total and high–molecular weight [HMW] form) and the severity and extent of coronary angiographic findings in both groups. Angiographic findings were assessed using the modified Gensini index; and 2 scores, scores 1 and 2, were used to assess the severity and extent. Both Gensini index scores 1 and 2 were higher in the AI group compared with the white group (144.4 ± 87.1 vs 93.5 ± 56.3 and 127.2 ± 86.5 vs 80.1 ± 39.3, respectively; $P < .05$). Adiponectin levels were similar in both groups. Total adiponectin and HMW adiponectin were positively associated with Gensini index score 1 ($r = 0.62$, $P = .004$ and $r = 0.64$, $P = .003$) and score 2 ($r = 0.51$, $P = .021$ and $r = 0.54$, $P = .013$), respectively, in AI men, whereas there was no significant association in white men. Thus, AIs had more severe CAD compared with whites; and in AI men with CAD, total adiponectin and HMW adiponectin were associated with the severity of angiographic scores.

1. Introduction

Several studies show that the prevalence of coronary artery disease (CAD) is up to 4-fold higher in Asian Indians (AIs) who live in India or in those living overseas compared with whites [1,2]. Furthermore, AIs with CAD tend to have an aggressive course of CAD, occurring at an earlier age and resulting in a higher rate of morbidity and mortality [1]. A few studies evaluated angiographic findings in AI patients and found a higher prevalence of triple-vessel disease compared with whites [3].

The pathogenesis of the accelerated atherosclerotic process in this population is not clear and is not explained by the traditional risk factors such as hypercholesterolemia, hypertension, and smoking. Other suggested mechanisms include smaller coronary arteries, high levels of lipoprotein (a), insulin resistance, and the associated glucose intolerance and type 2 diabetes mellitus [4-6].

It has been suggested that low levels of adiponectin, an adipokine with insulin-sensitizing properties and putative antiatherogenic properties, may partly explain the increased burden of CAD in AIs [7]. This hypothesis is supported by several small studies in which AI subjects had significantly lower adiponectin levels compared with whites [7] and by cross-sectional studies, conducted in other populations, showing that hypoadiponectinemia is associated with CAD [8,9]. However, prospective studies provided conflicting data [10-12]; and 2 recent studies conducted in whites with existing CAD even found that baseline high adiponectin levels were associated with increased risk of cardiac and all-cause mortality [13,14]. In contrast, in 2 other studies conducted in Japanese subjects, there was an inverse correlation between angiographic score and adiponectin levels [15,16].

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The aims of this study were (1) to determine the extent and severity of angiographic findings in 2 groups of CAD patients, AIs vs whites, and (2) to elucidate the potential relationship between adiponectin (total and high–molecular weight [HMW] form) and the severity and extent of coronary angiographic findings in both groups.

2. Subjects and methods

2.1. Subjects

A case-control study was conducted at the Institute of Cardiology and Metabolic Unit of Kaplan Medical Center, a university-affiliated hospital serving 300,000 people in central Israel. The study was approved by our Institutional Review Board, and all participants provided an informed consent. Our study group included consecutive AI patients who underwent coronary angiography between January 2003 and April 2006. Patients in the AI group had to have both parents of AI origin. Exclusion criteria were as follows: chronic renal failure (creatinine clearance <60 mL/min), chronic liver disease, type 1 diabetes mellitus, normal coronary arteries, or known malignancy. Eighty-one patients of AI origin underwent coronary angiography at this period: 14 patients met exclusion criteria, and 27 patients could not be reached or refused to take part in the study. The AI patients who refused to participate in the study or could not be reached were similar to the AI patients who were included regarding their age and sex distribution: 63.3 ± 3.3 years; 19 male and 8 female. Eleven AI patients died in the period between coronary angiography and the study's clinical evaluation. These AI patients were older than AI patients who were included in the study group (70.9 ± 4.3 vs 60.9 ± 7.1, $P = .02$), with similar sex distribution. Thus, 29 AI patients were finally enrolled. The control group included 30 age- and sex-matched white patients who underwent coronary angiography at the same period.

2.2. Clinical evaluation

The charts of all patients were reviewed for details of medical history, medications, and laboratory results done on admission to angiography or within 1 month prior. The laboratory results included renal and liver function tests, fasting lipid profile, and fasting plasma glucose (FPG).

All patients thereafter underwent a physical examination including anthropometric measurements and answered a detailed questionnaire about CAD risk factors including family history of cardiovascular disease. After a 12-hour fast, blood was drawn for adiponectin, insulin, and glucose. The serum was frozen in −80°C. Laboratory measurements of fasting glucose levels were made by standard automated procedures with commercially available kits (Roche Diagnostics, Basle, Switzerland) by the GOD-PAPP method with a BM/Hitachi (San Jose, CA) 717/911 analyzer. Insulin levels were measured using the Immulite 2000 analyzer from Diagnostics Products (Los Angeles, CA) with the manufacturer's reagents in a solid-phase chemiluminescent immunometric assay. Homeostasis model assessment of insulin resistance index (HOMA-IR) was calculated as follows: HOMA-IR = fasting insulin (in microunits per milliliter) × fasting glucose (in millimoles per liter)/22.5.

2.3. Fast protein liquid chromatography (FPLC) fractioning of adiponectin

2.3.1. Materials

A HiLoad 16/60 Superdex 200 prep grade column (GE Healthcare, Amersham Biosciences, Buckinghamshire, United Kingdom), a Smartline 1000 (Knauer, Berlin, Germany) pump with a 10-mL titanium pump head, an Autosampler 3800 (Knauer), and a fraction collector CHF122SB (Advantec, Dublin, CA) were used. As running buffer, phosphate-buffered saline (50 mmol/L phosphate, 150 mmol/L NaCL, 0.2% vol/vol Tween, 0.2% wt/vol Na azide, 0.2% bovine serum albumin [pH 7.2]) was used.

2.3.2. FPLC running conditions

Samples were fractioned using an in-house validated FPLC method as previously described [17]. A sample size of 500 μL, consisting of 50 μL of serum and 450 μL of buffer, was used with running buffer with a flow of 1.0 mL/min. Samples were fractioned into 12 fractions of varying volumes that were chosen to preserve the discrimination between the 3 polymer fractions. The fractions did not undergo any treatment before being assayed, and all assays were performed less than 30 hours after fractioning.

2.4. Adiponectin immunoassay

Serum concentrations of adiponectin polymers and total adiponectin were determined by a validated in-house time-resolved immunofluorometric assay as previously described [18]. In brief, 96-well DELFIA microtiter plates (Perkin Elmer Lifesciences, Turku, Finland) were coated with a monoclonal antibody MAB 10651 (R&D Systems, Abingdon, United Kingdom) diluted in a phosphate buffer. After blocking, wells were washed once. Assay standards were made from recombinant human adiponectin. By dilution in assay buffer, a series of concentrations ranging from 2 to 1000 μg/L was made. One hundred microliters of assay buffer containing a second antibody (BAM 1065) and streptavidin-europium in concentrations of 1:250 and 1:500 was added, and the plates were incubated for 3 hours at room temperature in the AutoDELFIA. Afterward, plates were washed 6 times before enhancement solution was added. High, medium, and low controls were included on each plate; and only assay runs with controls within given values were accepted.

The intra- and interassay coefficient of variation for the adiponectin assay was less than 5% and less than 10%, respectively [18]. The intra- and interassay coefficient of variation for the HMW fraction was less than 4% and less than 6%, respectively [17].

Table 1
Baseline and anthropometric characteristics of patients undergoing coronary angiography

Parameter	AI (n = 29)	Whites (n = 30)	*P*
Age (y)†	60.9 ± 7.1	60.4 ± 7.3	.83
Male/female	20/9	22/8	NS
Type 2 diabetes mellitus (%)	44.8	30.0	.24
Hypertension (%)	55.2	60.0	.71
Smoking (%)	17.2	30.0	.25
BMI (kg/m^2)*	25.2 ± 3.6	29.5 ± 4.5	.001
FPG (mg/dL)†	131.6 ± 47.4	123.8 ± 32.7	.59
HOMA†	2.8 ± 2.1	3.9 ± 4.8	.73
Adiponectin total (mg/L)†	8.9 ± 6.6	7.0 ± 2.3	.75
HMW adiponectin (mg/L)†	4.2 ± 4.2	2.8 ± 1.4	.76
Total cholesterol (mg/dL)*	191.3 ± 35.3	185.1 ± 42.9	.55
Triglycerides (mg/dL)†	172.8 ± 82.4	188.6 ± 94.5	.61
HDL cholesterol (mg/dL)†	43.2 ± 11.7	39.4 ± 8.0	.46
LDL cholesterol (mg/dL)*	119.8 ± 28.7	105.4 ± 31.0	.07
Waist circumference (cm)*	88.5 ± 8.9	100.0 ± 9.6	.002
Hip circumference (cm)†	95.0 ± 6.0	101.5 ± 8.6	.005
Waist-to-hip ratio†	0.93 ± 0.10	0.99 ± 0.07	.037
Subscapular-triceps skin fold ratio†	1.7 ± 0.7	1.5 ± 0.6	.39
Abdominal skin fold (cm)*	16.9 ± 7.9	21.2 ± 8.0	.04

The data represent means ± SD. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; NS, not significant.
For comparison of 2 groups: *t test; †Mann-Whitney-Wilcoxon test.

2.5. Assessment of angiographic CAD

All subjects underwent catheterization and coronary angiography using standard techniques. During cardiac catheterization, nitroglycerine was administrated routinely in all cases suspected of having coronary spasm. Angiograms were assessed independently by 2 experienced interventional cardiologists who were blinded to the clinical parameters of the patients. Angiography results of obstructive and *nonobstructive* lesions (defined as <50% obstruction) were assessed by the modified Gensini index as previously described [19]. Briefly, location, degree of stenosis (severity), and number of occluded segments (extent) were evaluated. Coronary vasculature was divided into 27 coronary segments, and each involved segment was weighted by a value from 0.5 (least important) to 5.0 (critical location) reflecting the location of coronary artery lesions. The severity (percentage of stenosis) was weighted as follows: <25%, 2; 26%-50%, 4; 51%-75%, 8; 76%-90%, 16; 91%-99%, 32; and 100%, 64. Extent was determined by the number of occluded segments (1-27). The product of the weights for location and severity is the total weight for each arterial segment, and the sum of all segments involved constitutes score 1 reflecting location, severity, and extent [19]. Score 2 is the sum of the weighted severity for all involved segments.

2.6. Statistical analyses

Univariate comparisons of the AI and white groups were performed by the 2-sample *t* test (for normally distributed continuous variables) or by the Mann-Whitney-Wilcoxon test (for other continuous variables). For categorical variables, univariate analyses were performed by the χ^2 test or the Fisher exact test, as appropriate. The Pearson correlation coefficient was used to measure linear association. A *P* value less than .05 was considered statistically significant. In multivariate analyses to determine predictors of angiographic scores, possible explanatory variables were first screened by stepwise linear regression. Thereafter, multiple linear regressions were performed using the explanatory variables alone and also interacting with the ethnicity variable.

3. Results

Baseline and anthropometric characteristics of the 2 groups are presented in Table 1. The AI patients had significantly lower body mass index (BMI) (*P* = .001), waist, hip, waist-hip ratio, and forearm circumferences. Skin folds thickness was measured; and whereas abdominal skin fold was reduced in AI patients (*P* = .04), subscapular-triceps skin folds ratio was similar (*P* = .39), indicating a relatively truncal accumulation of adipose tissue in the AI group despite having lower BMI.

Thirteen patients (45%) from the AI group had diabetes mellitus compared with 9 patients (30%) in whites; however, the difference was not statistically significant. There was no significant difference in FPG and HOMA levels between the 2 groups. There were no significant differences between the 2 groups in total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides.

The number of patients having hypertension, diabetes, and hyperlipidemia was similar in both groups. Only 5 patents (17%) from the AI-origin group smoked compared with 9 patients (30%) in the white group.

Because of the small number of women (n = 9 in the AI group and n = 8 in whites), further analysis included only male patients. In the AI group, the Gensini index score 1 was 144.4 ± 87.1 vs 93.5 ± 56.3 in whites (*P* < .05). The Gensini index score 2 was 127.2 ± 86.5 vs 80.1 ± 39.3 (*P* < .05) in whites (Fig. 1).

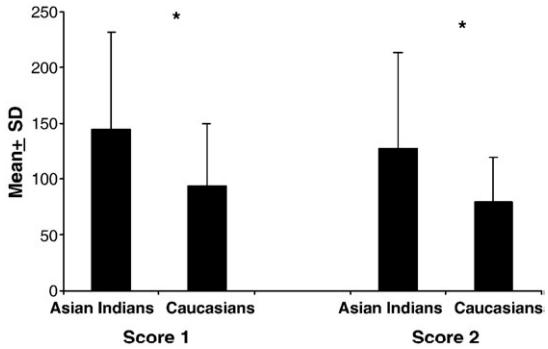

Fig. 1. Mean ± SD for scores 1 and 2 in AIs and whites. *P* less than .005 for comparison of 2 groups by Mann-Whitney-Wilcoxon test.

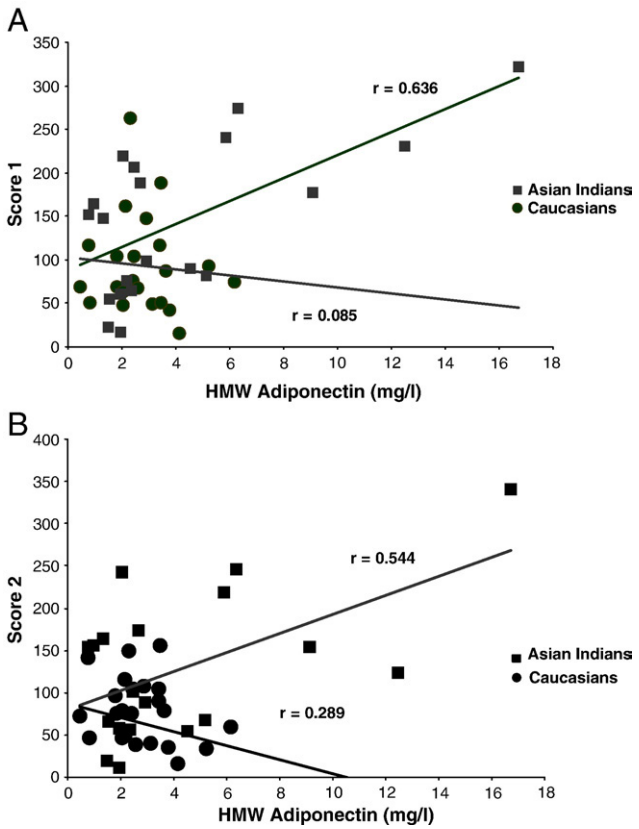

Fig. 2. A, Correlation of HMW adiponectin and score 1 in AIs and whites. *P* equals .003 in AI; *P* not significant in whites. Correlation was determined by the Pearson correlation test. B, Correlation of HMW adiponectin and score 2. In AI group. *P* equals .013 in AI; *P* not significant in whites. Correlation was determined by the Pearson correlation test.

The levels of mean total adiponectin and HMW adiponectin were 8.9 ± 6.6 and 4.2 ± 4.2 mg/L in the AI group and 7.0 ± 2.3 and 2.8 ± 1.4 mg/L in whites, and the differences were not statistically significant. The relationship between total and HMW adiponectin and angiographic scores was evaluated in both groups. We found that, in the AI group, total adiponectin and HMW adiponectin were positively related to Gensini index score 1 ($r = 0.62$, $P = .004$ and $r = 0.64$, $P = .003$, respectively) (Fig. 2A) and score 2 ($r = 0.51$, $P = .021$ and $r = 0.54$, $P = .013$, respectively) (Fig. 2B). In whites, there was no significant association (Fig. 2A and B).

Multiple regression analysis of the predictors of scores 1 and 2 was preformed in both study groups. Abdominal skin fold and both total and HMW adiponectin were significant predictors of scores 1 and 2 in AI patients ($P = .001$ and $P = .004$, respectively), but not in whites.

4. Discussion

In the present study, we found that angiographic findings assessed by Gensini index were significantly more severe in AI patients compared with whites. These data are in accordance with previous data studies showing up to 2-fold increase in the prevalence of 3-vessel disease in AI patients compared with whites and higher total atheroma score [2]. The strength of our study is the detailed quantitative analysis of coronary angiography including even minimal stenosis of less than 25% in both proximal and distal coronary arteries. This analysis of both obstructive and nonobstructive lesions reflects more accurately the severity of the atherosclerotic process. Our data and the data provided by previous studies imply that AI patients have a more severe and diffuse form of coronary atherosclerosis.

Coronary artery disease in AIs compared with whites also occurs at an earlier age and generally follows a more "malignant" clinical course with a higher mortality rate [1,2]. This higher rate of premature and severe CAD could not be explained only by conventional risk factors such as hypercholesterolemia, hypertension, and smoking. Other risk factors previously suggested include smaller-caliber coronary arteries in AI compared with whites, even after correcting for body surface area [4], and high levels of lipoprotein (a), a powerful independent risk factor for premature CAD [5,6]. In recent years, it has been suggested that insulin resistance that is present in high percentage in AI could explain some of the increased prevalence of CAD in this population [20,21]. Insulin resistance is strongly associated with obesity. However, several studies described that, although AI subjects have a relatively low BMI, they tend to have a higher percentage of body fat accumulating mainly in visceral and truncal regions and associated with increased insulin resistance [22,23]. In our study, AI patients had a significantly lower BMI compared with whites; but almost half of them had type 2 diabetes mellitus and, despite being significantly leaner, subscapular/triceps skin fold ratio, an index of truncal obesity, was similar in the 2 groups of patients, implying different fat distribution [22,24]. Insulin resistance has a central role in type 2 diabetes mellitus; however, we did not find an association between HOMA-IR, a marker of insulin resistance, and the angiographic scores. The question of whether insulin resistance has an independent role in CAD in the general population is the focus of an active debate with conflicting data [25-28,19]. Our data do not support the notion that insulin resistance is a risk factor for more extensive CAD in AI.

Another candidate factor that has been suggested to be related with the aggressive and highly prevalent CAD in AI is hypoadiponectinemia [7]. This hypothesis is based on the findings of several small studies conducted in relatively healthy individuals that showed lower levels of adiponectin in AIs compared with whites [7]. Adiponectin, a cytokine exclusively synthesized in adipose tissue, is an important modulator of insulin sensitivity; and it also has putative direct antiatherogenic and anti-inflammatory properties demonstrated in in vitro and animal studies [29]. Adiponectin exists in the circulation in both low–molecular weight and HMW forms, and the HMW form is considered to have more pronounced insulin-sensitizing and antiatherogenic activity

[26,30]. Several cross-sectional studies found hypoadiponectinemia to be associated with CAD [8,9]; however, prospective studies provided conflicting data [10-12]. Our data do not support the hypothesis that hypoadiponectinemia has a role in the accelerated CAD of AI patients. We did not observe a difference in total adiponectin levels or in the levels of the HMW form between AIs and whites. Furthermore, in the AI group, higher levels of total and HMW adiponectin were significantly associated with more severe and extensive coronary lesions. These intriguing findings confirm 3 recently published studies also conducted in patients with already established CAD [13,14,31]. In a cohort of 325 male subjects undergoing coronary angiography, baseline adiponectin was an independent predictor of all-cause mortality, cardiac mortality, and myocardial infarction [13]. In a study conducted in 3146 patients with and without CAD, adiponectin was lower in diabetic and CAD patients. However, in patients with CAD, but not in those without angiographic CAD, adiponectin was positively related to all-cause and cardiovascular mortality [14]. Adiponectin predicted mortality in particular in patients with CAD in another recent study [31]. The strength of our study is that we determined not only total adiponectin levels but also the HMW form, implying that this "paradoxical" positive association is not due to altered change in the isoform composition. Taken together, these findings may suggest that, in some patients with established CAD, there is either a compensatory up-regulation of adiponectin, that its protective role is attenuated ("adiponectin resistance"), or even that adiponectin may have undesirable effects [14]. Ethnic differences regarding the relationship between adiponectin and atherosclerosis have also to be taken into consideration as suggested by the different association demonstrated in our study in AI and white patients. The limitation of our study is the relatively small number of patients included; and therefore, further studies conducted in larger groups of AI subjects and in other ethnic groups with and without CAD are needed to evaluate the role of adiponectin in atherosclerosis.

In summary, the current study is the first to address the relationship between severity and extent of CAD and adiponectin levels in AI CAD patients. In this group, higher concentration of both total and HMW adiponectin was associated with more severe and extensive disease. This study is consistent with recent observations that, in some CAD patients, high, rather than low, adiponectin levels predict adverse outcome. The results of our study do not support the hypothesis that hypoadiponectinemia is a risk factor for the malignant course of CAD observed in AI.

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