CARDIOVASCULAR DISEASE PREVALENCE, ASSOCIATED RISK FACTORS, AND PLASMA ADIPONECTIN LEVELS AMONG FILIPINO AMERICAN WOMEN

Objectives: This cross-sectional study was designed to examine the association between adiponectin and cardiovascular disease (CVD) among an understudied ethnic group of Filipino American women.

Methods: We recruited 266 Filipino women aged 40–86 years from the University of California, San Diego Filipino Women’s Health Study (1995–1999). Plasma adiponectin was extracted from archive blood samples and measured by radioimmunoassay. CVD was defined as coronary heart disease, angina, myocardial infarction, or stroke by history, electrocardiogram (Minnesota coding), or Rose questionnaire.

Results: CVD prevalence among Filipinas was 20.7% (n = 55), of which 85.5% were newly diagnosed. Filipinas with versus without CVD had more antihypertensive medication use (44.4% vs 26.7%), more parental history of myocardial infarction (38.2% vs 21.8%), higher proinsulin levels (13.2 vs 11.0 pmol/L), lower adiponectin levels (5.09 vs 6.15 μg/mL), and higher prevalences of the metabolic syndrome (34.6% vs 28.0%) and microalbuminuria (24.0% vs 12.2%). Adiponectin (adjusted OR .46, 95% CI .23–.89, P = .021) was independently associated with CVD in multivariate analysis that adjusted for age, exercise, family history, diabetes, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and microalbuminuria.

Conclusions: Independent of known risk factors, adiponectin was associated with CVD among Filipinas. This finding suggests that adiponectin may be a useful CVD indicator among this ethnic population. (Ethn Dis 2008;18:458–463)

Key Words: Filipino, Women, Cardiovascular Disease, Adiponectin

INTRODUCTION

Adiponectin has been implicated as an antiatherogenic adipose hormone in both animal and epidemiologic studies. Adiponectin circulates at relatively high concentrations in plasma, and increased adiponectin levels have been inversely associated with obesity, insulin resistance, type 2 diabetes, and cardiovascular disease (CVD). Low levels of adiponectin have been associated with an elevated risk of myocardial infarction and coronary heart disease; however, these associations have been inconsistent among women.

Although population-based adiponectin and CVD studies have predominately been conducted among Caucasians, ethnic differences in low adiponectin levels in association with CVD risk factors or outcomes have been reported among South Asians, Japanese, and African Americans. In a more recent study, normoglycemic Filipino American women had half the adiponectin concentration of Caucasian women, even after adjusting for age and waist-to-hip ratio. Filipino Americans have higher prevalences of hypertension and type 2 diabetes than those of Caucasians, African Americans, or other Asian ethnicities. However, no study to date has examined the association between adiponectin and CVD among this high-risk ethnic group, although their lower adiponectin levels might further exacerbate their risk for CVD. In contrast, a study among African Americans demonstrated that elevated adiponectin levels increased the risk for CHD. Thus, the prospect that the association between adiponectin and CVD differs by ethnicity makes conducting such studies among ethnically diverse populations much more vital, particularly in those with an elevated prevalence of diabetes and hypertension, such as Filipinos.

Proinsulin, C-peptide, and microalbuminuria have also been correlated or associated with cardiovascular diseases, but their concurrent relationship with adiponectin and CVD has not been evaluated. The purpose of the present study was to assess the independent association of adiponectin with prevalent CVD among Filipino American women in San Diego County, California.

METHODS

Study Population

Community-dwelling Filipino American women aged 40 to 86 years were recruited from 1995 through 1999 in San Diego County, which has the second highest Filipino-American population (145,132) in California after Los Angeles County (296,708) to estimate the prevalence of several chronic diseases, including osteoporosis, hy-
pertension, type 2 diabetes, and CVD. Recruitment materials emphasized general health outcomes to reduce self-selection bias of Filipinas with CVD. Detailed recruitment methods have been previously described. Population-based sampling was not possible because Filipinos were not reported separately from other Asians in the 1990 US Census.

This study analyzed data from 266 Filipinas, in whom information on adiponectin, proinsulin, C-peptide, and microalbuminuria were complete. Study approval was granted by the institutional review boards at San Diego State University and the University of California, San Diego, and all study participants gave written informed consent.

**Data Collection**

A structured questionnaire was administered to determine demographic characteristics, lifestyle behaviors (including cigarette smoking, alcohol use, physical activity, and estrogen therapy use), physician-diagnosed diseases, parental history of diseases, including myocardial infarction (MI) and stroke, hospitalizations, and surgical procedures. Participants were instructed to bring medications, prescriptions, and nutritional supplements to the clinic to be verified and recorded by a nurse. At the time of study, none of the Filipina participants were taking thiazolidinediones, which have been shown to alter adiponectin levels, but 35 Filipinas were currently using statins.

Clinical evaluations took place at the University of California, San Diego Rancho Bernardo Research Clinic. The data instruments were administered by a Philippine-born native Tagalog speaker and translated when necessary. All participants spoke functional English.

Two morning blood pressure readings were recorded in seated participants by use of a mercury sphygmomanometer and adherence to the Hypertension Detection and Follow-up Program protocol. Pulse pressure was calculated as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). Anthropometric measurements were conducted on waist and hip circumference, percentage of body fat, and truncal fat. Waist and hip circumferences were measured at the natural bending point and the iliac crest, respectively. Body mass index (BMI) was used to estimate obesity, and waist-to-hip ratio was used to estimate central fat distribution. Body fat and truncal fat percentages were determined by dual-energy x-ray absorptiometry (QRD-2000 x-ray bone densitometers, Hologic, Waltham, Mass).

Blood samples were collected from participants to measure levels of adiponectin, proinsulin, C-peptide, plasma glucose, insulin, plasma lipids, and triglycerides. Plasma adiponectin levels were measured by radioimmunoassay using archived samples stored at −70°C (Linco Research; St. Louis, Mo) in 2004. A 75-g oral glucose tolerance test was administered in the morning after an 8-hour minimum fast. Blood was collected by venipuncture at 0 and 2 hours. Plasma glucose levels were measured by the glucose-oxidase method, and insulin levels were determined by radioimmunoassay (Fineberg Laboratory, Indiana University). Insulin resistance was estimated with the homeostasis model assessment. Proinsulin and C-peptide were measured by radioimmunoassay. Both proinsulin and C-peptide were measured in the Fineberg Laboratory (Indiana University). Fasting plasma lipids and lipoproteins, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured using enzymatic techniques (Lipid Research Clinics Program Manual of Laboratory Operations). Low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald formula.

Electrocardiogram (ECG) tracings were recorded for five seconds per lead on a Hewlett-Packard cardiov crimachine (model HP 4750A) at the University of Minnesota. ECGs were coded by certified coders in the Minnesota ECG Coding Laboratory of Dr Ron Prineas. First morning urine samples were collected from study participants and tested quantitatively for creatinine and by nephelometry for albumin in the National Institutes of Health/National Institutes of Diabetes and Digestive and Kidney Diseases Phoenix laboratory. Microalbuminuria was defined as a urinary albumin/creatinine ratio of 30–300 mg/g. Type 2 diabetes was defined by the 1999 World Health Organization criteria. The metabolic syndrome was defined by the National Cholesterol Education Program criteria.

Prevalence of cardiovascular disease (CVD) in this study was defined as having any of the following: coronary heart disease, hospitalization for coronary revascularization procedures, angina pectoris, MI, or history of stroke. Prevalence of CVD was defined as ECG abnormalities from a 12-lead resting ECG (Minnesota codes 1.1–1.2 [large Q and QS waves], 1.3 [small Q and QS], 4.1–4.4 [ST-T depression], 5.1–5.3 [flattened or inverted T waves], or 7.1.1 [complete left bundle branch block]); a positive Rose questionnaire for angina or prolonged chest pain, hospitalization for coronary revascularization procedures, or reported physician-diagnosed stroke or myocardial infarction. Rose angina was defined according to standard criteria as chest pain or discomfort that was brought on by exertion (walking on flat ground or uphill), was situated in the central or left anterior chest, forced the participant to slow down or stop, and was relieved within 10 minutes if she did so.

**Statistical Analysis**

Tests of normality were conducted for continuous variables before statistical analyses and were skewed for cholesterol, triglyceride, pulse pressure, fasting glucose, postchallenge glucose,
fasting insulin, postchallenge insulin, proinsulin, C-peptide, and adiponectin levels. As such, all probability values were based on logarithmic values, but geometric means are presented. Descriptive statistics included 2-sided Student t tests and χ² analyses where appropriate. Pearson correlation coefficients were calculated between continuous variables. Univariate analyses were conducted to determine crude associations between putative predictor variables and CVD. A backward-stepwise regression analysis was then used to explore variables independently associated with CVD. SAS version 9.1 (SAS Institute, Inc, Cary, NC) was used for all statistical analyses. Statistical significance was set at P<.05.

Results

Of the 266 Filipina study participants, 55 (20.7%) had prevalent CVD and 211 (79.3%) had no CVD. Eight Filipinas (14.5%) had been previously diagnosed with CVD, but most (n=47, 85.5%) were diagnosed during this clinical evaluation. Among the 47 women newly diagnosed with CVD, 20 (42.6%) had coronary heart disease by ECG, 17 (36.2%) had angina by Rose questionnaire, 8 (17.0%) had an MI, and 2 (4.2%) had both angina and CHD.

Filipinas with and without CVD did not differ by mean age, completed college education, smoking history, exercise, alcohol use, estrogen use, and parental history of stroke (Table 1). Filipinas with CVD were more likely to have a parental history of MI (38.2% vs 21.8%) and use antihypertensive medications (44.4% vs 26.7%).

Filipinas with and without CVD did not differ across all variables of body size, body fat distribution, lipids, lipoproteins, statin use, or blood pressure values. However, there was an increasing trend of LDL cholesterol among those with CVD compared to those without (140 mg/dL vs 129 mg/dL, P=.061). Despite this trend, statin use did not differ between women with and without CVD (18.5% vs 11.4%, P=.165). Similarly, fasting glucose, postchallenge glucose, fasting insulin, postchallenge insulin, insulin resistance and C-peptide levels were not significantly different between these two groups. Conversely, proinsulin (13.2 pmol/L vs 11.0 pmol/L, P=.025) was higher and adiponectin (5.09 µg/mL vs 6.15 µg/mL, P=.031) was lower for Filipinas with versus without CVD.

Although the groups did not differ significantly with regard to prevalence of hypertension or diabetes, there was a trend of increase in these disease prevalences among the CVD group. In addition, although 30 women had been diagnosed with diabetes before study enrollment (mean duration 6.7 years), separate analysis showed that mean duration of diabetes between Filipinas with (12.3 years) and without (6.4 years) CVD did not differ (P=.069). Contrastingly, the prevalence of the metabolic syndrome and microalbuminuria were higher among those with versus without CVD (34.6% vs 28.0% and 24.0% vs 12.2%, respectively).

Table 1. Characteristics of 266 Filipino-American women by CVD status, San Diego, California, 1995–1999

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>No CVD (n=211)</th>
<th>CVD (n=55)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>57.3 (±0.68)</td>
<td>57.9 (±1.36)</td>
<td>.678</td>
</tr>
<tr>
<td>College graduate, %</td>
<td>44.1</td>
<td>47.3</td>
<td>.671</td>
</tr>
<tr>
<td>Smoker (ever), %</td>
<td>14.3</td>
<td>9.26</td>
<td>.331</td>
</tr>
<tr>
<td>Exercise ≥3 times per week, %</td>
<td>62.6</td>
<td>76.4</td>
<td>.055</td>
</tr>
<tr>
<td>Alcohol ≥3 drinks per week, %</td>
<td>.95</td>
<td>1.82</td>
<td>.586</td>
</tr>
<tr>
<td>Fasting insulin, μg/mL</td>
<td>5.09 (4.35–4.73)</td>
<td>4.01 (4.19–4.73)</td>
<td>.009</td>
</tr>
<tr>
<td>Postchallenge insulin, μg/mL</td>
<td>2.92 (2.47–3.46)</td>
<td>2.47 (2.18–2.80)</td>
<td>.115</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>138 (120–158)</td>
<td>130 (119–142)</td>
<td>.064</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>136 (±3.15)</td>
<td>130 (±1.33)</td>
<td>.056</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>79.7 (±1.42)</td>
<td>78.5 (±1.60)</td>
<td>.397</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>93.7 (54.9–58.5)</td>
<td>49.5 (47.5–51.5)</td>
<td>.069</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>104 (98.1–111)</td>
<td>101 (98.7–105)</td>
<td>.383</td>
</tr>
<tr>
<td>C-peptide, ng/mL</td>
<td>1.37 (1.18–1.59)</td>
<td>1.17 (1.10–1.26)</td>
<td>.062</td>
</tr>
<tr>
<td>Adiponectin, µg/mL</td>
<td>5.09 (4.35–5.97)</td>
<td>6.15 (5.69–6.65)</td>
<td>.031†</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>58.8</td>
<td>72.7</td>
<td>.058</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>27.5</td>
<td>32.7</td>
<td>.444</td>
</tr>
<tr>
<td>Metabolic syndrome, %</td>
<td>34.6</td>
<td>34.6</td>
<td>.034†</td>
</tr>
<tr>
<td>Microalbuminuria, %</td>
<td>24.0</td>
<td>24.0</td>
<td>.034†</td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease; MI, myocardial infarction; BMI, body-mass-index; DEXA, dual energy x-ray absorptiometry; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance.
* Values are mean (± standard error) unless otherwise indicated.
† Significant at P<.05.
‡ Log transformed for analysis; values are geometric mean (95% confidence interval).
§ Type 2 diabetes excluded.
When stratified by adiponectin quintile, CVD prevalence of almost 30% was apparent in the lowest quintile compared to 13% in the highest quintile (P = .019 for trend) (Figure 1). Moreover, low adiponectin concentration (adjusted OR .46, 95% CI .23–.89, P = .021) was associated with CVD after adjustment for age, exercise, parental history of MI, LDL cholesterol, HDL cholesterol, diabetes, hypertension, and microalbuminuria (Table 2). After controlling for covariates in the model, Filipinas with a parental history of MI were 2.81 times more likely to have CVD (95% CI 1.37–5.74, P = 0.005), and Filipinas with microalbuminuria were 2.52 times more likely to have CVD (95% CI 1.08–5.88, P = .032).

**DISCUSSION**

In this study of Filipino American women recruited for general health outcomes, 20.7% (n=55) had CVD. Of these, 85.5% (n=47) were not previously diagnosed, which suggests CVD may be underdiagnosed in this population with elevated prevalence of type 2 diabetes, hypertension, and dyslipidemia. Our analyses found an inverse association between plasma adiponectin and prevalent CVD among these community-dwelling Filipino American women. Parental history of MI and microalbuminuria were also associated with CVD, independent of age, exercise, LDL cholesterol, HDL cholesterol, diabetes, and hypertension.

Among studies of women, examination between adiponectin and CVD lacks consistency and provides no firm consensus in a significant association. A strong inverse association was found between serum adiponectin and CHD in female age-matched controls, but in the 4-year prospective British Women’s Heart and Health study, adiponectin did not predict CHD outcomes in either their unadjusted or adjusted analyses. Furthermore, the Rancho Bernardo Study revealed prospectively that adiponectin did not independently predict CHD incidence. Although the results of our study contribute to conclusions that adiponectin is a strong inverse indicator of CVD prevalence, collectively, these literature findings may implicate adiponectin as a cardio-protective marker rather than a risk factor for CVD among women.

In addition to sex, literature has also suggested ethnic differences as a key factor in varying adiponectin concentration levels in relation to CVD and its associated risk factors. Filipino
Americans share similar metabolic predispositions as South Asians and African Americans, such as type 2 diabetes and hypertension, and all three groups have lower adiponectin levels than Caucasians. However, compared to African American women, a subgroup of our Filipina cohort without known CVD had higher visceral adipose tissue, as measured by computed tomography. Excess amounts of visceral adipose tissue have been suggested to contribute to hypoadiponectinemia and systemic inflammation. Using waist-to-hip ratio as a marker of central fat distribution did not deter a significant association between adiponectin and CVD during multivariate logistic regression analysis, suggesting adiponectin and central fat distribution work independently from one another relative to the prevalence of CVD among Filipinos.

To our knowledge, this is the first study to examine adiponectin concomitantly with proinsulin, C-peptide, and microalbuminuria with CVD among a cohort of Filipinas. As demonstrated in the Rancho Bernardo Study, rising proinsulin levels more than doubled the risk of CHD in men and nearly doubled the risk in women, and C-peptide levels increased the risk of CHD in women but not in men. However, we found null associations of proinsulin and C-peptide with CVD in our Filipina cohort. Microalbuminuria is a common marker for generalized vascular function and doubles the risk for CVD in patients with type 2 diabetes and hypertension. Therefore, our finding of an independent association between microalbuminuria and CVD among our Filipina participants in agreement with previous studies, in which high prevalences of microalbuminuria were common type 2 diabetes sequela among Asians.

Contrary to our expectations, type 2 diabetes and hypertension had no independent association with CVD in the multivariate analysis of this study. There are many possible reasons for this unexpected anomaly. First, this study was conducted cross-sectionally, and temporal associations were disallowed; second, many of the participants were newly diagnosed with type 2 diabetes, and CVD complications may not have yet fully manifested. Among the 76 women with diabetes in this cohort, most (61%, n=46) were so diagnosed during this clinical evaluation. Among these, 34 women had normal fasting glucose levels but had 2-hour glucose levels >200 mg/dL. Thus, diabetes diagnosis would have been missed in 74% of the newly diagnosed diabetics if screening was limited to fasting glucose measures only. Moreover, in a subset of our Filipina participants without CVD (n=181), type 2 diabetes and hypertension were independently associated with coronary artery calcification 4 years later. Although this is the first study to evaluate prevalence of CVD and associated risk factors among Filipino American women, several potential limitations require acknowledgment. First, acquiring Filipinas into this study were by means of convenience sampling and not population based. Thus, it is difficult to determine whether Filipinas in this study were generalizable to all Filipinas in San Diego County. However, the 2000 US Census data showed that about 44% of all Filipino American women aged ≥25 were college graduates, which is similar to the findings of our study. This may suggest that our sample was indeed representative of all Filipino American women with regard to education and, presumably, socioeconomic status. In addition, other studies with Filipino participants have demonstrated similar infrequent smoking and alcohol consumption, increased physical activity, and high prevalence of glucose abnormalities and hypertension. Secondly, the cross-sectional study design made it difficult to infer duration of diseases. Therefore, future prospective study designs are essential in addressing this limitation.

In conclusion, this is the first study to measure CVD prevalence and present significant associations of parental history of MI, microalbuminuria, and low levels of adiponectin with prevalent CVD, independent of other risk factors, in an understudied ethnic group of Filipino American women. Although a prospective study is warranted to confirm the etiologic relationship between adiponectin and CVD, our study suggests that adiponectin could be a relevant indicator of CVD among Filipinas and a potential target of therapy among multiethnic cohorts presenting similar vascular and endocrinologic co-morbidities. Furthermore, even in the advent of prospective adiponectin screening methods, it is nevertheless essential for clinicians to detect more accessible CVD risk markers such as family history and monitor and manage renal function, to reduce CVD risk in the Filipina patient.

ACKNOWLEDGMENTS
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