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Adiponectin as a Protective Factor Against the Progression Toward Type 2 Diabetes Mellitus in Postmenopausal Women

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Abstract: Serum adiponectin levels have been suggested to be predictors of type 2 diabetes mellitus in diverse populations. However, the relationship between circulating adiponectin levels and the risk of development of type 2 diabetes in postmenopausal women has not been investigated.

A total of 382 healthy postmenopausal women who participated in a prospective cohort study were followed for 5.8 years. Type 2 diabetes mellitus was defined according to the criteria set out by the American Diabetes Association. Adiponectin, osteoprotegerin (OPG), and high-sensitivity C-reactive protein (hs-CRP) levels were measured using ELISA.

Of 195 women who did not have diabetes at baseline and who were reexamined in the second phase of the study for diabetic status, 35 subjects (17.9%) developed type 2 diabetes mellitus during the 5.8 years follow-up period. The women with type 2 diabetes had lower adiponectin levels than the healthy postmenopausal women. Multiple regression analysis showed that, after adjustments were made for age, cardiovascular risk factors, OPG, and hs-CRP levels, higher baseline adiponectin levels were associated with a lower relative risk (RR) of having type 2 (RR = 0.07, confidence interval [CI]: 0.01–0.66, $P = 0.021$).

Higher baseline adiponectin levels functioned as a predictor of a lower risk of developing type 2 diabetes mellitus among postmenopausal women during a 5.8 years follow-up study. Therefore, it is suggested that elevated adiponectin levels may offer protection against the development of type 2 diabetes mellitus after the menopause.

(*Medicine* 94(33):e1347)

Editor: Yongjie Ma.

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The authors have no conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001347

Abbreviations: CI = confidence interval, hs-CRP = high-sensitivity C-reactive protein, OPG = osteoprotegerin, RR = relative risk.

INTRODUCTION

Adipose-derived cytokines that are collectively called “adipocytokines” may be considered to be insulin sensitizers/insulin-mimetics, and some others may induce insulin resistance.¹ Adiponectin is a good adipocytokine that has attracted great attention due to its antidiabetic, antiinflammatory, and antiatherogenic properties.² Adiponectin is negatively correlated with different obesity measures, as well as with insulin resistance indices.³

Baseline adiponectin levels have been suggested for use as predictors of type 2 diabetes mellitus by a number of different studies.⁴ A systemic review and meta-analysis of 13 prospective studies reported that higher adiponectin levels were associated with a lower risk of type 2 diabetes in diverse populations.⁵

Variations in the adiponectin gene have been reported to be associated with insulin resistance and type 2 diabetes mellitus.⁶ Longitudinal data have shown that adiponectin gene polymorphisms are associated with the development of hyperglycemia.⁷ Furthermore, genetic variations in the ADIPOQ gene promoter have been associated with altered serum adiponectin levels and the progression toward type 2 diabetes.⁸

Adiponectin suppresses hepatic gluconeogenesis and stimulates fatty acid oxidation, insulin secretion, and glucose uptake in skeletal muscles.⁹ Therefore, this important adipocytokine, which plays a significant role in crosstalk between adipose tissue and glucose metabolism, should be considered in glucose homeostasis.

Despite the fact that adiponectin is considered by various studies to be among the robust biochemical markers for the prediction of type 2 diabetes mellitus,¹⁰ the majority of these studies have involved Asian populations, or Caucasians from Europe or North America.¹¹ No study focusing on the prospective association between adiponectin and type 2 diabetes mellitus among general populations from the Middle East or the Eastern Mediterranean region, who are known to be at increased risk of diabetes, can be found.¹² The prevalence of type 2 diabetes mellitus in the total population of the northern part of the Persian Gulf, in the heart of the Middle East, is 13%.¹² The main aim of this prospective, population-based study is to investigate the potential link between baseline adiponectin levels and the future development of type 2 diabetes mellitus in women. To the best of our knowledge, the present study is the first to evaluate circulating adiponectin as a predictor for diabetes among postmenopausal women.

METHODS

Community Sampling and Physical Examinations

The study design has been described previously.¹³ Briefly, the participants in the present study consisted of an age-stratified random sample of 382 postmenopausal women, who participated in the extension of the Iranian Multicenter Osteoporosis Study. The subjects were randomly selected from 13 clusters in the port city of Bushehr (the center of Bushehr Province, which has the longest border with the Persian Gulf).

The study was approved by the medical ethical committee of the Bushehr University of Medical Sciences, and written informed consent was obtained from all subjects.

The baseline examination took place from April 4 to September 22, 2006. All of the women, who were community dwelling and ambulatory, were asked to fast and to come to the survey center between 7:30 and 9:30 AM. On arrival at the survey site, information regarding the participants' age, sex, marital status, and education was recorded. Further questions were asked about their smoking status, use of postmenopausal hormone replacement therapy, and any drugs taken for angina, as well as whether they had any history of hypertension, diabetes, or dyslipidemia. Trained interviewers noted down the information using the WHO MONICA questionnaire.¹⁴

The participants' blood pressure was assessed twice, via the right arm, after a 15-minute rest in sitting position. A standard mercury sphygmomanometer was used. The women's heights and weights were measured using a stadiometer (heavy outer garments and shoes were removed first) and their body mass indexes (BMI) were calculated. The participants' waist circumferences were measured at the midway level between the costal margins and the iliac crests, and hip circumferences were measured at the level of the greater trochanters. A resting 12-lead EKG was also administered.

Laboratory Measurements

Fasting blood samples were taken and promptly centrifuged and separated, and analyses were carried out at the Persian Gulf Health Research Center on the day of blood collection using a Selectra 2 autoanalyzer (Vital Scientific, Spankeren, Netherlands). Glucose was assayed by the enzymatic (glucose oxidase) colorimetric method using a commercial kit (Pars Azmun, Inc., Tehran, Iran). Serum total cholesterol and HDL cholesterol were measured using a cholesterol oxidase phenol aminoantipyrine, and triglycerides were measured using a glycerol-3 phosphate oxidase phenol aminoantipyrine enzymatic method. Serum LDL-cholesterol was calculated using the Friedewald formula; LDL-cholesterol was not calculated when the triglyceride concentration was >400 mg/dL.

To detect adiponectin in the serum samples, commercially available ELISA kits (Cat. No. AG-45A-0001EK-KI01; AdipoGen, Incheon, Korea) were used according to the manufacturer's instructions. The detection limit of the assay was 100 pg/mL; the intra- and interassay coefficients of variance were 2.9% to 3.8% and 2.8% to 5.5%, respectively.

Serum osteoprotegerin (OPG) levels were measured using an ELISA commercial kit (BiomedicaGruppe, Vienna, Austria). The detection limit of the assay was 0.14 pmol/L. The mean intra- and interassay coefficients of variation of the OPG assay were 4% to 10% and 7% to 8%, respectively.

C-reactive protein (CRP) was measured using CRP HS enzyme-linked immunosorbent assay (ELISA) (DRG Instruments GmbH, Germany), a highly-sensitive (hs) CRP

assay. A concentration of 0.1 mg/L for CRP was estimated to be the lowest concentration detectable via the CRP HS ELISA assay. According to the interassay coefficient of variation (CV) $<20\%$, the functional sensitivity of the CRP measurement was determined to be 0.1 mg/L.

Definitions

Using the American Diabetes Association's criteria, the existence of diabetes in a patient was defined either by a fasting plasma glucose level ≥ 126 mg/dL or by the use of antidiabetic measures.¹⁵

The cut-off points for the serum total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and serum triglyceride distributions, which were used to assign subjects to different risk groups, were derived from the National Cholesterol Education Program (NCEP) guidelines in the United States (Adult Treatment Panel [ATP] III).¹⁶ A subject was considered hypertensive if her blood pressure was at least 140/90 mm Hg.

Smoking was considered to be present when the subject smoked cigarettes or used hubble-bubble in a regular daily fashion. Respondents were classified as active at the recommended level if they reported sufficient physical activities of moderate intensity (ie, ≥ 30 minutes per day, ≥ 5 days per week) or of vigorous intensity (ie, ≥ 20 minutes per day, ≥ 3 days per week).

Follow-Up Data Collection and Outcome Classification

The participants were contacted to participate in a 5-year follow-up study. The follow-up examination occurred at a median of 5.8 years. At 5-year follow-up study, the baseline evaluations were repeated and the participants were examined by an expert endocrinologist in our university research clinic.

New cases of type 2 diabetes mellitus were defined as the presence of any one of the following: use of prescription medication for diabetes management or treatment, fasting blood glucose ≥ 126 mg/dL. The diagnosis of diabetes was confirmed by repeat testing in subjects with negative history of diabetes who had fasting blood glucose ≥ 126 mg/dL in follow-up study (11 subjects).¹⁵

Statistical Analysis

The distribution of the data was controlled using the Kolmogorov-Smirnov test. The significance of differences between the results of any 2 groups was determined via Chi-square analysis, using 2×2 contingency tables for categorical variables. A 2-tailed *t* test was used to compare the mean values across groups. We found that log transformation of adiponectin, CrossLaps, sRANKL, and OPG gave a better fit to a Gaussian distribution. The geometric mean for those biochemical variables was defined as the arithmetic mean of the log-transformed data \pm SD, raised to the power of 10.

Pearson's correlation analysis was used to study the relationships between the adiponectin values and the anthropometric and biochemical variables.

Binary logistic regression analysis was used to determine the association between circulating baseline adiponectin levels and the future development of type 2 diabetes mellitus. In the full model, baseline adiponectin was the independent variable of interest, and age, smoking status, physical activity, high blood pressure, low HDL-cholesterol, high LDL-cholesterol, high

TABLE 1. Baseline Characteristics of 382 Postmenopausal Women, Stratified by Serum Adiponectin Below/Equal or Above Median

	Adiponectin ≤ Median	Adiponectin > Median	P-Value
Age	57.45 ± 7.38	60.33 ± 8.31	0.001
Body mass index (kg/m ²)	28.93 ± 4.61	27.87 ± 4.98	0.048
Systolic blood pressure (mm Hg)	125.21 ± 19.95	127 ± 19.64	0.350
Diastolic blood pressure (mm Hg)	81.19 ± 25.86	78.60 ± 10.82	0.242
Fasting blood glucose (mg/dL)	123.87 ± 56.62	103.20 ± 36.54	<0.0001
Total cholesterol (mg/dL)	229.14 ± 44.49	236.51 ± 46.64	0.146
LDL-cholesterol (mg/dL)	150.23 ± 40.48	159.60 ± 40.91	0.039
HDL-cholesterol (mg/dL)	38.26 ± 10.58	43.96 ± 9.91	<0.0001
Triglyceride (mg/dL)	203.14 ± 113.13	164.86 ± 74.46	<0.0001
hs-CRP (mg/L)*	2.01 ± 2.95	1.67 ± 2.77	0.116
Osteoprotegerin (pmol/L)*	3.68 ± 1.61	3.54 ± 1.52	0.426
Adiponectin (μg/mL)*	7.64 ± 1.30	15.45 ± 1.37	<0.0001

Data are given as mean ± SD unless otherwise indicated.

* Geometric mean ± SD. LDL-cholesterol = low-density lipoprotein-cholesterol, HDL-cholesterol = high-density lipoprotein-cholesterol, hs-CRP = high-sensitivity C-reactive protein.

triglyceride, BMI, hs-CRP, and OPG levels were considered covariates.

A P-value of less than 0.05 was accepted as significant. All statistical analyses were performed using PASW Statistics GradPack 18 (SPSS, Inc., Chicago, IL).

RESULTS

Cross-Sectional Analysis

Table 1 shows the baseline characteristics of the studied postmenopausal women, stratified into low (below or equal to the median) and high (above the median) adiponectin groups. The mean age (mean ± SD) of the women was 58.6 ± 7.4 years. Serum adiponectin for the total population (n = 382) was at a median level of 10.81 μg/mL.

There were no differences between the 2 groups with regard to systolic and diastolic blood pressures, total cholesterol, hs-CRP levels, and OPG levels. However, the women with low a diponectin levels (below median) were younger and had higher BMIs, as well as higher fasting glucose and triglyceride levels. They had lower HDL-C and LDL-C levels (Table 1).

There was a significant correlation between serum adiponectin levels and age, BMI, fasting blood glucose level, HDL-cholesterol level, triglyceride level, and hs-CRP level. However, serum adiponectin levels had no significant correlations with systolic and diastolic blood pressures, total cholesterol, LDL-cholesterol, and OPG (Table 2).

Of the studied population, 102 subjects (26.7%) had type 2 diabetes mellitus. The patients with type 2 diabetes were found to have lower adiponectin levels (9.24 ± 1.46 ng/mL) than the healthy controls (11.49 ± 1.60 ng/mL) (P < 0.0001).

Prospective Analysis

Of 195 women who did not have diabetes at baseline and who were reexamined in the second phase of the study for their diabetic status, 35 subjects (17.9%) had developed type 2 diabetes mellitus over the course of the 5.8 years follow-up period. The women developed type 2 diabetes mellitus had lower adiponectin levels than the healthy controls.

Table 3 shows the unadjusted and adjusted relative risk (RR) (95% confidence interval [CI]) for serum adiponectin

levels and the development of type 2 diabetes mellitus. Age-adjusted higher baseline adiponectin levels were associated with a lower RR of having type 2 diabetes mellitus (Table 3). In logistic regression analysis, this association remained unchanged after adjusting for further variables, including cardiovascular risk factors, hs-CRP level, and OPG level (RR = 0.07, CI: 0.01–0.66, P = 0.021) (Table 3).

DISCUSSION

In the present study, we found that patients with type 2 diabetes mellitus had significantly lower levels of adiponectin compared with healthy postmenopausal women. Moreover, the baseline circulating adiponectin level was a reliable predictor of

TABLE 2. Bivariate Correlation Analysis Between Adiponectin and Age, Cardiovascular Risk Factors, Osteoprotegerin (OPG), and High-Sensitivity C-Reactive Protein (hs-CRP) in Postmenopausal Women

	Log (Adiponectin)	
	R	P-Value
Age	0.187	0.001
Body mass index	−0.160	0.004
Systolic blood pressure	0.048	0.392
Diastolic blood pressure	−0.043	0.439
Fasting blood glucose	−0.209	<0.0001
Total cholesterol	0.029	0.605
LDL-cholesterol	0.057	0.305
HDL-cholesterol	0.276	<0.0001
Triglyceride	−0.203	<0.0001
Log (hs-CRP)	−0.127	0.022
Log OPG	−0.018	0.747

Correlation coefficients and P values were calculated using Pearson correlation analysis.

LDL-cholesterol = low-density lipoprotein-cholesterol, HDL-cholesterol = high-density lipoprotein-cholesterol, hs-CRP = high-sensitivity C-reactive protein, OPG = osteoprotegerin.

TABLE 3. Relative Risk (RR) and Their 95% Confidence Intervals (CI) for Prediction of Type 2 Diabetes (as Dependent Variable) and Adiponectin Levels (as Independent Variable) in Different Models

	Type 2 Diabetes		
	RR	CI	P-Value
Adiponectin (\leq median)			
Unadjusted	0.07	0.01–0.58	0.013
Age-adjusted	0.06	0.01–0.48	0.008
Model 1	0.09	0.01–0.75	0.026
Model 2	0.09	0.01–0.79	0.030
Model 3	0.07	0.01–0.66	0.021

Model 1 included adiponectin levels, age and body mass index.

Model 2 included adiponectin levels, age, body mass index, and high-sensitivity C-reactive protein.

Model 3 included adiponectin levels, age, smoking status, physical activity, high blood pressure, low high-density lipoprotein-cholesterol, high low-density lipoprotein-cholesterol, high triglyceride, high-sensitivity C-reactive protein, and osteoprotegerin.

future development of type 2 diabetes mellitus in postmenopausal women during a 5.8 years follow-up period. Higher levels of serum adiponectin were associated significantly with a lower risk of development of diabetes after adjustments for age, cardiovascular risk factors, OPG, and hs-CRP were made.

In multiple cross-sectional studies, the inverse relationship between adiponectin levels, insulin resistance indices, and type 2 diabetes mellitus has been shown.^{4–17} In addition, the role of adiponectin in the prediction of type 2 diabetes mellitus has been clarified in multiple prospective cohort studies from North America, Europe, and East Asia.^{11,18,19–23} In accordance with these studies, we found that adiponectin levels were associated independently with the development of type 2 diabetes mellitus during a 5.8 years period. To the best of our knowledge, the present study provides the first prospective cohort information on circulating adiponectin and diabetes among postmenopausal women. However, Goodarzi et al²⁴ reported that diabetic postmenopausal women had lower adiponectin levels compared with age-matched healthy women in a small case–control study.

Adiposity may be a potential confounding factor in the relationship between adiponectin and diabetes. We have demonstrated an inverse association between adiponectin levels and adiposity measures like BMI and waist-to-hip ratio in postmenopausal women. In previous studies, different measures of adiposity, including BMI, waist-to-hip ratio, and body composition indices, have been considered using multivariate adjustments.⁵ In the present study, adiponectin remained a significant predictor of type 2 diabetes mellitus after adjustments were made for BMI.

Previous studies have suggested that low-grade systemic inflammation is involved in the pathogenesis of type 2 diabetes mellitus,²⁵ which promotes the inclusion of hs-CRP in a type 2 diabetes risk prediction score.²⁶ Adiponectin is an important antiinflammatory cytokine.²⁷ This adipocytokine has been found to be negatively correlated with markers of inflammation and inflammatory responses in vivo and in vitro studies.^{28–29} In line with these findings, we found that there was a significant negative correlation between adiponectin levels and hs-CRP in postmenopausal women. However, the efficacy of adiponectin levels as a

predictor for type 2 diabetes mellitus remained evident after adjustments were made for hs-CRP levels in the present study. This finding suggests that the link between adiponectin and the development of type 2 diabetes mellitus goes beyond to its association with low-grade systemic inflammation.

The levels of OPG circulation, as an inhibitor of bone resorption, seem to be elevated in patients with cardiovascular disorders and diabetes.³⁰ We have reported that circulating OPG levels are associated significantly with diabetes, and that this association is independent of the cardiovascular risk factors of postmenopausal women.³⁰ Hence, we used OPG levels as a potential confounding factor in the multivariate models utilized in the present study. The results showed that the level of adiponectin, as a predictor of the development of diabetes, can be seen as independent from the OPG level.

We acknowledge several limitations. The participants were not screened for glucose intolerance using oral glucose tolerance tests. Previous studies confirmed that oral glucose tolerance test diagnose more people with diabetes mellitus than HbA1C and fasting blood glucose cut points.³¹ The power of our study might be increased to clarify any association between adiponectin and diabetes by the detection of more new cases of type 2 diabetes mellitus using oral glucose tolerance test. We measured total adiponectin and did not differentiate between the various isoforms of the protein. In some studies, slightly stronger associations between the risk of diabetes and high-molecular-weight adiponectin (compared with total adiponectin) have been reported.⁵ We lost one-third of our cohort during the 5.8 years follow-up period, which might limit the ability to generalize the findings. The participants were not screened for glucose intolerance using oral glucose tolerance tests, which resulted in a limited ability to detect diabetics via elevated postchallenge glucose levels. Given that we assessed adiponectin levels using a single measurement, the changes in this adipocytokine over time could not be demonstrated in the present study. As the studied adipocytokines are involved in insulin resistance and the metabolic syndrome, we did not adjust the regression models for measures of insulin resistance, including HOMA-IR. Furthermore, measurements for additional inflammatory markers, proinflammatory cytokines, and chemokines, which are indicators of insulin resistance, merit consideration to elucidate the complex system that regulates glucose homeostasis and energy balance.

Our study demonstrates that higher baseline adiponectin levels are predictors of a lower risk of type 2 diabetes mellitus among postmenopausal women during a 5.8 years follow-up period. Elevated adiponectin levels may be a protective factor, therefore, against the development of type 2 diabetes mellitus after the menopause.

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