

# Predictive role of adiponectin and high-sensitivity C-reactive protein for prediction of cardiovascular event in an Iranian cohort study: The Isfahan Cohort Study

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## Original Article

### Abstract

**BACKGROUND:** Numerous studies have been conducted on the predictive effects of high-sensitivity C-reactive protein (hs-CRP) on cardiovascular events. Few studies have been conducted to investigate the effects of adiponectin for the prediction of the incident of cardiovascular events in the Middle East area. This study compared the predictive effect of hs-CRP and adiponectin on healthy volunteers for the prediction of cerebrovascular disease (CVD).

**METHODS:** This nested case-control in original Isfahan Cohort Study (ICS) was conducted from 2001 to 2011. Participants were selected from ICS. The case group included participants with CVD while the control group included participants without CVD. The level of hs-CRP and adiponectin was measured in the blood samples collected in the year 2007. Thereafter, the statistical analyses were performed to determine the predictive value of hs-CRP and adiponectin in CVD prediction.

**RESULTS:** The results showed that before the elimination of diabetes effect; there was a significant difference between the two groups, in terms of the mean of adiponectin ( $P = 0.019$ ) and no significant difference was observed in hs-CRP levels ( $P = 0.673$ ). However, after eliminating the factor of diabetes, there was no significant difference between the case and control groups in adiponectin and hs-CRP levels ( $P = 0.184$ ,  $P = 0.946$ ). The results showed that the odds ratio (OR) of the adiponectin level was 0.879 [95% confidence interval (CI): 0.719-1.075,  $P = 0.210$ ] while the OR of hs-CRP was 1.045 (95% CI: 0.922-1.185,  $P = 0.491$ ). Furthermore, it was shown that after adjustment for age, sex, and diabetes; the OR of adiponectin was 0.875 (95% CI: 0.701-1.091,  $P = 0.235$ ) and that of hs-CRP was 1.068 (95% CI: 0.935-1.219,  $P = 0.333$ ).

**CONCLUSION:** The results show that adiponectin and hs-CRP cannot be predictors for cardiovascular events in a healthy population. Risk factors such as diabetes limit the use of adiponectin as a CVD predictor.

**Keywords:** Adiponectin, High-Sensitivity C-Reactive Protein, Cardiovascular Disease

*Date of submission:* 5 Feb 2015, *Date of acceptance:* 11 Apr 2016

### Introduction

Cardiovascular disease (CVD) is the main cause of death worldwide.<sup>1</sup> Furthermore, in Iranian population, CVD is a major cause of morbidity and mortality.<sup>2</sup> The current evidence shows that

fat tissue works not only as a storage source but also as an endocrine tissue.<sup>3,4</sup> Adiponectin is a recently introduced inflammatory cytokine and some studies revealed its important metabolic effects.<sup>5</sup> Few studies have reported on

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adiponectin's anti-inflammatory and anti-atherogenic effects.<sup>6</sup> Some studies discussed the probable anti-atherogenic role of adiponectin while its real physiologic functions are still unknown.<sup>7-10</sup> On the other hand, high-sensitivity C-reactive protein (hs-CRP) has been proposed as a predictive factor for cardiovascular events.<sup>11</sup>

Adiponectin is a protein secreted by adipocytes, so its serum levels may differ with changes in body weight and visceral fat tissues. Lower levels of adiponectin (< 4  $\mu\text{g}/\text{ml}$ ) may be correlated with diabetes II, insulin resistance, hypertension (HTN), metabolic syndrome, dyslipidemia, and hyperuricemia. Adiponectin has also been mentioned as an anti-atherosclerotic agent. It has been investigated as a biomarker in association with weight gain disorders in some recent studies.<sup>12</sup>

CRP is an acute phase reactant which is synthesized in the liver by stimulation of cytokine interleukin-6 and is also a factor in atherosclerosis plaque development.<sup>13</sup> Several prospective and case-control studies conducted in the United States have shown that CRP is a risk factor for cardiovascular diseases and hs-CRP is a strong predictive factor of mortality and morbidity in cardiovascular patients.<sup>14-17</sup>

It is proposed that physiologic concentrations of adiponectin will inhibit the production of tumor necrosis factor in macrophages connected to the endothelium and thus, will avoid the expression of molecules such as E-selectin, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1.<sup>18-20</sup> Hotta *et al.*<sup>18</sup> and Kumada *et al.*<sup>21</sup> showed that a reduction in adiponectin levels is associated with increased risk of cardiovascular events and will double the chance of disease independently.<sup>12</sup>

As a result of increasing rate of cardiovascular events in the Middle East, knowing more about predictive factors with higher predictive values and lower costs are essential. The purpose of this study was to explore the association of adiponectin and hs-CRP with the incidence of CVD events in adults who participated in the Isfahan Cohort Study (ICS).

## Materials and Methods

This is a nested case-control study in the ICS conducted from 2001 to 2011. The ICS is a part

of a community trial for prevention and control of CVD, named the Isfahan Healthy Program. In fact, the ICS is a population-based continuing longitudinal study of adults with 35 years or more which are residents in urban and rural places of three countries in central Iran.<sup>22</sup>

In the ICS, initially, the informed written consent is taken and then medical interview and physical examination were performed. After that, information about measurable characteristics of every participants and a fasting blood sample was taken which followed standard protocol and using tuned devices that are previously described.<sup>23</sup> All participants in ICS were followed by phone interview every 2 years using standard questionnaires.

For this nested case-control study, the case groups were selected among participants in ICS who had fatal, non-fatal myocardial infarction (MI) and stroke (ischemic) between September 2007 and September 2013, and before the year 2007, they had none of the diseases mentioned. The criteria for the diagnosis of MI were based on the following criteria which the patient who had two of three following characteristics considered MI: (1) Typical chest pain which prolonged for more 30 minutes, (2) ST-elevation for more than 40.1 mV in two contiguous leads, and (3) cardiac biomarkers increasing. The diagnosis of ischemic stroke was defined as rapid-onset focal neurological deficit which sustained for more than 24 hours.<sup>22</sup> The controls were selected among those without the aforementioned events but were matched with the case group during follow-up (density sampling) to make time for risk to be similar between each pair. For each case, the controls were chosen randomly from those members of the cohort who were at risk at the failure time (event date) of the case and matched in terms of age, sex, and hyperlipidemia (HLP). It is noteworthy that all patients in both groups had no history of vascular events such as MI and stroke at the baseline. Identifying the case and control groups were done using the information in the records. They were contacted according to their information in the documents and people with documented ischemic heart disease and stroke were identified.

Demographic data such as age, sex, marital

status, and cardiovascular risk factors such as diabetes (fasting blood sugar  $\geq 126$ ), HTN (systolic blood pressure  $\geq 140$ , diastolic blood pressure  $\geq 90$ ), smoking, obesity (body mass index  $\geq 30$ ), and HLP (total cholesterol  $\geq 200$ , triglyceride  $\geq 150$ ) were collected from the two groups. Blood samples of participants were collected in 2007 and stored at  $-70\text{ }^{\circ}\text{C}$  in Isfahan Cardiovascular Research Center. Adiponectin and hs-CRP levels were measured using commercial kits (DRG, Germany) of radioimmunoassay (RIA) (human) adiponectin. Ethical approval was obtained from the Ethics Committee of Isfahan Cardiovascular Research Centre, the World Health Organization (WHO) collaborating center.

Numerical values were presented as a mean  $\pm$  standard deviation (SD). Categorical factors were reported as number (percentage). T-test or Mann-Whitney test and Chi-square test were used to compare the case and control groups for quantitative and qualitative factors, respectively. The analysis of covariance was used to compare means of adiponectin or hs-CRP in the case and control groups while statistically controlling for diabetes, age, and sex. The conditional logistic regression was used to estimate the odds ratios (ORs). CVD events were assumed to be dependent on variables and adiponectin and hs-CRP as an independent variable while adjusting for age, sex and diabetes.<sup>2</sup>

The data were analyzed using the software package used for statistical analysis SPSS software (version 15.0, SPSS Inc., Chicago, IL, USA).  $P < 0.050$  were considered as statistically significant.

## Results

In this study, 39 patients with cardiovascular disease (cases) and 41 healthy individuals (controls) were included. From the 80 patients studied, 48 patients were males (60%) and 32 were females (40%). The sex distribution between the case and control groups was not significant.

As shown in table 1, the two groups showed no significant difference in terms of age. The other risk factors were also not significantly different in the case and control groups and only diabetes mellitus (DM) was different between the case and control groups ( $P = 0.007$ ).

After the initial analysis of the results, comparison of adiponectin levels between the two groups showed that there were significant differences between the case and control groups ( $P = 0.019$ ).

However, because the prevalence of diabetes differed significantly between the two groups, the factor of diabetes in the comparison between the two groups was adjusted. The results showed that there was no significant difference between the groups in levels of adiponectin ( $P = 0.184$ ) and hs-CRP ( $P = 0.946$ ). The results are shown in table 2.

**Table 1.** Comparison of demographic and risk factors between the case and control groups

Variable	Case (n = 39)	Control (n = 41)	P
Demographics			
Gender (%)			
Male	22 (56)	26 (63.4)	0.523*
Female	17 (44)	15 (36.6)	
Marital status			
Single	3 (7)	5 (12.0)	0.479*
Married	36 (93)	35 (86.0)	
Risk factors			
DM (%)	21 (53)	10 (24.3)	0.007*
HTN (%)	24 (61)	22 (53.6)	0.476*
HLP (%)	31 (79)	30 (73.1)	0.507*
Smoking (%)	6 (15)	7 (17.0)	0.761*
Triglyceride (mg/dl)	194.84 $\pm$ 110.86	164.56 $\pm$ 126.91	0.260**
BMI	27.42 $\pm$ 4.82	26.83 $\pm$ 3.29	0.523**
FBS (mg/dl)	129.77 $\pm$ 68.47	96.95 $\pm$ 26.94	0.006**
SBP (mmHg)	132.05 $\pm$ 22.16	130.70 $\pm$ 19.15	0.770**
DBP (mmHg)	80.76 $\pm$ 13.51	80.06 $\pm$ 10.14	0.790**
Cholesterol (mg/dl)	217.71 $\pm$ 38.84	214.89 $\pm$ 42.22	0.750**
Age	60.21 $\pm$ 9.64	60.42 $\pm$ 10.65	0.927**

\*Chi-square; \*\* t-test; DM: Diabetes mellitus; HTN: Hypertension; HLP: Hyperlipidemia; BMI: Body mass index; FBS: Fasting blood sugar; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

**Table 2.** Comparison of serum parameters between the two groups, with adjustment for confounding risk factors (sex, diabetes, hypertension)

Variable	Case	Control	P*
Lab tests			
Adiponectin ( $\mu\text{g/ml}$ )	$2.637 \pm 2.375$	$3.303 \pm 2.293$	0.184
Hs-CRP ( $\mu\text{g/ml}$ )	$3.671 \pm 3.821$	$3.128 \pm 3.288$	0.946

\* Analysis of covariance analysis; Hs-CRP: High-sensitivity C-reactive protein

They were also detrimentally associated with adiponectin and hs-CRP on CVD and obtained OR. The results showed that the OR of adiponectin level was 0.879 [95% confidence interval (CI): 0.719-1.075,  $P = 0.210$ ] and OR of hs-CRP was 1.045 (95% CI: 0.922-1.185,  $P = 0.491$ ). Moreover, the results showed that after adjustment for age, sex and diabetes, the OR of adiponectin was 0.875 (95% CI: 0.701-1.091,  $P = 0.235$ ) and that of hs-CRP was 1.068 (95% CI: 0.935-1.219,  $P = 0.333$ ).

## Discussion

In this study, the association of adiponectin and hs-CRP with the incidence of cardiovascular events in adults who participated in the ICS was assessed. No prediction role of adiponectin and hs-CRP in CVD was observed.

Oliveira et al.<sup>24</sup> discussed adiponectin as an independent predictive factor for cardiovascular events. Another study conducted with 48 percutaneous coronary intervention-needed patients with coronary diseases (left anterior descending involvement) and a 66-month period of follow-up revealed that the lower serum levels of adiponectin are associated with future cardiovascular events.<sup>25</sup> Although, adiponectin as an adipocytokine has a considerable role in causing cardiovascular events, its clinical importance is still controversial.

A prospective study including 171 patients with ischemic stroke and 171 matched controls compared the serum levels of adiponectin in days 0, 3, 7 and 90 of the event across groups. Adiponectin serum level was significantly lower in the patients, and this level could predict an atheroemboli stroke (OR: 0.75; 95% CI: 0.58-0.91,  $P = 0.009$ ). Adiponectin serum levels also had a positive correlation with the severity of the neurologic defect. The results of this study also showed that plasma levels of adiponectin may be different in the classification of stroke

subtypes and is able to predict neurological defects and stroke outcome.<sup>26</sup>

Animal studies suggest that reduced adiponectin levels in the acute phase of ischemic stroke are a dynamic process. In a study of 31 patients with the first episode of stroke, at intervals of 24 hours, 2-4 days and 5-10 days after ischemic stroke, plasma adiponectin levels were measured three times. On the basis of their results, adiponectin levels were significantly lower in patients with ischemic stroke when compared with other causes of stroke. This may reflect the effect of adiponectin on the predictive value of the occurrence of ischemia.<sup>27</sup>

However, results of studies on the predictive effects of adiponectin on cardiovascular events are conflicting in some cases. In a prospective meta-analysis performed in Europe, the predictive value of adiponectin for cardiovascular events was studied. The relative risk of stroke in adiponectin levels higher than 5  $\mu\text{g/ml}$  was about 1.10 with 95% CI: 0.89-1.37. The patients with higher levels of adiponectin have higher levels of high-density lipoprotein cholesterol and lower triglycerides and CRP.<sup>28</sup> The difference between the present study and studies in America can be attributed to differences in resource classification and naming of different kinds of stroke among various European and American resources.

The mechanism of action of adiponectin in predicting cardiovascular events remains unclear, and several hypotheses have been proposed. For example, adiponectin as an insulin sensitizing hormone was introduced with the assumption that the plasma adiponectin levels in metabolic disorders such as DM Type 2 is reduced and shows the relationship between adiponectin levels, increased risk of cardiovascular events and related deaths.<sup>29</sup>

Results of a cohort study on 4571 at risk African-Americans revealed that adiponectin is

more associated with stroke in females. This study showed that the mechanism of prediction of adiponectin is still unclear but hypotheses have been proposed that the production of this substance is in response to vascular inflammation and deals with atherosclerosis.<sup>30</sup>

Several large prospective epidemiological studies showed that hs-CRP is a strong predictor of cardiovascular events such as MI and stroke.<sup>13</sup> In a cohort study which was conducted with 1086 apparently healthy middle-aged men, participants in the quartile with the highest CRP values had 3 and 2 times the risk of MI and ischemic stroke, respectively, in contrast to subjects with the lowest CRP.<sup>31</sup>

The results of this study show that adiponectin and hs-CRP cannot be predictors for cardiovascular events in a healthy population. The difference between these results and the results of other studies could be because of diabetes which is a confounding factor.

This study had some limitations which could affect the results. One of the restrictions was the small sample size which had impact on the results. Another limitation of this study was the presence of confounding variables such as DM in both groups.

However, as mentioned, the use of adiponectin as an independent predictor of cardiovascular events continues to be associated with controversy. On the other hand, there is no population-based study to evaluate this effect. Future studies to examine the predictive effects of adiponectin as compared to other biomarkers with larger sample sizes are recommended.

### Conclusion

The results of this study show that adiponectin and hs-CRP cannot be predictors for cardiovascular events in a healthy population. Risk factors such as diabetes, limit the use of adiponectin as a CVD predictor. Further studies with larger sample size should be conducted to determine the predictive role of adiponectin and hs-CRP in CVD.

### Acknowledgments

We are thankful to the team of the ICRC, Isfahan Provincial Health Center, Najafabad

Health Office and the Arak University of Medical Sciences, Iran.

### Conflict of Interests

Authors have no conflict of interests.

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**How to cite this article:** Kazemi-Saleh D, Koosha P, Sadeghi M, Sarrafzadegan N, Karbasi-Afshar R, Boshtam M, et al. **Predictive role of adiponectin and high-sensitivity C-reactive protein for prediction of cerebrovascular event in an Iranian cohort study: The Isfahan Cohort Study.** *ARYA Atheroscler* 2016; 12(3):132-7.