Tropical Journal of Pharmaceutical Research November 2020; 19 (11): 2447-2452
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v19i11.28

Original Research Article

Role of adiponectin in the pathology of early-stage coronary heart disease in Chinese Type 2 diabetes mellitus patients

Biling Ye[1], Ling Zeng[2], Zhan Xu[1], Wenji Lin[1]*
[1]Department of Intensive Care Unit, [2]Department of Nursing, Shenzhen Nanshan District Shekou People's Hospital, Shenzhen 518067, China

For correspondence:* ***Email:* *IanAlvisuMvFn@yahoo.com*

Sent for review: 23 April 2020 *Revised accepted: 21 October 2020*

Abstract

Purpose: *To investigate the role of adiponectin in the pathogenesis of diabetes-induced coronary heart disease (CHD) in Chinese type 2 diabetes mellitus (T2DM) patients.*
Methods: *Serum ADpN levels were measured every 3 months in T2DM patients in early stage of heart disease who were followed up for 5 years. Adiponectin (ADpN) was measured using a turbidimetric immunoassay method. At the same time, ADpN was measured every 3 months for up to 5 years in T2DM patients with no sign of heart diseases (control). Hazard ratios (HR) for analysis of progression-free survival outcomes were assessed using appropriate statistical tools.*
Results: *At baseline, ADpN levels in male and female patients were similar ($p < 0.05$). However, male and female T2DM patients who developed heart disease had history of uncontrolled diabetes, dyslipidemia and hypertension. Patients (males and females) who had significantly lower levels of HDL developed heart disease ($p < 0.05$). The hazard ratio (HR) for low ADpN was favorable in male and female patients with early heart disease who experienced heart disease after baseline demography covariates such as age, BMI and gender.*
Conclusion: *These results suggest that low ADpN level is a significant independent potential risk factor for CHD in Chinese T2DM patients with early stage of cardiac disease who were taking biguanide- and thiazolidinedione-based drugs. Intervention strategies that raise ADpN levels > 7.0 µg/ml could be helpful in preventing CHD in these T2DM patients.*

Keywords: *Adiponectin, Coronary heart disease, Early-stage heart disease, Diabetes*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Adiponectin (ADpN), one of the key proteins produced by adipocytes, has been found to possess anti-inflammatory and anti-atherosclerotic properties [1-3]. The role of ADpN in cardiovascular diseases has already been investigated in western countries, mainly amongst Caucasians [4-10]. It has been reported that ADpN levels are associated with poor cardiovascular outcomes, and that they increase the risk of atherosclerosis in healthy patients [4-10]. In a TIMI trial, clinical outcomes and ADpN levels were measured in patients with

acute coronary disorder (ACS), and the results showed that patients with ACS who had increased ADpN levels had poor prognosis (assessed by number of death and cardiovascular events) [11].
In contrast, it was found that patients with ACS who had low ADpN levels had better survival outcomes. In other studies, ADpN was measured in patients who were undergoing angioplasty with myocardial infraction. Lower ADpN level was found to exert protective effect against acute myocardial infarction in white patients with ACS [10,11]. Although the role of ADpN has been investigated in white/Caucasian patients with acute cardiac diseases [5-11], it is not clear whether ADpN level is also a predictor of pathology of diabetes-induced coronary heart disease in Chinese patients in early stages of heart disease. Thus, the present preliminary investigation was designed to investigate the role of ADpN in pathology of early stages of coronary heart disease in Chinese T2DM patients.

EXPERIMENTAL

Patients and ethics

Chronic diabetes mellitus patients of Chinese origin aged between 30 to 65 years, with confirmed diagnosis of early stage of heart diseases (atherosclerosis) were enrolled at Shenzhen Nanshan District Shekou People's Hospital after obtaining their written informed consent forms. All study-related documents including protocol, ICFs and CRFs were submitted to institutional ethical committee of Shenzhen Nanshan District Shekou People's Hospital for review and subsequent approval. The study was commenced only after receiving written approval from the ethics committee, vide IEC approval no. IEC/SNDSP/20-2983/04-19. This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and applicable laws and regulations [12].
To assess the eligibility criteria, patients were subjected to screening visit where blood samples for cholesterol tests were collected. Moreover, the patients were instructed to undergo coronary angiography, chest x-ray, and electrocardiogram. Patients who were addicted to drug/alcohol, and those with severe heart diseases, renal impairment, liver diseases, lung diseases and thyroid diseases were excluded from the study. Other excluded patients were those with cognitive impairment due to Huntington's disease, and patients with other pathologies that may affect the outcome of the study (based on the discretion of consulting physician), or patients who received prohibited concomitant medications.
Fasting blood samples collected from the patients were frozen at – 80o Celsius. Blood glucose, insulin and lipid profiles were estimated in order to confirm eligibility criteria. Moreover, serum ADpN was measured using immunoassay (turbidometric method) with a computerized analyzer. In this assay, antigen-antibody reaction (agglutination) occurs between ADpN and bunny rabbit anti-humanoid ADpN antibody immobilized on gutta-percha globules.
Serum ADpN levels were measured every 3 months in T2DM patients in early stages of heart disease who were followed up for 5 years. At the same time, ADpN was measured every 3 months for up to 5 years in T2DM patients with no sign of heart disease (control). Risk ratios for the analysis of free survival outcome were assessed using appropriate statistical tool. Baseline covariate variables such as demography (age, BMI and gender) and clinical characteristics (BP, smoking, DM status, cholesterol level, HDL level, LDL level; and use of anti-hypertensive medication) were compared at baseline as covariates. The data were stratified by gender: male and female.

Statistical analysis

The present pilot study was designed to evaluate the effect of ADpN in the pathology of diabetes-induced coronary heart diseases at the early stages in Chinese T2DM patients. Hence, there was no formal calculation of sample size. At least 100 Chinese patients with early stage of heart disease in each treatment group were enrolled. Mann Whitney test was used to analyze non-normal data (numerical data), where unpaired test was used to analyze normal data (numerical data). Fisher exact test or chi-square test was used to analyze categorical data. Hazards ratio for adiponectin after adjustments of baseline was calculated using log rank test.

RESULTS

The demographic and baseline characteristics of male and female Chinese DM patients with early stage of heart disease are presented in Table 1. It was observed that women had significantly higher levels of ADpN than male patients. Other demographic and baseline characteristics were similar in both genders. Moreover, glucose and lipid levels were comparable in male and female groups. Based on the menopausal status of the female patients, the data were divided into two groups: pre- and post-menopausal.

Table 1: Demographic and baseline characteristics of male and female Chinese DM patients with early stage of heart disease

Outcome variable	Male	Female	*P*
Age	53.34±4.2	55.14±5.3	>0.05
BMI	26.2±2.3	27.6±1.2	>0.05
Waist (cm)	101.3±12.2	109.1±10.3	>0.05
SBP	132.12±13.2	128.2±4.2	>0.05
DBP	78.2±6.1	82.3±4.3	>0.05
Hypertension (% of pts)	41.2	45.7	>0.05
DM (% of pts)	100	100	>0.05
Glucose, fasting (mg/dL)	130.3±3.5	134.5±4.2	>0.05
Insulin	7.3±2.1	8.5±4.4	>0.05
TC	210.34±32.1	200.14±21.3	>0.05
HDL	32.3±2.3	30.2±1.1	>0.05
LDL	135.2±21.2	131.1±21.2	>0.05
TG	123.2±2.6	113.4±2.6	>0.05
ADpN	7.2±3.1	7.7±2.3	>0.05

Values are mean (SD) for all variables except hypertension and DM (categorical variables)

The demographic and baseline characteristics of pre- and post-menopausal female Chinese patients in early stage of heart disease were comparable. These results are presented in Table 2.

Table 3 shows the fasting blood glucose, insulin and ADpN levels in Chinese patients with early stage of heart disease, in terms of gender (male vs female) and menopausal status (pre- and post-menopausal women). For glucose measurement, the mean fasting blood glucose level was comparable in both male and female groups. In the female sub-group, post-menopausal women had slightly higher mean blood glucose level than pre-menopausal women, but the difference was not statistically significant.

Table 3: Mean fasting blood glucose, insulin and ADpN levels of Chinese patients with early stage of heart disease, in terms of gender and menopausal status

Variable		Mean (SD)
Insulin		
Male		13.2±1.8
Female		12.1±1.3
	PreMW	17.2±1.3
	PostMW	19.1±1.8
Glucose		
Male		123.3±8.8
Female		121.1±9.3
	PreMW	117.2±12.3
	PostMW	129.3±2.8
ADpN		
Male		9.1±1.1
Female		8.2±1.2
	PreMW	10.1±1.4
	PostMW	11.3 1.5

PreMW: pre-menopausal; PostMW: post-menopausal

Table 2: Demographic and baseline characteristics of pre- and post-menopausal female Chinese patients with early stage of heart disease

Variables	Premenopausal	Postmenopausal	*P*-value
	52.14±3.1	51.24±3.3	>0.05
BMI	25.2±1.3	24.2±1.2	>0.05
Waist (cm)	96.1±8.1	97.2±9.3	>0.05
SBP	112.2±8.2	122.1±7.2	>0.05
DBP	78.2±6.1)	82.3±4.3	>0.05
Hypertension (% of pts)	39.2	40.1	>0.05
DM (% of pts) Glucose,	100	100	>0.05
fasting (mg/dL)	120.1±2.5	124.2±3.2	>0.05
Insulin	6.8±2.1	7.3±3.1	>0.05
TC	201.14±8.1	210.14±7.3	>0.05
HDL	31.1±1.3	28.2±2.1	>0.05
LDL	112.1±18.2	118.1±17.2	>0.05
TG	113.1±1.6	103.4±1.3	>0.05
ADpN	7.1±2.1	7.2±2.3	>0.05

Values are as mean ± SD for all variables except hypertension and diabetes mellitus (categorical variables)

Similarly, insulin level was comparable in both male and female groups. Post-menopausal women had slightly higher mean blood insulin level than pre-menopausal women, although the difference was not statistically significant. In contrast, ADpN level was significantly higher in females than in males. Post-menopausal women had slightly higher mean ADpN level than pre-menopausal women. Overall, gender had no significant impact on glucose and insulin levels. However, gender had a slight impact on ADpN level.

Data on the hazards ratio (HR) for ADpN after adjustments of baseline are shown in Table 4. The HR for low ADpN was 0.48 ($p < 0.005$) in male patients with early stage of heart disease. The HR for low ADpN in male patients with early stage of heart disease was statistically significant at 0.52 ($p < 0.005$) after adjustment for all clinical risk factors such as BP, smoking, DM status, cholesterol level, HDL level, LDL level, and use of anti-hypertensives medication (Table 4). In female patients with early heart disease, the HR for low ADpN was 0.52 ($p < 0.005$) after baseline demography covariates such as age, BMI and gender.

The HR for low ADpN in female patients with early heart disease who experienced disease progression was statistically significant at 0.39 ($p < 0.005$), after adjustment for all clinical risk factors such as BP, smoking, DM status, cholesterol level, HDL level, LDL level, and use of anti-hypertensive medication (Table 4).

Table 4: Hazards ratio for ADpN after adjustments of baseline

Variable	Male		Female	
	HR	***P***	***HR***	***P***
Model (M) 1	0.423	0.001	0.54	<0.002
M 2	0.49	<0.002	0.59	>0.05
M 3	0.52	0.0005	0.49	>0.05
M 4	0.59	<0.001	0.48	>0.05

M 1: Adjusted for covariates of age, BMI, waist circumference (cm); M2: adjusted for covariates of SBP and DBP; M3: adjusted for covariates of hypertension and DM; M4: adjusted for covariates of glucose, insulin, TC, HDL, LDL, TG, and ADpN

Kaplan-Meyer curves on the relationship between ADpN level and cardiac diseases in males and females are shown in Figure 1 and Figure 2, respectively. The trend in these results shows association of increased risk of cardiac diseases with low levels of ADpN in male patients with early heart disease.

Moreover, the trend in Figures 1 and 2 shows association of increased risk of cardiac diseases with low levels of ADpN in female patients with early heart diseases. These results indicate that low ADpN level irrespective of gender, is a potential risk factor for pathogenesis of cardiac diseases in Chinese patients with T2DM.

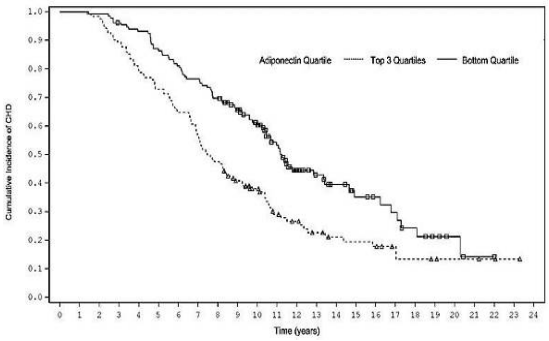

Figure 1: KM curve in Chinese male patients with early stage of heart diseases

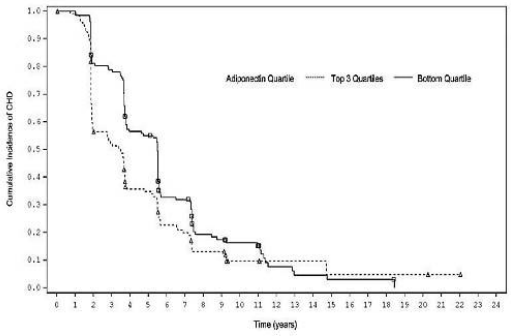

Figure 2: KM curve for Chinese female patients with early stage of heart diseases

DISCUSSION

This is the first study to investigate the role of ADpN in the pathology of diabetes-induced coronary heart disease in Chinese DM patients with early stage of heart diseases. The results of the present study showed that low ADpN level is a significant independent and potential risk factor for CHD in T2DM patients at the early stages of cardiac disease, irrespective of gender

These results are consistent with previous findings in the Framingham Offspring Study which reported that low ADpN is a significant independent risk factor for CHD in white patients [5]. The Framingham Offspring Study showed that ADpN level less than 7.0 µg/mL is a strong independent predictor of CHD in men in the United States. This is consistent with the results of the present Chinese study which revealed that ADpN level less than 7.0 µg/mL is a potent independent predictor of heart disease in male and female patients.

The Framingham Offspring Study analyzed data after adjusting for all potential confounding variables such as age, BMI, smoking status, blood pressure, treatment status of hypertension, status of DM, usage of anti-hyperlipidemic class of drugs, and lipid profile. The results of the present study showed that the HR did not significantly change after adjusting for all the potential confounding variables such as age, BMI, smoking status, blood pressure, hypertension treatment status, diabetes status of DM, usage of anti-hyperlipidemia class of drugs, and lipid profile. This indicates that demography and baseline characteristics had no impact on the association between ADpN levels and heart disease.

High plasma ADpN level may not be problematic. However, a low ADpN level is problematic in male and female Chinese DM patients with early stage of cardiac disease. It was also observed in published articles that exercise and weight loss may increase plasma ADpN levels. Furthermore, some medications such as antidiabetics and statins were found to increase plasma ADpN levels in patients taking biguanide, thiazolidinedione and other statin classes of medications [13-17].

The present study revealed that low level of ADpN is a significant independent potential risk factor for CHD in T2DM patients with early stages of cardiac diseases who are taking biguanide and thiazolidinedione classes of drugs. Plasma ADpN levels were assayed using automated analyzer (with assay kits). This automated analyzer has outstanding coefficient of variation (CV). There are other available assay kits for ADpN, but apart from not being automated, these assay methods are laborious, and are associated with higher level of CV.

Limitations of the study

Since the present trial was conducted at a single hospital in China, the findings cannot to be generalized to the Chinese population. Due to low sample size, there is need for a larger clinical trial with appropriate sample size so as to confirm the present findings.

CONCLUSION

The results obtained in this study show that low ADpN is a significant independent potential risk factor for CHD in Chinese T2DM patients who take biguanide and thiazolidinedione classes of drugs. Intervention strategies for raising ADpN levels below 7.0 µg/ml may be helpful in preventing CHD in these T2DM patients.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

Open Access

REFERENCES

1. *Yamauchi T, Nio Y, Maki T, et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 2007; 13:332–339.*
2. *Ouchi N, Kihara S, Arita Y, et al. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. Circulation 2001; 103:1057–1063.*
3. *Turer AT, Scherer PE. Adiponectin: mechanistic insights and clinical implications. Diabetologia 2012; 55:2319–2326.*
4. *Wildman RP, Mancuso P, Wang C, Kim M, Scherer PE, Sowers MR. Adipocytokine and ghrelin levels in relation to cardiovascular disease risk factors in women at midlife: longitudinal associations. Int J Obes (Lond) 2008; 32:740–748.*
5. *Masumi A, Seiko O, Bela FA, Charles CW. Adiponectin: an Independent Risk Factor for Coronary Heart Disease in the Framingham Offspring Study. Atherosclerosis 2011; 217(2): 543–548.*
6. *Zhang H, Mo X, Hao Y, Huang J, Lu X, Cao J, Gu D. Adiponectin levels and risk of coronary heart disease: a meta-analysis of prospective studies. Am J Med Sci 2013; 345:455–461.*
7. *Zhang BC, Liu WJ, Che WL, Xu YW. Serum total adiponectin level and risk of cardiovascular disease in Han Chinese populations: a meta-analysis of 17 case-control studies. Clin Endocrinol (Oxf) 2012; 77:370–378.*

8. Hao G, Li W, Guo R, Yang JG, Wang Y, Tian Y, Liu MY, Peng YG, Wang ZW. Serum total adiponectin level and the risk of cardiovascular disease in general population: a meta-analysis of 17 prospective studies. Atherosclerosis 2013; 228:29–35.
9. Sook Lee E, Park SS, Kim E, Sook Yoon Y, Ahn HY, Park CY, Ho Yun Y, Woo Oh S. Association between adiponectin levels and coronary heart disease and mortality: a systematic review and meta-analysis. Int J Epidemiol 2013; 42:1029–1039.
10. Kanhai DA, Kranendonk ME, Uiterwaal CS, van der Graaf Y, Kappelle LJ, Visseren FL. Adiponectin and incident coronary heart disease and stroke. A systematic review and meta-analysis of prospective studies. Obes Rev 2013; 14:555–567.
11. Jessica LM, Eugene B, Stephen DW, Jean-Pierre B. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366(1):9-19.
12. World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997; 277:925–926.
13. Miyazaki Y, Mahankali A, Wajcberg E, Bajaj M, Mandarino LJ, DeFronzo RA. Effect of pioglitazone on circulating adipocytokine levels and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 2004; 89:4312–4319.
14. Yang WS, Jeng CY, Wu TJ, Tanaka S, Funahashi T, Matsuzawa Y, Wang JP, Chen CL, Tai TY, Chuang LM. Synthetic peroxisome proliferator-activated receptor-gamma agonist, rosiglitazone, increases plasma levels of adiponectin in type 2 diabetic patients. Diabetes Care 2002; 25:376–380.
15. Phillips SA, Ciaraldi TP, Kong AP, Bandukwala R, Aroda V, Carter L, Baxi S, Mudaliar SR, Henry RR. Modulation of circulating and adipose tissue adiponectin levels by antidiabetic therapy. Diabetes 2003; 52:667–74.
16. Westphal S, Borucki K, Taneva E, Makarova R, Luley C. Extended-release niacin raises adiponectin and leptin. Atherosclerosis 2007; 193:361–365.
17. Lamon-Fava S, Diffenderfer MR, Barrett PH, Buchsbaum A, Nyaku M, Horvath KV, Asztalos BF, Otokozawa S, Ai M, Matthan NR, Lichtenstein AH, Dolnikowski GG, Schaefer EJ. Extended-Release Niacin Alters the Metabolism of Plasma Apolipoprotein (Apo) A-I-and ApoB-Containing Lipoproteins. Arterioscler Thromb Vasc Biol 2008; 28:1672–1678.