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Total Adiponectin and Risk of Symptomatic Lower Extremity Peripheral Vascular Disease in Type 2 Diabetes Mellitus

Research Article

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Abstract

Objective: Adiponectin is an adipocyte-derived protein that has gained considerable research interest because of its pleiotropic effects on insulin sensitivity, atherosclerosis and inflammation. Lower concentrations of adiponectin have been linked to subsequent risk of coronary heart disease in healthy individuals. Whether similar relationships exist for the development of systemic atherosclerosis, such as peripheral vascular disease (PVD), is uncertain. We investigated the association between total adiponectin and risk of lower extremity PVD.

Methods and Results: We performed a case control study among 60 diabetic patients in tertiary center, PBM Hospital, bikaner, who were free of diagnosed cardiovascular disease. Among 60 patients, 6 developed PVD. Using risk set sampling, controls were selected and matched on age, no smoking status, fasting status, lipid profile, HbA1c, RFT and BMI. On distributing cases according to Adiponectin level in Relation to PVD, total of 60 patients were included in study and distributed in two groups of either decreased or normal adiponectin level. A total of 6 patients had PVD of which adiponectin levels were decreased in 5 patients and normal in 1, and on application of test of significance they were found to be statistically significant with p value of 0.01.

Conclusion: Total adiponectin is inversely associated with risk of symptomatic lower extremity PVD in diabetes patients.

Keywords: Adiponectin; Peripheral Vascular Disease; Diabetes Mellitus; Atherosclerosis.

Abbreviations: PVD: Peripheral Vascular Disease; CVD: Cardiovascular Disease; HDL: High-Density Lipoprotein; MI: Myocardial Infarction; TNF-α: Tumor Necrosis Factor Alpha; NF-ϰB: Nuclear Factor Kappa B.

Introduction

Adiponectin is an adipocyte-derived protein that has gained considerable research interest because of its pleiotropic effects on insulin sensitivity, atherosclerosis and inflammation [1]. In addition to a consistently lower risk of type 2 diabetes [2], higher adiponectin concentrations have also been associated with lower risk of cardiovascular disease (CVD) in several studies [3-5]. More recent epidemiological reports, however, observed weaker inverse associations [4, 6] after adjustment for high-density lipoprotein (HDL) cholesterol [7-9], questioning the putatively protective and independent role of adiponectin in atherosclerotic diseases.

Peripheral vascular disease (PVD) is a manifestation of systemic atherosclerosis that affects an estimated 10 million U.S. adults and is associated with reduced functional capacity [10] and increased risk for cardiovascular morbidity and mortality [12, 13]. Although cholesterol and inflammatory risk factors are also strong predictors in this form of CVD [14, 15], PVD is characterized by progressive luminal obstruction in peripheral arteries and may be less related to thrombosis or plaque rupture than are myocardial infarction (MI) or ischemic stroke [16, 17]. This raises the possibility that factors with anti-atherosclerotic and anti-inflammatory properties, like adiponectin, may be of particular importance in the development of this type of CVD.

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To evaluate the association of total adiponectin with risk of PVD in the lower extremities, we studied diabetes patients in tertiary care center.

Method and Results

We performed a case control study among 60 diabetic patients in tertiary center, PBM Hospital, bikaner, who were free of diagnosed cardiovascular disease. Among 60 patients, 6 developed PVD. Using risk set sampling, controls were selected and matched on age, no smoking status, fasting status, lipid profile, HbA1c, RFT and BMI. We found a strong inverse association between total adiponectin and risk of lower extremity PVD in otherwise healthy patients. On distributing cases according to Adiponectin level in Relation to PVD, total of 60 patients were included in study and distributed in two groups of either decreased or normal adiponectin level.

Baseline characteristics of cases and controls are presented in table 1. Both case and control are matchable in all background characteristics.

As shown in table 2, out of 60 cases 6 patients had PVD. So the prevalence of PVD in our study was found to be 10%.

Table 3 shows distribution of cases According to Age Group in Relation to PVD. Out of total of 60 patients, 1 patient fall under the age group of <40 years while 7 and 18 patients belongs to age group of 41-50 and 51-60 age group respectively, 23 patients had their age between 61-70 years while 11 patients were of 71-80 years age group.

In present study total 6 patients had their PVD positive and out of them 1, 1 and 4 were belonged to age group less than <40, 51-60 and 61-70 years respectively and this relation was found to be statistically significant.

Table 4 shows distribution of cases According to Sex in Relation to PVD, out of 60 patients, 6 had PVD and among them 3 were males and 3 were females, On applying chi square test, the difference was found to be statistically insignificant (p=0.86).

Table 5 shows Distribution of cases According to ABI in Relation to PVD. 10 percent of patient had severe as well as abnormal value of ABI with none of the patient falling in severely diseased, while 80 percent of patients had normal ABI.

Table 6 shows distribution of cases according to adiponectin level in Relation to PVD, total of 60 patients were included in study and distributed in two groups of either decreased or normal adiponectin level, a total of 6 patients had PVD of which adiponectin levels were decreased in 5 patients and normal in 1, and on application of test of significance they were found to be statistically significant with p value of 0.01. The same findings are represented graphically in graph 1.

Discussion

In this study, we found a strong inverse association between total adiponectin and risk of lower extremity PAD in otherwise healthy patients, on distributing cases according to Adiponectin level in Relation to PVD, total of 60 patients were included in study and distributed in two groups of either decreased or normal adiponectin level, a total of 6 patients had PVD of which adiponectin levels were decreased in 5 patients and normal in 1, and on application of test of significance they were found to be statistically significant with p value of 0.01.

To our knowledge, only one prospective study has investigated the effect of adiponectin on risk of incident PAD [18]. Several potential mechanisms could explain the lower risk of PAD associated with higher adiponectin concentrations. Adiponectin may suppress smooth muscle cell proliferation and foam cell formation of macrophages and inhibit monocytic cell adhesion to endothelial cells. It may suppress inflammatory pathways in endothelial cells through down regulation of the nuclear factor

Table 1. Baseline characteristics of cases and controls.

Characteristics	Cases (n=6)	Control (n=54)
Age	58.33	61.29
Smoking	Nil	Nil
Alcohol	Nil	Nil
Lipid profile	Normal	Normal
Hb_{A1c}	8.4	8.1
RFT	Normal	Normal
CRP	Negative	Negative
BMI	24.8	24.6
Physical activity	Moderate	Moderate
Cardiovascular disease	None	None

Table 2. Prevalence of PVD (ABI<0.90).

Prevalence of PVD	Number of cases	%
Total number of cases	60	100
PVD cases	6	10

Table 3. Distribution of cases According to Age Group in Relation to PVD.

Age Group	PVD Present		PVD Absent		Total
	NO	%	NO	%	
<40	1	16.67	0	0.00	1
41–50	0	0.00	7	12.9	7
51–60	1	16.67	17	31.48	18
61–70	4	66.67	19	35.19	23
71–80	0	0.00	11	20.3	11
Total	6		54		60
Mean = 12 (Positive = 1.2; Negative = 10.8) S.D. = 21.16 (Positive = 2.68; Negative = 18.73)					

Chi Square - 12.79, p value - 0.01

Table 4. Distribution of cases According to Sex in Relation to PVD.

Sex	PVD Present		PVD Absent		Total
	NO	%	NO	%	
Male	3	50	25	46.30	28
Female	3	50	29	53.70	32
Total	6		54		60

Chi Square - 0.029, p value - 0.86

Table 5. Distribution of cases According to ABI.

ABI	Cases	
	No.	%
Critical (<0.5)	0	0
Severe (0.5–0.9)	6	10
Abnormal (<0.91–1)	6	10
Normal (>1)	48	80

Table 6. Distribution of cases According to Adiponectin level in Relation to PVD.

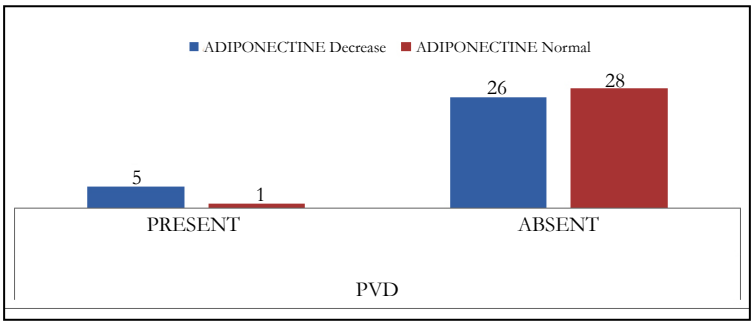
Adiponectin Level	PVD				Total
	Present		Absent		
	No	%	No	%	
Decrease	5	83.33	26	48.15	31
Normal	1	16.67	28	51.85	29
Total	6		54		60

Chi Square - 12.57, p value - 0.01

kappa B (NF-κB) pathway, a key regulator in tumor necrosis factor alpha (TNF-α) and other cytokines [19]. Adiponectin also reduces the development of atherosclerosis in mice prone to its development [20], whereas in humans, low adiponectin may predict coronary artery disease severity and progression [21, 22]. Also, adiponectin may lower the risk of atherosclerosis through its effect on insulin sensitivity [23], and subsequently lower risk of type 2 diabetes.

Although compelling experimental evidence suggests a protective role of adiponectin in atherosclerosis, prospective data on adiponectin and risk of forms of CVD other than PAD seem less consistent. There are a number of possible explanations for this discrepancy. First, heterogeneity in case definitions may play a role: combining atherosclerotic events inversely related to adiponectin with other cardiovascular outcomes less immediately related to atherosclerosis, such as heart failure and fatal CVD (including sudden cardiac death). Second, the discrepancy may relate to the paradoxically increased risk of all-cause and CVD mortality associated with adiponectin mostly observed among older adults

Graph 1. Distribution of cases According to Adiponectin level in Relation to PVD.



[24-26] and patients with prevalent heart failure [27], CVD [28, 29], PAD [30] or on hemodialysis [28] but also among apparently healthy men free of coronary artery disease [29]. Adiponectin has pleiotropic roles beyond its known insulin-sensitizing actions, including clearance of apoptotic cells [29]. As a result, it may directly improve insulin sensitivity and endothelial function even as levels rise in response to ongoing processes that lead to cellular apoptosis and necrosis and presumably mortality. In conclusion, we observed a strong linear inverse association between total adiponectin and risk of symptomatic lower extremity PAD in men free of manifest atherosclerotic disease. The association appeared to be independent of important biochemical or traditional clinical risk factors of CVD. These findings suggest a prominent role of adiponectin in the initiation and progression of atherosclerotic diseases such as PAD. Future mechanistic studies and prospective studies with well-characterized individuals are warranted to better understand the role of adiponectin in atherosclerosis.

Conclusion

Total adiponectin is inversely associated with risk of symptomatic lower extremity PVD in diabetes patients.

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