ORIGINAL ARTICLE

NOVEL RISK FACTORS FOR CORONARY HEART DISEASE IN TYPE II DIABETES MELLITUS

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ABSTRACT

Objective: To evaluate adiponectin, a novel biomarker, and other known cardiovascular risk factors in type 2 diabetic subjects belonging to Khyber Pakhtunkhwa.

Material and Methods: This cross-sectional and analytical study was conducted in Bio-Chemistry Department Khyber Medical College, Peshawar, Pakistan from January 2016 to December 2016, the participants were randomly selected from the OPDs of three tertiary care hospitals of Peshawar. The study comprised of two groups. Group A contained 60 type 2 diabetic subjects having coronary heart disease and group B consisted of healthy control. Detailed history of all participants was recorded on a questionnaire including their blood pressure and body mass index. Fasting blood samples were collected and were analyzed for serum adiponectin level, glycosylated hemoglobin, fasting blood sugar and fasting lipid profile including cholesterol, triglycerides, low density lipoprotein, high density lipoprotein and very low density lipoprotein. Analysis of the data was done with Statistical Package for the Social Sciences, version 19.

Results: Patients who had type 2 diabetes and coronary heart disease were found to have low adiponectin (3.2±1.1 vs. 11.7±2.6, P=<0.01) and high density lipoprotein (33.05±8.6 vs. 42.86±9.4, p=<0.01)) and significantly high levels of fasting blood glucose (198.1±106.7 vs. 90.5±15.7, p=<0.01), glycosylated hemoglobin (8.7±1.5 vs. 5.1±0.3, p=<0.01), total cholesterol (218.6±44.02 vs. 195.8±30.3), triglycerides (235.1±66.7 vs. 200.86±64.2) and low density lipoprotein (136.5±42.3 vs. 112.02±29.5). Moreover; they were mostly males and were of increased age group (60.6±9.7 vs. 46±5.3). All known risk factors of CHD such as use of tobacco, alcohol, physical inactivity, hypertension, genetic history of diabetes and coronary heart disease were present in higher percentage in diabetics having coronary heart disease than the healthy control group.

Conclusion: Marked hypoadiponectinemia, and traditional risk factors such as poor glycemic control and dyslipidemia are present in diabetic subjects having coronary heart disease.

Key Words: Adiponectin, Glycosylated, Hemoglobin, Lipid profile, Type II, diabetes mellitus, Coronary Heart disease.

This article may be cited as: Durrani S, Rahman UR, Ubaidullah, Ali S, Arif S, Khan MA, Wazir SUR. Novel risk factors for coronary heart disease in diabetes mellitus. J Med Sci 2017; 25: (2) 195-199.

INTRODUCTION

Coronary heart disease is among the biggest causes of death in type II diabetic patients. It is the most common complication of diabetes accounts for about 80% of deaths occurring in the affected population[1]. Subjects with type 2 diabetes mellitus (DM) have 2-4 folds higher risk of fatal and non-fatal coronary heart disease (CHD) related events[2]. Defective insulin secretion or action, the resultant hyperglycemia and associated metabolic disturbances such as hypertension and dyslipidemia lead to increased prevalence of CHD in these subjects[3].

Besides classical cardiovascular risk factors, which include increasing age, male gender, dyslipidemia especially hypercholesterolemia, hypertension, diabetes mellitus, physical inactivity, obesity and family history of CHD, attention has been drawn to other measurable factors like adiponectin which may modulate CHD risk in type 2 diabetes mellitus[4,5].

First identified in 1995, adiponectin is a hormone which is protein in nature. It contains 244 amino acids and is secreted mostly by the adipose tissue[6]. A 30 KDa adiponectin monomer has a structure made up of globular head and collagenous tail. These monomers have the ability to multimerize into higher order stable complexes which are classified as: Low Molecular Weight (LMW), Medium Molecular Weight (MMW) and

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Date Received: January 12, 2017
Date Revised: March 20, 2017
Date Accepted: May 10, 2017

Higher Molecular Weight (HMW)[7]. Adiponectin hormone constitutes nearly 10% of all circulating proteins. Its serum level ranges between 2-30 μg/ml and is more in females than males[8]. Adiponectin has three receptors, Adipo R1, Adipo R2 found on skeletal muscle and liver respectively and T Cadherin present on cardiovascular system[9]. Adiponectin possesses anti-inflammatory, anti-hyperlipidemic, anti-hypertensive, anti-atherogenic, insulin sensitizing and cardioprotective properties[10]. Hypoadiponectinemia has been strongly linked with insulin resistance, dysfunction of pancreatic beta cells, type 2 diabetes, hypertension, obesity, atherogenesis and coronary heart disease[11,12]. We studied a novel cardiovascular risk factor, adiponectin, along with classical risk factors, in patients of type 2 diabetes who also have CHD.

MATERIAL AND METHODS

Our study is cross-sectional and analytical. It is performed on two groups. Group A included sixty subjects with type 2 diabetes and coronary heart disease having first episode of myocardial infarction during the previous ten days. Group B contained sixty healthy subjects who had no major disease such as diabetes mellitus, ischemic heart disease, hypertension, any malignancy, kidney, liver or thyroid disease. All the participants were randomly selected from the tertiary health care hospitals of Peshawar, i.e Hayatabad Medical Complex (HMC), Khyber Teaching Hospital (KTH), and Lady Reading Hospital (LRH). Their complete history and physical examination details including blood pressure (BP) and BMI (Body Mass Index, which is calculated as weight in Kg divided by height in m^2) were noted down on a questionnaire after receiving a signed consent. The Ethical Committee of Khyber Medical College (KMC), Peshawar approved this study. Five mL of blood sample was drawn from the participants under aseptic and fasting conditions and was centrifuged at 4000 rpm to get clear serum. Blood glucose (fasting) along with lipid profile were detected using fresh samples. Calculation of glycosylated hemoglobin was done on blood in EDTA tubes. Estimation of adiponectin level was done at on serum which was frozen (-70 ºC).

Fasting blood sugar (FBS), cholesterol and triglyceride (TG) were determined through enzymatic colorimetry, the kits were of Elitech-Sees, France. High density lipoprotein (HDL) was determined colorimetrically with a kit of Diasys Holzheim. Friedewald's formula[13] and Delong's formula[14] were used to find low density lipoprotein (LDL) as well as very low density lipoprotein (VLDL), respectively. Glycosylated hemoglobin (HbA1c) was measured with enzymatic colorimetric method using kit provided by Human Diagnostics, Germany. Adiponectin level was measured on kit from Human Adiponectin ELISA obtained from Biovendor, Germany (Cat. No. RD 195023100). SPSS version 19 was used for statistical analysis of the data obtained. Results were written as mean ± SD (standard deviation). Data was compared between groups using student's t test and the p value less than 0.05 was considered significant.

RESULTS

This study consisted of two groups: group A, type 2 diabetic subjects with CHD and group B, healthy control. Each group comprised of 60 participants out of which 36 (60%) were male and 24 (40%) were female. Group A patients were elderly having mean age of 60.6±9.7 while group B control were younger in comparison and had mean age of 46±5.3 years. Participants of both groups mostly lived in urban areas (group A 55%; group B 67%). Education level of groups was studied under three categories: Uneducated, Matric, and Bachelors. Group A patients showed highest percentage of illiterate participants i.e 66.6% vs. 51.6%, followed by matriculate i.e 25% vs. 28.3% and those with bachelors degree 8.3% vs. 20 % as compared to the control. Socioeconomic status was recorded as: Low (i.e monthly income ≤ Rs. 10,000), Moderate (i.e monthly income upto Rs. 20,000) and High (i.e monthly income ≥ Rs. 20,000). Both studied groups contained greater percentage of participants belonging to the moderate socioeconomic status i.e group A 63.3%; group B 65%, followed by low i.e group A 26.6%; group B 25% and high socioeconomic status i.e 8.3% in both groups.

The comparison of the classical and the non-classical cardiovascular risk markers between groups can be seen in the Table 1. Subjects with type 2 diabetes and coronary heart disease had significantly lower serum adiponectin (3.2±1.1 vs. 11.7±2.6, P=<0.01) and HDL-C (33.05±8.6 vs. 42.86±9.4, p=<0.01)) levels than the healthy control. They also showed worse metabolic profile with significantly high levels of FBS (198.1±106.7 vs. 90.5±15.7, p=<0.01), HbA1c (8.7±1.5 vs. 5.1±0.3, p=<0.01), total cholesterol (218.6±44.02 vs. 195.8±30.3), triglycerides (235.1±66.7 vs. 200.86±64.2) and LDL-C (136.5±42.3 vs. 112.02±29.5. Non-significant results were obtained after comparison of BMI, SBP and DBP. Diabetic subjects with CHD were more frequent users of tobacco (33.3% vs. 10%) and alcohol (28.3% vs. 8.3%). They were mostly hypertensive (75%) and had a strong family history of diabetes (43.3% vs. 8.3%) and coronary heart disease (36.6% vs. 14.6%). High percentage of participants in group A (91.6%) and group B (85%) was physically inactive.

Table 1: Demographic, clinical and biochemical characteristics

Variables	Group A n=60	Group B n=60	p-value
Age (years)	60.6±9.7	46±5.3	< 0.01**
BMI (kg/m2)	26.9±3.2	27.7±2.7	0.133
SBP (mmHg)	124.5±30.2	124.1±7.9	0.904
DBP (mmHg)	81.5±16.7	80.7±5.6	0.439
FBS (mg/dL)	198.1±106.7	90.5±15.7	< 0.01**
HbA1C (%)	8.7±1.5	5.1±0.3	<0.01**
TC (mg/dL)	218.6±44.02	195.8±30.3	0.001**
TG (mg/dL)	235.1±66.7	200.86±64.2	0.004**
HDL-C(mg/dL)	33.05±8.6	42.86±9.4	< 0.01**
LDL-C (mg/dL)	136.5±42.3	112.02±29.5	< 0.01**
VLDL-C(mg/dL)	46.9±13.03	40.8±12.8	0.011*
Adiponectin(μg/mL)	3.2±1.1	11.7±2.6	< 0.01**
Smoking status (%)	33.3	10	< 0.05
Alcohol Use (%)	28.3	8.3	< 0.05
Physical inactivity (%)	91.6	85	NS
Family history of diabetes (%)	43.3	8.3	< 0.05
Hypertension (%)	75	_	< 0.05
Family history of CHD (%)	36.6	14.6	< 0.05

Note: P value <0.05 is considered significant

DISCUSSION

Circulating adiponectin level in health and disease varies to a great extent depending on gender, age, ethnicity and life styles. Limited literature is available on serum adiponectin level in healthy and diabetic subjects belonging to Khyber Pahthunkhwa.

We observed significantly lower levels of adiponectin in type 2 diabetics having coronary heart disease in comparison to healthy subjects. Similar results have been observed by other studies[15-20]. Zoccali et al[21] were the first to associate low serum adiponectin level in CHD patients in a prospective cohort study. Schulze et al[22] performed a Health Professionals Follow-up Study upon diabetic men and reported a significant relationship of low adiponectin with risk of CHD. Framingham Offspring Study and Pischon et al also reported similar results in non-diabetic population[23,24]. Obata et al confirmed the association of hypoadiponectinemia with CHD risk in type 2 diabetic Japanese patients independent of other cardiovascular risk factors. They suggested that increase in serum adiponectin level may prove beneficial in prevention of CHD[25].

Several mechanisms may participate in adiponectin's cardioprotective ability. These include: raised sensitivity of insulin, high nitric oxide (NO) secretion by endothelium, decreased adhesion of monocytes to vascular endothelium, decreased formation of foam cells from macrophages, decreased proliferation, migration and calcification of smooth muscle cells in the vessels[26].

We observed deranged glycemic control (high HbA1C), dyslipidemia (high TG and low HDL-C) and hypertension, the classical risk factors of CHD[27]. Results similar to our results have been observed in studies performed in different parts of the world on populations of variable ethnicity[28-32]. Hypoadiponectinemia contributes to high triglycerides by lowering the activation of PPAR α; peroxisome proliferator activated-receptor and increasing VLDL output by liver. It also reduces the activity of lipoprotein lipase enzyme leading to low HDL[33]. Decreased insulin sensitivity associated with hypoadiponectinemia plays a role in the development as well as progression of type 2 diabetes mellitus resulting in complications such as CHD[34].

Some studies have however reported contradictory results[35-36]. These negative studies may be explained on the basis of underlying differences in incidence or risk of CHD or sample size.

The results of this study raise a question whether or not the modification of serum level of a novel biomarker, adiponectin, can help to reduce CHD events in type 2 diabetic subjects.

LIMITATIONS

The relatively smaller sample size and study subjects with a particular age group (40 and above) may be the limitations of the study. Different results might be observed if similar studies are conducted on large sample size including subjects with variable age groups and lifestyles. This study is based on a randomized design which is its strength.

CONCLUSION

Adiponectin is markedly reduced in type 2 diabetic subjects having CHD. The traditional risk factors like glycolipid abnormalities, hypertension, alcohol/tobacco consumption, physical inactivity, family history of DM and CHD are also associated with these subjects.

ACKNOWLEDGEMENT

The authors acknowledge the participants, technical staff working in Research Laboratory, Biochemistry Department, Khyber Medical College and the Ethical Committee. Special gratitude is expressed to the Higher Education Commission (HEC) for funding this project.

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CONFLICT OF INTEREST: Authors declare no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE Funding by HEC

AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Durrani S: Idea.

Rahman UR: Idea, data collection, analysis.

Ubaidullah: Data collection

Ali S: Statistics.

Khan MA: Final approval, critical review

Wazir SUR: Biochemical analysis.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.