HYPOADIPONECTINEMIA AND DYSLIPIDEMIA IN RELATION TO GLYCEMIC STATUS IN TYPE 2 DIABETES AND CORONARY HEART DISEASE

Sadaf Durrani[1✉], Jasmin Shah[2], Mudassir Ahmad Khan[3], Muhammad Rasul Jan[4]

[1✉] Demonstrator Biochemistry Department, Khyber Medical College, Peshawar Khyber Pakhtunkhwa, Pakistan
E-mail: sdurrani77@hotmail.com
[2] Meritorious Professor, Institute of Chemical Sciences, University of Peshawar Pakistan
[3] Chairman, Biochemistry Department, Khyber Medical College, Peshawar, Pakistan
[4] Professor Emiratus, Institute of Chemical Sciences and Vice Chancellor, University of Peshawar, Pakistan

Date Submitted: August 21, 2014
Date revised: October 05, 2014
Date accepted: October 06, 2014

ABSTRACT

OBJECTIVE: to study the relationship of adiponectin level with lipid profile and glycemic control in type 2 diabetic subjects with and without coronary heart disease (CHD).

METHODOLOGY: This cross-sectional/ analytical study consisted of three groups. Group A consisted of 60 healthy subjects, group B consisted of 60 type 2 diabetic subjects and group C consisted of 60 type 2 diabetic subjects with coronary heart disease. The study participants were analyzed for serum adiponectin level, triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c).

RESULTS: Significantly high adiponectin level was observed in female subjects as compared to male subjects. Type 2 diabetic subjects with and without coronary heart disease presented with significantly higher FBG, HbA1c, TC and TG (p value <0.05) and significantly lower levels of serum adiponectin and HDL-C (p value <0.001). Adiponectin level showed significant positive association with HDL-C in control group (female: r 0.988; p=<0.01, male: r 0.948; p=<0.01), type 2 diabetic group (female: r 0.908; p=<0.01, male: r 0.860; p=<0.01) and type 2 diabetic group having coronary heart disease (female: 0.775; p=<0.01, male: 0.650; p=<0.01). Significant (p value <0.01) negative association of adiponectin was observed with TG, FBG and HbA1c in type 2 diabetic subjects with and without coronary heart disease.

CONCLUSION: Hypoadiponectinemia in type 2 diabetic subjects with and without coronary heart disease is related with un-controlled glycemic status and dyslipidemia.

KEY WORDS: Adiponectin, Dyslipidemia, Glycemic status, Type 2 diabetes mellitus, Coronary heart disease.

THIS ARTICLE MAY BE CITED AS: Durrani S, Shah J, Khan MA, Jan MR. Hypoadiponectinemia and dyslipidemia in relation to glycemic status in type 2 diabetes and coronary heart disease. Khyber Med Univ J 2014;6(4): 157-162.

INTRODUCTION

Type 2 diabetes mellitus or non-insulin dependent diabetes mellitus (NIDDM) is characterized by defective insulin receptors causing insulin resistance in peripheral tissues.[1] Resistance to insulin action and the resultant hyperglycemia are usually associated with advanced age, decreased physical activity, obesity, dyslipidemia, hypertension, risk of atherosclerosis, coronary heart disease and other complications.[2] Coronary heart disease is the commonest complication of diabetes mellitus and the top most cause of morbidity and mortality throughout the world. Fatal and non-fatal CHD related events tend to be 2-4 folds higher in type 2 diabetic subjects.[3]

Being the commonest form of diabetes, type 2 diabetes mellitus accounts for 90-95% of global diabetic population and is increasing at the rate of 3% per year. The prevalence of diabetes in Pakistan may increase from 5.2 million (2000) to 13.9 million (2030) and may affect 330 million world population till 2030.[4]

Adiponectin is a 244 amino acid containing protein hormone secreted by adipose tissue. It constitutes about 10% of all plasma proteins. Circulating adiponectin level ranges between 2-30 μg/mL and is more in females than males.[5] The sexual dimorphism of adiponectin level is explained on the basis of sex hormones (androgen and estrogen) and pattern of body fat deposition.[6,7] Males may have less adiponectin due to two reasons. First, they possess a mechanism of testosterone induced inhibition of adiponectin secretion from adipocytes. Second, they have excess of visceral adipose tissue (VAT) as compared to subcutaneous adipose tissue (SAT) in females, leading to dysregulation of adiponectin expression and secretion.[8] Adiponectin monomers have the capa-

bility to associate themselves into three higher order complex forms namely; trimer [LMW, low molecular weight form], hexamer [MMW, medium molecular weight form] and oligomer [HMW, high molecular weight form].[9] Adiponectin has three receptors, Adipo R1, Adipo R2 and T-Cadherin. The first two are found on skeletal muscle and liver respectively while the third is present on cardiovascular system.[10] Adiponectin has anti-inflammatory, anti-atherogenic, anti-hypertensive, anti-hyperlipidemic, anti-diabetic and cardioprotective properties.[11] Hypoadiponectinemia has been associated with insulin resistance, type 2 diabetes mellitus, hypertension, obesity, atherogenesis and coronary heart disease.[12,13]

We have determined fasting blood glucose, glycosylated hemoglobin, lipid profile and adiponectin levels in type 2 diabetic subjects with and without coronary heart disease to find any possible relationship of adiponectin with glycemic control and lipid metabolism in these subjects.

METHODOLOGY

This cross-sectional and analytical study consisted of three groups. Group A consisted of sixty healthy control subjects with no major disease such as diabetes mellitus, hypertension, coronary heart disease, thyroid or kidney disease. Group B consisted of sixty type 2 diabetic subjects diagnosed with type 2 diabetes mellitus, at least for the last four years. Group C consisted of sixty type 2 diabetic subjects with coronary heart disease; those who manifested first attack of myocardial infarction within the previous 10 days. All the study subjects were randomly selected from the tertiary care hospitals of Peshawar, namely; Hayatabad Medical Complex (HMC), Lady Reading Hospital (LRH), Khyber Teaching Hospital (KTH) and Rehman Medical Institute (RMI). History, blood pressure, height, weight and BMI (body mass index: weight in Kg/height in m^2) of all subjects were noted down on a well-formed questionnaire. All subjects signed a well informed consent and the study was approved by the Ethical Committee of Khyber Medical College, Peshawar.

Blood collection:

All study subjects provided 5 mL fasting blood sample. Serum was obtained by centrifuging blood at 4000 rpm for 5 minutes. Fresh serum samples were used for the estimation of fasting blood glucose and lipid profile while glycosylated hemoglobin was calculated using blood collected in EDTA tubes. Serum was stored at -70 °C for determination of adiponectin level.

Biochemical analysis

Fasting blood glucose (FBG), serum total cholesterol (TC) and serum triglyceride (TG) were measured using enzymatic colorimetric method with kits provided by Elitech-Sees, France. High density lipoprotein cholesterol (HDL-C) was estimated colorimetrically with a kit obtained from Diasys Holzheim, Germany. Low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) were determined with Friedewald's formula[14] and Delong's formula[15], respectively. Glycosylated hemoglobin (HbA1c) was found using enzymatic colorimetric method with kit provided by Human Diagnostics, Germany. Serum adiponectin level was measured using Human adiponectin ELISA kit (Biovendor Cat. No. RD 195023100, Germany).

Statistical analysis

Data analysis was carried out with SPSS version 19. All results were expressed as mean ± SD (standard deviation). Independent student's t test was used for comparison of variables among the groups. Results with p value less than 0.05 were considered as significant. Association of adiponectin with glycemic status (glycosylated hemoglobin, fasting blood glucose) and lipid profile was found using Pearson correlation coefficient r.

RESULTS

Tables I shows the demographic, clinical and biochemical characteristics of the studied groups. Each group consisted of 60 subjects. Group A (control) contained 36 (60%) male subjects having mean age of 47.2±5.5 years and 24 (40%) female subjects having mean age of 44±4.6 years. The female control had significantly higher serum adiponectin level than the male control (12.7±2.5 in females vs. 11.06±2.5 in males, p=<0.05). Group B (subjects with diabetes mellitus, DM) consisted of 34 (56.6%) male subjects having mean age of 56.1±9.7 and 26 (43.3%) female subjects having mean age of 56.8±11.3. Female subjects showed significantly higher HDL-C (39.04±11.3 in females vs. 32.4±9.6 in males) and TG (251.7±77.02 in females vs. 211.7±68.4 in males). Group C (diabetes mellitus with coronary heart disease, DM+CHD) consisted of 36 (60%) male subjects having mean age of 61.8±9.9 and 24 (40%) female subjects having mean age of 58.7±9.1. The comparison of variables between male and female subjects of the group revealed non-significant results.

Pearson correlation coefficient r was used to establish association of serum adiponectin with various clinical and biochemical variables. Table II shows association of adiponectin with different variables in female subjects of the studied groups. The female subjects having diabetes mellitus with and without CHD showed a strong negative association of adiponectin with FBG and HbA1c having correlation coefficient r -0.497, p=0.01 and r -0.814, p=<0.01 in group B and r -0.874, p=<0.01 and r -0.937, p=<0.01 in group C. These two groups also showed negative correlation of adiponectin with TC (r -0.733, p=<0.01 in

group B and r -0.423, p=0.039 in group C), TG (r -0.790, p=<0.01 in group B and r -0.669, p=<0.01 in group C) and LDL-C (-0.707, p=<0.01in group B). Adiponectin was positively associated with HDL-C in all female subjects with r 0.988 and p=<0.01 in control, r 0.908 and p=<0.01 in diabetic females and r 0.775 and p=<0.01 in females having diabetes with CHD. Female subjects belonging to control group maintained negative association of adiponectin with TG (r -0.515, p=0.01).

Table III shows association of adiponectin with variables in male subjects

TABLE I: DEMOGRAPHIC, CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF THE STUDIED GROUPS

Variables#	Group A (n=60)		Group B (n=60)		Group C (n=60)	
	M (n=36)	F (n=24)	M (n=34)	F (n=26)	M (n=36)	F (n=24)
Age(years)	47.2±5.5*	44±4.6	56.1±9.7	56.8±11.3	61.8±9.9	58.7±9.1
BMI(Kg/m²)	27.02±2.02	28.8±3.3*	26.7±3.7	27.1±4.2	26.2±3.3	27.9±3.02
SBP(mmHg)	124.7±7.6	123.1±8.5	134.9±19.6	136.9±18.7	121.9±29.4	128.5±31.7
DBP(mmHg)	81.±4.1	80±4.1	83.9±9.2	85.5±9.8	78.4±17.5	86.04±14.5
FBG(mg/dL)	86.8±16.7	96.0±12.5*	190.4±83.9	182.7±83.3	191.08±104.5	208.7±111.3
HbA1C(%)	5.2±0.3	5.1±0.41	8.8±1.8	8.1±1.2	8.7±1.4	8.8±1.6
TC(mg/dL)	202±29.6	186.6±29.5	213.7±36.1	223.6±37.5	220.8±43.2	215.3±45.8
TG(mg/dL)	212.6±54.8	183.1±73.8	211.7±68.4	251.7±77.0*	246.5±58.8	218.1±75.2
HDL-C(mg/dL)	42.4±8.6	43.5±10.6	32.4±9.6	39.04±11.3*	31.7±8.9	35.04±7.7
LDL-C(mg/dL)	115.9±29.4	106.1±29.3	137.7±33.4	134.1±36.8	136.4±43.2	136.7±41.8
VLDL-C(mg/dL)	43.7±10.4*	36.4±14.9	42.4±13.4	50.4±15.5*	49.2±11.7	43.5±15.1
Adiponectin(μg/mL)	11.06±2.5	12.7±2.5*	3.2±1.3	3.3±1.4	3.02±1.1	3.5±1.1

*P value <0.05 when the male and female subjects were compared with in the same group

BMI (Body mass index), SBP (systolic blood pressure), DBP (diastolic blood pressure), FBG (fasting blood glucose), HbA1C (Glycosylated haemoglobin),TC (total cholesterol), TG (triglycerides), HDL-C (high density lipoprotein-cholesterol), LDL-C (low density lipoprotein-cholesterol).. Data is expressed as mean ± SD (standard deviation).

TABLE II: CORRELATION OF ADIPONECTIN WITH DIFFERENT PARAMETERS IN FEMALE SUBJECTS OF THE STUDIED GROUPS (A, B, C)

Variables#	Group A (female)		Group B (female)		Group C (female)	
	r	p	r	p	r	p
Age	-0.96	0.654	0.117	0.568	-0.130	0.545
BMI	-0.136	0.526	-0.190	0.354	-0.244	0.251
SBP	-0.089	0.680	0.103	0.617	-0.096	0.654
DBP	-0.167	0.435	0.148	0.471	-0.085	0.694
FBG	0.258	0.223	-0.497	0.010**	-0.874	<0.01**
HbA1C	-0.160	0.456	-0.814	<0.01**	-0.937	< 0.01**
TC	-0.030	0.889	-0.733	< 0.01**	-0.423	0.039*
TG	-0.515	0.010*	-0.790	< 0.01**	-0.669	< 0.01**
HDL-C	0.988	< 0.01**	0.908	< 0.01**	0.775	< 0.01**
LDL-C	-0.104	0.629	-0.707	< 0.01**	-0.367	0.077
VLDL-C	-0.532	0.007**	-0.793	< 0.01**	-0.668	< 0.01**

*Significance at 0.05 level, ** Significance at 0.01 level

#: BMI (Body mass index), SBP (systolic blood pressure), DBP (diastolic blood pressure), FBG (fasting blood glucose), HbA1C (Glycosylated haemoglobin),TC (total cholesterol), TG (triglycerides), HDL-C (high density lipoprotein-cholesterol), LDL-C (low density lipoprotein-cholesterol).

TABLE III: CORRELATION OF ADIPONECTIN WITH DIFFERENT PARAMETERS IN MALE SUBJECTS OF THE STUDIED GROUPS (A, B, C)

Variables#	Group A (male)		Group B (male)		Group C (male)	
	r	p	r	p	r	p
Age	0.262	0.122	0.170	0.336	0.006	0.974
BMI	-0.457	0.005**	0.036	0.838	-0.064	0.713
SBP	0.488	0.003**	-0.148	0.403	-0.096	0.578
DBP	0.305	0.071	-0.441	0.009**	-0.086	0.616
FBG	0.097	0.573	-0.596	<0.01**	-0.332	0.048*
HbA1C	-0.251	0.140	-0.695	< 0.01**	-0.818	<0.01**
TC	-0.154	0.369	-0.758	< 0.01**	0.036	0.836
TG	-0.537	0.001**	-0.747	< 0.01**	-0.640	< 0.01**
HDL-C	0.948	<0.01**	0.860	< 0.01**	0.650	< 0.01**
LDL-C	-0.498	0.002**	-0.754	< 0.01**	0.067	0.697
VLDL-C	-0.535	0.001**	-0.738	< 0.01**	-0.643	< 0.01**

*Significance at 0.05 level, **Significance at 0.01 level
BMI (Body mass index), SBP (systolic blood pressure), DBP (diastolic blood pressure), FBG (fasting blood glucose), HbA1C (Glycosylated haemoglobin),TC (total cholesterol), TG (triglycerides), HDL-C (high density lipoprotein-cholesterol), LDL-C (low density lipoprotein-cholesterol).

of the studied groups. Negative association of adiponectin was observed with FBG and HbA1c in male subjects having diabetes mellitus (r -0.596, p=<0.01 and r -0.695, p=<0.01) and diabetic males having CHD (r-0.332, p=0.048, r -0.818, p=<0.01). Positive association of adiponectin was observed with HDL-C in all male subjects with the following corresponding values: r 0.948, p=<0.01 in control, r 0.860, p=<0.01 in males with diabetes and r 0.650, p=<0.01 in males with diabetes and CHD. Negative association between serum TG and serum adiponectin was observed in male subjects belonging to the three groups with correlation coefficient r -0.537, p=0.001 in group A control, r -0.747, p=<0.01 in group B and r -0.640, p=<0.01 in group C. Male subjects with diabetes mellitus also showed negative association of TC with adiponectin (r -0.758, p=<0.01).

DISCUSSION

Adiponectin is a 30 kilodalton (KDa) protein hormone and is described as insulin sensitizing agent because it can act as a biomarker of liver peroxisome-proliferator activation receptor ϒ (PPAR ϒ). Insulin sensitizing drugs such as pioglitazone and thiazolidinedione have been found to boost serum adiponectin level in diabetic subjects.[16] Adiponectin not only decreases hepatic glucose output but also increases glucose uptake by skeletal muscles and fatty acid oxidation through activation of AMPK pathway (adenosine monophosphate-activated protein kinase).[17]

Adiponectin acts as cardioprotective hormone by causing decreased inflammation, endothelial adhesion and foam cell formation. The molecular mechanisms involved in cardioprotection by adiponectin include down regulation of nuclear factor kappa B (NFκB), decreased smooth muscle cell proliferation, increased production of prostaglandin E_2 (PGE_2) through cyclo-oxygenase-2 (COX-2) pathway and AMPK related: increased nitric oxide (NO) production, decreased apoptosis and decreased cardiac hypertrophy in response to pressure overload.[18]

High TG and low HDL-C levels in circulation are important risk factors for type 2 diabetes mellitus as well as coronary heart disease.[19] HDL-C acts as anti-atherogenic agent and plays a role in reverse cholesterol transport (RCT), taking up excess cholesterol from tissues for its excretion through bile. HDL-C also has anti-oxidant, anti-thrombotic, endothelium protecting and anti-inflammatory properties.[20] Oxidized LDL (ox-LDL) particles are elevated in type 2 diabetes and CHD and are detrimental towards endothelium due to their atherosclerotic action.[21] Serum adiponectin level is inversely related to TG and ox-LDL levels and positively to serum HDL-C level. Adiponectin activates peroxisome-proliferator activation receptor α (PPARα) in muscle and liver leading to increased HDL-C.[22] Adiponectin also increases VLDL receptor expression and skeletal muscle lipoprotein lipase (LPL) activity leading to decreased TG and TG-VLDL breakdown.[23]

We found significantly high serum adiponectin and HDL-C and low serum

TC, TG and LDL-C ($p<0.01$) levels in control group than the diseased groups. Adiponectin was negatively associated with TG, FBG and HbA1c in diabetic subjects with and without CHD. A significant negative correlation of adiponectin was also seen with TC and LDL-C in type 2 diabetic subjects. However, a strong positive association of HDL-C and adiponectin were seen in all the studied groups.

Studies in different parts of the world performed on populations of variable ethnicity have reported similar results.[24-26] Saely et al[27] compared normal control, patients of type 2 diabetes, type 2 diabetic patients with CHD and non-diabetic patients with CHD and recorded lowest HDL-C level and highest TG level in subjects having type 2 diabetes with CHD. The results were highly significant, having p value of <0.001.

Luo et al[28], reported adiponectin to be negatively associated with HbA1c in Asian Indian females with impaired glucose tolerance (IGT). In our study the association was the same for both genders as observed in other studies such as Rasul et al[29], Katsiki et al[30], Kawamoto et al[31], and Tabak et al[32]. Snijder et al[33] associated high adiponectin level with low risk of type 2 diabetes mellitus in a study performed on elderly Caucasian males and females. These results support the hypothesis that high adiponectin has a relationship with an improved lipid profile and glycemic control in type 2 diabetes mellitus.

Eynatten et al[34] studied subjects having CHD and reported positive association of adiponectin with HDL-C (r 0.25; p=<0.0001) while a negative association with TG (r -0.21; p=<0.0001) and concluded adiponectin to be a predictor of deranged lipid profile in coronary heart disease.

No contradiction is reported about the role of adiponectin in type 2 diabetes mellitus however the beneficial role of adiponectin in coronary heart disease is found to be controversial depending upon factors such as age, gender, diet, physical activity, lifestyle, ethnicity and pre-existing vascular disease[35,36], thus demanding more research work.

LIMITATIONS OF STUDY

The small sample size and inclusion of subjects with a specific age (40 and above), might be the limitations of this study. Large sized studies performed on subjects having different age groups and lifestyles might reveal different results. The randomized design is the strength.

CONCLUSION

This study confirmed association of hypoadiponectinemia with dyslipidemia (low HDL-C and high TG) and uncontrolled glycemic status (high FBG and HbA1c) in type 2 diabetic subjects with and without coronary heart disease. Serum adiponectin was negatively associated with FBG, HbA1c and TG while positively associated with HDL-C in the studied population.

ACKNOWLEDGEMENTS

We are thankful to the participants of the study, staff of the Research Laboratory, Department of Biochemistry, Khyber Medical College, Peshawar and the Ethical Committee. We express special gratitude to the Higher Education Commission (HEC), Pakistan for funding this project.

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AUTHOR'S CONTRIBUTION

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

SD: Acquisition of data, drafting the manuscript, final approval of the version to be published

JS: Analysis of data, drafting the manuscript, final approval of the version to be published

MAK: Concept, study design, final approval of the version to be published

MRJ: Critical revision, final approval of the version to be published

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.

CONFLICT OF INTEREST

Authors declare no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE

NIL