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ORIGINAL ARTICLE

RELATIONSHIP OF HYPOADIPONECTINEMIA WITH GLYCEMIC STATUS AND LIPID PROFILE IN TYPE 2 DIABETIC WOMEN WITH AND WITHOUT CORONARY HEART DISEASE

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ABSTRACT

Objective: To find circulating adiponectin concentration in type 2 diabetic women with and without coronary heart disease and to establish a relationship of adiponectin level with glycemic status and lipid profile of these women.

Study Design / Methods: It was a cross – sectional analytical study. The study consisted of twenty four healthy females, twenty six type 2 diabetic females and twenty four type 2 diabetic females having coronary heart disease. All the participants were selected randomly. Fasting blood samples were obtained from the participants and were analyzed for serum adiponectin level, fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), triglycerides (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and very low density lipoprotein cholesterol (VLDL-C).

Results: Type 2 diabetic females with and without coronary heart disease revealed significantly low (p value < 0.001) serum adiponectin level and significantly high (p value < 0.001) FBG and HbA1c level as compared to the healthy females. Female diabetic participants with and without coronary heart disease showed significant negative association of adiponectin with FBG (r -0.874, p = < 0.01); (r -0.497, p = 0.010), HbA1c (r -0.937, p = < 0.01); (r -0.814, p = < 0.01), total cholesterol (r -0.423, p = 0.039); (r -0.733, p = < 0.01) and triglycerides (r -0.669, p = < 0.01); (r -0.790, p = < 0.001). A significant positive association of adiponectin was sun in all three groups i.e healthy females (r 0.988, p = < 0.01), type 2 diabetic females with coronary heart disease (r 0.775, p = < 0.01) and type 2 diabetic females without coronary heart disease (r 0.908, p = < 0.01).

Conclusion: Serum adiponectin level is markedly reduced in type 2 diabetic females with and without coronary heart disease. Moreover, hypoadiponectinemia in these women is related with un-controlled glycemic status and abnormal lipid level in the circulation.

Key words: Adiponectin; Type 2 diabetes mellitus; Coronary heart disease; Glycemic status; Lipid profile.

INTRODUCTION

Type 2 diabetes mellitus is increasing in prevalence and has become a global problem. Type 2 diabetes mellitus is the commonest type of diabetes and is responsible for more than 90% of diabetic population and it affects 5.1% adult population world over.[1] It is growing fast i.e at the rate of 3% yearly and is expected to affect about 330 million people world over till 2030.[2]. Diabetes has a high prevalence in Pakistan lying in the range of 7.6 – 11%.[3] Wild et al[2] stated that Pakistani diabetic population may increase from 5.2 million (2000) to 13.9 million (2030). Coronary heart disease is one of the commonest complications of diabetes mellitus, and it leads to more deaths alone than the combined deaths occurring from accidents, cancer, diabetes mellitus and chronic lower respiratory diseases.[4] The prevalence of coronary heart disease is expected to double from 1990 – 2020, and 82% of the increase will be caused by the increased burden in the developing countries rather than the developed countries.[5]

First studied around 1995, adiponectin has recently attracted much attention due to its widespread role in health and disease.[6] It is secreted by adipose tissue along with other adipokines and is a protein hormone having 244 amino acids.[7] Adiponectin molecules have the ability to self – associate and can exist in at least three higher order complex forms namely, LMW [low molecular weight form (trimer)], MMW [medium molecular weight form (hexamer)] and HMW [high molecular weight form (oligomer)].[8] Adiponectin affects carbohydrate and lipid metabolism and acts as insulin sensitizing, anti-hyperlipidemic, anti-inflammatory,

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anti-atherogenic, anti-hypertensive and cardio-protective agent.[9] The normal human serum level of adiponectin ranges from 2 to 30 µg/ml and tends to be higher in females than males.[7] Circulating adiponectin level is found to be decreased in obesity and obesity related problems such as insulin resistance, type 2 diabetes mellitus, hypertension, atherosclerosis and coronary heart disease.[6,7] The role of adiponectin in type 2 diabetes mellitus and coronary heart disease depends on age, gender, race, ethnicity, lifestyle changes and pre-existing vascular disease.[10]

In this study we have compared serum adiponectin level between normal female participants and type 2 diabetic females with and without CHD and have tried to establish a relationship between hypoadiponectinemia and glycemic control and lipid profile in the studied population.

MATERIAL AND METHODS

This was a cross-sectional and analytical study and it consisted of three groups, A, B and C. Group A contained twenty four healthy control female participants having no major illness such as diabetes mellitus, coronary heart disease, diseases of kidney or thyroid. Group B contained twenty six type 2 diabetic female participants having type 2 diabetes mellitus for the previous four years. Group C contained twenty four type 2 diabetic female participants with coronary heart disease i.e those who were diagnosed with first attack of myocardial infarction within previous 10 days. The study sample was selected randomly from tertiary care hospitals of Peshawar, Khyber Teaching Hospital (KTH), Hayatabad Medical Complex (HMC), Lady Reading Hospital (LRH) and Rehman Medical Institute (RMI). A well – structured questionnaire was used to record history, blood pressure, height, weight and BMI (weight in Kg/height in m^2) of the participants. An informed consent was taken from all the participants and approval of the study was obtained from the Ethical Committee of Khyber Medical College, Peshawar.

Blood Collection

About 5 mL fasting blood samples was collected from all participants and 3 mL clotted blood was centrifuged at 4000 rpm for 5 – 10 minutes to obtain clear serum. Fasting blood glucose and lipid profile were estimated using fresh samples. Blood collected in EDTA tubes was used for the estimation of glycosylated hemoglobin. Adiponectin levels were determined using serum stored at -70°C.

Biochemical Analysis

Enzymatic colorimetric method was used to measure fasting blood glucose, serum total cholesterol and serum triglyceride with kits obtained from Elitech – Sees, France. High density lipoprotein cholesterol was determined colorimetrically with a kit provided by Diasys Holzheim, Germany. Low density lipoprotein cholesterol (LDL – C) and very low density lipoprotein cholesterol (VLDL – C) were calculated using Friedewald's formula[11] and Delong's formula,[12] respectively. Glycosylated hemoglobin was measured colorimetrically using kit provided by Human Diagnostics, Germany. Human adiponectin ELISA kit (Bio-vendor Cat. No. RD 195023100, Germ-any) was used for the determination of adiponectin level.

Table 1: *Demographic, clinical and biochemical characteristics of the studied groups.*

Variables	*Group A*	*Group B*	*Group C*
Age (years)	44 ± 4.6	56.8 ± 11.3	58.7 ± 9.1
BMI (kg/m^2)	28.8 ± 3.3	27.1 ± 4.2	27.9 ± 3.02
SBP (mmHg)	123.1 ± 8.5	136.9 ± 18.7	128.5 ± 31.7
DBP (mmHg)	80 ± 4.1	85.5 ± 9.8	86.04 ± 14.5
FBG (mg/dL)	96.0 ± 12.5	182.7 ± 83.3	208.7 ± 111.3
HbA1C (%)	5.1 ± 0.41	8.1 ± 1.2	8.8 ± 1.6
TC (mg/dL)	186.6 ± 29.5	223.6 ± 37.5	215.3 ± 45.8
TG (mg/dL)	183.1 ± 73.8	251.7 ± 77.02	218.1 ± 75.2
HDL – C (mg/dL)	43.5 ± 10.6	39.04 ± 11.3	35.04 ± 7.7
LDL – C (mg/dL)	106.1 ± 29.3	134.1 ± 36.8	136.7 ± 41.8
VLDL – C (mg/dL)	36.4 ± 14.9	50.4 ± 15.5	43.5 ± 15.1
Adiponectin (µg/mL)	12.7 ± 2.5	3.3 ± 1.4	3.5 ± 1.1

Body mass index (BMI); Systolic blood pressure (SBP); Diastolic blood pressure (DBP); Fasting blood glucose (FBG); Total cholesterol (TC); Triglycerides (TG); High density lipoprotein – cholesterol (HDL – C); Low density lipoprotein – cholesterol (LDL – C). Data is expressed as mean ± SD.

Statistical Analysis

The data was analyzed using software SPSS version 19. The results were expressed as mean ± SD. Comparison of variables among the groups was carried out using independent student's t test. P value less than 0.05 was considered as significant. Pearson's correlation coefficient r was used to find association of adiponectin with glycosylated hemoglobin, fasting blood glucose and lipid profile.

RESULTS

Table 1 shows the demographic, clinical

and biochemical characteristics of the studied groups. Group A consisted of 24 healthy female participants with a mean age of 44 years (SD ± 4.6), Group B consisted of 26 type 2 diabetic female participants with a mean age of 56.8 years (SD ± 11.3) and Group C consisted of type 2 diabetic female participants having CHD with a mean age of 58.7 years (SD ± 9.1). Serum adiponectin level was highest in the control group i.e (12.7 ± 2.5) as compared to type 2 diabetic females (3.3 ± 1.4) and type 2 diabetic females with CHD (3.5 ± 1.1). Serum HDL – C level was the lowest in type 2 diabetic females with CHD (35.04 ± 7.7), as compared to type 2 diabetic females (39.04 ± 1.3) and the control females (43.5 ± 10.6).

Table 2: *Comparison of different characteristics between the studied groups.*

Variables	*Group A vs. Group B*	*Group A vs. Group C*	*Group B vs. Group C*
Age	< 0.001	< 0.001	NS
BMI	NS	NS	NS
SBP	< 0.05	NS	NS
DBP	< 0.05	NS	NS
FBG	< 0.001	< 0.001	NS
HbA1C	< 0.001	< 0.001	NS
TC	< 0.05	< 0.05	NS
TG	< 0.05	NS	NS
HDL – C	NS	< 0.05	NS
LDL – C	< 0.05	< 0.05	NS
VLDL – C	< 0.05	NS	NS
Adiponectin	< 0.001	<0.001	NS

P value is significant at < 0.05 and < 0.001 level, NS non-significant

Table 2 shows the comparison of different variables between the studied groups. Type 2 diabetic females with and without CHD revealed significantly high FBG and HbA1c each with p value of < 0.001 as compared to the healthy females. Similarly, the two diseased groups also showed significantly high total cholesterol (p value < 0.05) and triglyceride level (p value < 0.05) when compared to the control group. Serum adiponectin level was significantly high in the healthy females with a p value of < 0.001 than the type 2 diabetic females with and without CHD. The comparison of the two diseased groups was non-significant although both showed poor glycemic control and deranged lipid profile.

Table 3 shows the association of adiponectin with different parameters. A significant negative association of adiponectin was seen with FBG and HbA1c in the female diabetic patients with and without CHD having correlation coefficient r -0.497, p = 0.010 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, respectively. Moreover, they also showed negative association of adiponectin level 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 = < 0.01 in group B). A significant positive association of adiponectin with HDL – C was seen in all three groups, with r 0.988, p = < 0.01 in control, r 0.908, p = <0.01 in diabetic females and r 0.775, p = < 0.01 in females having diabetes with CHD. A strong negative association of adiponectin with TG was maintained in the control females (r -0.515, p = 0.010).

Table 3: *Correlation of adiponectin with different parameters in the studied groups.*

Variables	*Group A*		*Group B*		*Group C*	
	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

DISCUSSION

Insulin resistance accounts for the basic etiology of type 2 diabetes mellitus rendering hyperglycemia as the main diagnostic and prognostic biomarker.[13] Good glycemic control of

these patients requires HbA1c reduction to less than 7%.[14] Adiponectin plays important role in glucose metabolism and hypoadiponectinemia is found to be linked with insulin resistance and type 2 diabetes mellitus.[15] The exact biochemical route through which adiponectin affects glucose metabolism is still unclear however; several phenomena have been proposed. Adiponectin is a biomarker of liver peroxisome – proliferator activation receptor γ (PPAR γ) which makes it an insulin sensitizing agent.[16] Mice if administered with recombinant adiponectin after fat rich diet exhibit decreased circulating levels of glucose and free fatty acids. This is explained due to adiponectin activation of AMP activated protein kinase (AMPK) leading to increased fatty acid oxidation and muscular uptake of glucose.[17] It has been seen that the use of insulin sensitizing agents like proglitazone and thiazolidinedione in diabetic people tend to increase adiponectin concentration.[18] Type 2 diabetes mellitus has also been related with polymorphism of adiponectin gene (apM1), which is situated on a diabetes susceptibility locus present on chromosome 3q27.[19]

Adiponectin has cardioprotective ability. It activates Peroxisome – proliferator activation receptor α (PPARα), modulates adhesion molecules and inhibits signaling of nuclear factor κB.[20] Through AMPK (adenosine monophosphate activated protein kinase) activation in cardiovascular system, adiponectin leads to increased production of nitric oxide which helps in maintaining the blood pressure and protects the cardiac myocytes from hypertrophy in response to pressure overload.[21] Adiponectin protects against atherogenesis by causing decreased proliferation of smooth muscle cells and inhibiting macrophage transformation to foam cell.[22] Decreased adiponectin level decreases HDL cholesterol and increases triglycerides because of decreased PPAR α activation, reduced lipoprotein lipase activity and increased VLDL formation.[23] HDL cholesterol is atheroprotective as it excretes excess cholesterol through reverse cholesterol transport (RCT) in bile.[24] High TG and low HDL-C levels contribute to type 2 diabetes and coronary heart disease.[25] Hypoadiponectinemia is also associated with coronary heart disease.[26]

The study results showed that serum adiponectin level was decreased significantly in type 2 diabetic women with and without coronary heart disease as compared to the healthy control women. Studies have confirmed hypoadiponectinemia in type 2 diabetic patients with and without coronary heart disease.[27] Godaarzi et al[27] compared serum adiponectin level between normal women and type 2 diabetic women. They found significant hypoadiponectinemia in diabetic women (7.29 ± 1.42 vs. 10.29 ± 1.93, p = < 0.001). Menghua et al[28] confirmed hypoadiponectinemia in Asian Indian females with impaired glucose tolerance (IGT).

Dyslipidemia also accompanied hypoadiponectinemia in the studied groups. Significant low HDL cholesterol and high total cholesterol, triglycerides and LDL cholesterol were seen in type 2 diabetic participants with and without CHD. Similar results have been reported by other studies.[29]

In this study adiponectin was found to be negatively associated with fasting blood glucose, glycosylated hemoglobin, and triglycerides and positively associated with high density lipoprotein cholesterol in type 2 diabetic women with and without CHD.

Similar results were obtained by other studies.[30,31] Some studies have contradicted the protective role of adiponectin against coronary heart disease[32] however; so far there is no contradiction about the beneficial role of adiponectin in type 2 diabetes mellitus.

In ***conclusion*** our study confirms low level of adiponectin and HDL-C and high level of TG in type 2 diabetic women with and without CHD. Moreover adiponectin showed significant negative association with FBG, HbA1c and TG and significant positive association with HDL – C in the studied population.

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REFERENCES

1. Wagner JA, Wright E C, Ennis MM,Prince M, Kochan J, Nunez DJR, Schneider B, Wang MD, Chen Y, Ghosh S, Musser BJ, Vassileva MT. Utility of adiponectin as a biomarker predictive of glycemic efficacy is demonstrated by collaborative pooling of data from clinical trials conducted by multiple sponsors. Clin Pharma Therap. 2009; 86: 619-25.
2. Wild S, RoglicG, Green A, SicreeR, King H. Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. Diabetes Care, 2004; 27: 1047-53.
3. International Diabetes Federation. Prevalence estimates of diabetes mellitus [DM], 2010-MENA IDF. Diabetes Atlas. 2010. International Diabetes Federation. 2010; 3-9.
4. RimmermanC. M. Coronary Artery Disease. Cleveland Clinic Centre for Continuing Education. 2013.
5. Okrainec K, Banerjee DK, Eisenberg MJ. Coronary artery disease in the developing world. Am Heart J. 2004; 148: 7-15.
6. Takemura Y, Walsh K, Ouchi N. Adiponectin and cardiovascular inflammatory responses. Current Atheroscler Report, 2007; 9: 238-43.
7. Robinson K, PrinsJ, VenkateshB. Clinical review: Adiponectin biology and its role in inflammation and critical illness. Critical Care, 2011; 15: 221-29.
8. Hytest News. Adiponectin. August 2009.
9. Wolfson N, Gawish D, Matas Z, Boaz M, Sharyorodsky M. Relation of adinopectin to glucose tolerance status,

Adiposity and cardiovascular risk factor. Exp Diabetes Res. 2012; 1-5.
10. Karastergiou K, Mohamed-Ali V, Jahangiri M, Kaski J. Adiponectin for prediction of cardiovascular risk? Brit J Diabet Vascul Disease, 2009; 9: 150-54.
11. Friedwald WT, Levy PI, Fredrickson DS. Estimation of concentration of low density lipoprotein cholesterol in plasma, without use of the preparative centrifuge. Clin Chem. 1972; 18: 449-502.
12. Delong DM, Delong ER, Wood PD, Lippet K, Rifkind BM. A comparison of methods for the estimation of plasma low and very low density lipoprotein cholesterol. J Am Med Assoc. 1986; 256: 2372-77.
13. Fernandez-Real J, Botas – Cervero P, Bermano AL, Casamitjana R, Funahashi T, Delgado E, Kihara S, Ricart W. Adiponectin is independently associated with glycosylated hemoglobin. Eur J Endocrinol. 2004; 150: 201-05.
14. Gerstein HC. Fasting versus postload glucose levels: Why the controversy? Diabet Care, 2001; 24: i855-57.
15. Wang J, Li H, Franco OH. Adiponectin and metabolic syndrome in middle-aged and elderly Chinese. Obesity, 2008; 16: 172-78.
16. Karastergiou K, Mohamed-Ali V, Jahangiri M, Kaski J. Adiponectin for prediction of cardiovascular risk? Bri J Diabet Vascul Diseases, 2009; 9: 150-54.
17. Tomas E, Tsao TS, Saha AK, Murrey HE, Zhang Cc, Itani Si, Lodish HF, Ruderman NB. Enhanced muscle fat oxidation and glucose transport by Acrp30 globular domain: Acetyl co A carboxylase inhibition and AMP – activated protein kinase activation. Proceed Nat Acad Sci USA, 2002; 99: 16309-13.
18. Yu JG, Javorschi S, Hevener AL, Kruszynska YT, Norman RA, Sinha M, Olefsky JM. The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. Diabetes, 2002; 51: 2968-74.
19. Li LL, Kan XL, Ran XJ. Association Between 45T/G Polymorphism of the adiponectin gene and plasma adiponectin levels with type 2 diabetes. Clin Exp Pharmacol Physiol. 2007; 34: 1287-90.
20. Hashimoto N, Kanada J, Nakamura T, Horie A, Kurosawa H, Hashimoto T. et al. Association of hypoadiponectinemia in men with early onset of coronary heart disease and multiple coronary artery stenosis. Metabolism, 2006; 55: 1653-57.
21. Hopkins T, Ouch N, Shibata R, Walsh K. Adiponectin actions in the cardiovascular system. Cardiovascul Res. 2007; 74: 11-18.
22. Ouchi N, Kihara S, Atria Y, Nishida M, Matsuzawa A, Okamota 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: 1057-63.
23. Karsuki A, Sumida Y, Urakawa H, Gabazza EC, Murashima S, Matsumoto K. et al. Plasma levels of adiponectin are associated with insulin resistance and serum levels of triglyceride in Japanese metabolically obese, normal weight men with normal glucose tolerance. Diabet Care, 2003; 26: 2964-65.
24. Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L. Endogenous glucose production is inhibited by the adipose – derived protein Acrp30. J Clin Investig. 2001; 108: 1875-81.
25. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM,Ridker PM. Fasting compared with non-fasting triglycerides and risk of cardiovascular events in women. J Am Med Assoc. 2007; 298: 299-308.
26. Lam KS, Xu A. Adiponectin protection of the endothelium. Current Diabet Rep. 2005; 5: 254-59.
27. Goodarzi MT, Babaahmadi – Rezaei H, Kadkhodaei M, Haddadinezhad S. Relationship of serum adiponectin with blood lipids, HbA1c, and hs-CRP in type II diabetic postmenopausal women. J Clin Lab Anal. 2007; 21: 197-200.
28. Luo M, Oza-Frank R, Narayan KMV, Gokulakrishnan K, Mohan V. Serum total adiponectin is associated with impaired glucose tolerance in Asian Indian females but not in males. J Diabet Sci Technol. 2010; 4: 645-50.
29. Mohan V, Deepa R, Pradeepa R, Santhanakrishnan V, Mohan A, Velmurugan K, Radha V. Association of low adiponectin levels with the metabolic syndrome-the Chennai Urban Rural Epidemiology Study (CRUES – 4). Metabolism, 2005; 54: 476-81.
30. Izadi V, Farabad E, Azadbakht L. Epidemiologic evidence on serum adiponectin level and lipid profile. Int J Preven Medicine, 2013; 4: 133-40.
31. Anietabasi SO, Chinyere AO, Anousta CN, Edmund RE, John UE, Anthony JU. Adiponectin and cardiovascular risk factors in relation with glycemic control in type 2 diabetics. Int J Res Med Sci. 2013; 1: 563-70.
32. Sattar N, Wannamethee G, Sarwar N, Tchernova J, Cherry L, Wallace AM, Danesh J, Whincup PH. Adiponectin and coronary heart disease: a prospective study and meta-analysis. Circulation, 2006; 114: 623-29.