Asian Journal of Research in Medical and Pharmaceutical Sciences

1(4): 1-8, 2017; Article no.AJRIMPS.35998

Cut Off Value of Serum Adiponectin Levels in Egyptian Patients with Metabolic Syndrome

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Authors' contributions

This work was carried out in collaboration between all authors. Authors TAA and ESAES designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors LAAB and AAAE managed the analyses of the study. Authors TAA and ESAES managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJRIMPS/2017/35998
Editor(s):
(1) Alex Xiucheng Fan, Department of Biochemistry and Molecular Biology, University of Florida, USA.
(2) Lokendra Bahadur Sapkota, Department of Biochemistry, Chitwan Medical College, Bharatpur, Nepal.
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(3) O. Wai Sum, The University of Hong Kong, Hong Kong.
Complete Peer review History: http://www.sciencedomain.org/review-history/21465

Original Research Article

Received 7th August 2017
Accepted 17th September 2017
Published 19th October 2017

ABSTRACT

Background: Cardiometabolic disease (metabolic syndrome) is an umbrella term for complex metabolic abnormalities that end in type 2 diabetes mellitus (T2DM) and cardiovascular disease. It share pathophysiologic abnormalities including hypertension, dyslipidemia, central obesity, glycemic dysregulation and inflammation. The burdens of these conditions are very high. Adiponectin is secreted exclusively by adipocytes and has been linked to glucose, lipid, and cardiovascular regulation. Despite that adiponectin is produced only by adipose tissue, plasma level was found to be decreased in obese patients.
Purpose: We aimed to investigate the levels of serum adiponectin in obese and diabetic subjects together with their correlations to cardiometabolic risk factors in Egyptian subjects.
Materials and Methods: We measured serum adiponectin in one hundred sixty five Egyptian

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subjects divided as controls, obese and obese diabetics. Body mass index (BMI), waist circumference (WC) and blood pressure were measured in all subjects. Insulin resistance was assessed using the homeostasis model assessment for insulin resistance (HOMA-IR). Lipid profile (total cholesterol, HDL-C, non HDL-C, and triglycerides levels) were also measured. Cut off value were assessed for serum adiponectin levels as a marker for metabolic syndrome.

Results: Serum adiponectin levels were highly significantly different among the study groups ($p<0.01$). Serum adiponectin concentration showed highly significant negative correlation with BMI, diastolic blood pressure, HbA1c and HOMA-IR. Cut off value of 4.9 mg/l was significantly predicting the presence of metabolic syndrome.

Conclusion: Serum adiponectin levels have significant negative correlation with obesity and T2DM. Therefore it could be used as a biomarker to assess cardiometabolic risk in obesity and T2DM.

Keywords: Adiponectin; cardiometabolic syndrome; BMI; HOMA-IR; obesity.

1. INTRODUCTION

The cardiometabolic syndrome (metabolic syndrome) is a combination of metabolic abnormalities associated with increased incidence of type 2diabetes mellitus (T2DM) and cardiovascular event [1]. In view of this, the syndrome should be considered by the physicians to assess high risk population, usually underestimated and undermanaged [2].

The cardiometabolic syndrome manifestations include abdominal obesity, insulin resistance, dyslipidemia and increased blood pressure [3].

The pathogenesis of insulin resistance greatly linked to adipose tissue. intra-abdominal fat cells release free fatty acids and other adipocytokines which produce an inflammatory response and could have hormonal effect [4]. Insulin resistance subsequently lead to elevated blood pressure and dyslipidemia [5].

Based on this data, these adipocytokines could be beneficial as biomarkers which provide a minimally-invasive means for early detection and specific treatment of these metabolic syndrome and related disorders [6].

Adiponectin is one of the adipocytokines and has a physiological role in glucose and lipid, as well as cardiovascular regulation [7]. Adiponectin is interestingly different from other adipocytokines being negatively correlated with increased body fat [8]. Despite the fact that adipose tissue is the unique source of adiponectin, its levels seen with lower levels in obese subjects [9], higher levels seen associated with decreased body weight, could be explained by negative feedback in obesity [10].

It is believed that adiponectin affects the cardiometabolic syndrome pathogenesis through its negative effect on blood glucose and free fatty acids levels [11]. The link between adiponectin secretion and insulin resistance seem to be bidirectional. Adiponectin improve the sensitivity of insulin receptors in peripheral tissues, affect food intake and metabolic rate [12]. On the other side, increased insulin levels related to decreased bioactive adiponectin levels, which lead to further insulin resistance. Inflammation and oxidative stress associated with insulin resistance decrease adiponectin levels [13].

We assessed adiponectin levels in one hundred sixty five Egyptian subjects non obese non diabetics, obese non diabetics and obese diabetics, also evaluated their correlation with cardiometabolic risk factors.

2. MATERIALS AND METHODS

This was a hospital based study including age-matched one hundred sixty five Egyptians attending General Ismailia hospital. Study subjects were divided into three groups:-

- Group1 (control group): Fifty five non obese non diabetic subjects.
- Group 2: Fifty five obese, non diabetic subjects.
- Group 3: Fifty five obese, diabetic patients.

Diabetes mellitus was diagnosed based on the WHO criteria, as reported in 2000 [14]. Consent were obtained from all subjects after being informed the purpose of the study. Anthropometric data for each subject, including weight, height and waist circumferences (WC) were recorded and the body mass index (BMI) was calculated using Quetelet's formula (weight

(kg)/height (m^2). Blood pressure was also measured in all subjects. Fasting blood glucose and serum insulin levels were assessed [15]. The type of antidiabetic drug in the fifty diabetic subjects (group III) was recorded as well as the duration of treatment for each subject in this group.

Glycated hemoglobin A1c (HbA1c) was measured [16], and insulin resistance was also measured using the homeostasis model assessment of insulin resistance (HOMA-IR), being calculated as fasting insulin X glucose level/22.5 [17]. Subjects were classified to have metabolic syndrome according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [18], when they have any three of the following components: abdominal obesity, dyslipidemia (high levels of triglycerides, low HDL-C), hypertension, and elevated fasting glucose.Serum adiponectin was measured using a human adiponectin ELISA kit according to manufacturer instructions (SRB/Shanghai). Subjects also were assayed for Lipid profile [19,20]. Non HDL was calculated as following: Non-HDL-C = total cholesterol minus HDL-C [21].

2.1 Statistical Analysis

Tables and graphs for data analysis were obtained using SPSS version 16 soft ware. Correlation tests were determined by Pearson's Product correlation coefficient (r) to test the strength of association between serum adiponectin and other variables. Bonferroni's correction was applied to analyses. Differences were considered statistically significant at $p<0.05$ and highly significant at $p<0.01$.

ROC curve analysis was performed to establish threshold of serum adiponectin for the existence of cardiometabolic syndrome.

3. RESULTS

There were no statistically significant differences between cases and control in age or gender distribution. There were statistically significant differences among studied groups in BMI, FBG, HbA1C and HOMA-R. Bonferroni test showed no significant difference in BMI between group II & group III as well as no significant difference in FBG, HbA1c between group I & group II ($p>0.05$), while the difference is significant between group II & group III ($p<0.05$). There were significant difference in HOMA-R ($p<0.05$) between group I & group II, group II & group III and between group I & group III while there were significant differences between group I & group III in FBG, HbA1C and HOMA-R ($p <0.05$).

Serum adiponectin was highly significantly ($p<0.01$) different among the three groups, mean serum adiponectin concentration decreased from non-obese to obese non diabetic to diabetic subjects. The means are highest in group III followed by group II and group I scored lowest value. Bonferroni adjustment revealed that there was significant difference between controls & obese subjects (Table 1).

On analyzing group III according to the type of antidiabetic drug and the duration of treatment (Table 2), 13 subjects were on insulin injection with or without combined oral hypoglycemic (all of them more than year on treatment), 11 on thiazolidinediones TZDs (7 less than a year & 4 more than a year on treatment) and 24 on another types of oral hypoglycemic (9 less than one year & 15 more than one year on treatment). Serum adiponectin scored significantly higher levels in the subjects treated with TZDs for less than one year.

ADP showed significantly negative correlation with BMI, DBP, HA1C and HOMA-R while no correlation was seen with WC, SBP, Non-HDL-C, TG and HDL-C (Fig. 1 & Table 3). Cut-off point of ADP to predict metabolic syndrome in this study was 4.9 mg/l with specificity of 82.25% and sensitivity of 45.45% (Fig. 2). This is the best cut off point as calculated according to Youden-index (the point for which sensitivity + specificity is maximal).

4. DISCUSSION

Obesity is associated with an increased risk of developing insulin resistance. Excess adipose tissue releases increased amounts adipocytokines that are involved in the development of insulin resistance. When insulin resistance is accompanied by defect in insulin secretion by the pancreas, hyperglycemia and then T2DM results [22].

This study revealed significant increase of FBG, HbA1C and insulin resistance in the obese diabetic group compared to the non-diabetic groups, HOMA-IR seen significantly increased in obese group in comparison with non-obese group. The study of Rao [23] and the study of Azab et al. [24] confirmed the association

between T2DM and insulin resistance [23,24]. Also Despres [25] reported insulin resistance increased in obese subjects (visceral obesity).

Our study revealed significant decrease in adiponectin levels in obese subjects in comparison with non obese and further significant decrease in the diabetic group. These results are consistent with many other studies [26]. Adiponectin improve insulin sensitivity by stimulating glucose and fatty acids utilization in the skeletal muscle and liver by enhancement of AMP-activated protein kinase [27].

Table 1. Serum adiponectin and other variables in groups of the study (values are mean±SD)

Variable	Group I (n=55)		Group II (n=55)		Group III (n=55)		F	p
Age (year)	51.62 ± 13.42		50.69 ± 10.15		50.29 ± 14.23		0.16	NS
Sex	**No**	**%**	**No**	**%**	**No**	**%**	**χ^2**	**P**
Male	32	58.2	25	45.5	25	45.5	1.78	NS
Female	23	41.8	30	54.5	30	54.5		
BMI	22 ± 2.18		31.57 ±7.41		33.92 ±9.39		18.21	<0.01
FBG (mg/dl)	85 ± 17.68		89.57 ±15.45		195.98 ±55.44		16.59	<0.01
Hb A1c (%)	5.75 ± 1.01		5.63 ± 1.66		9.73 ± 2.66		20.18	<0.01
HOMA-R	1.91 ± 0.62		3.98 ± 1.08		6.01 ± 2.03		20.18	<0.01
Adiponectin (ADP): (mg/l)	9.63 ± 2.10		8.42 ± 1.79		5.42 ± 2.19		16.5	<0.01

p<0.05 significant and p<0.01 highly significant, NS: non-significant

Table 2. Adiponectin levels with analysis of group III according to the type of antidiabetic drug and the duration of treatment

	Subjects on TZDs		Subjects on other oral hypoglycemic		Subjects with insulin in therapy		p
Duration of treatment	< 1 year	> 1 year	< 1 year	> 1 year	< 1 year	> 1 year	< 0.05
	n= 7	n= 4	n= 9	n= 15	n= 0	n= 15	
Adiponectin level (mg/l)	6.18 ± 2.72	5.49 ± 1.99	5.32 ± 2.3	5.44 ± 1.89	5.4 ± 2.22	5.38 ± 2.34	

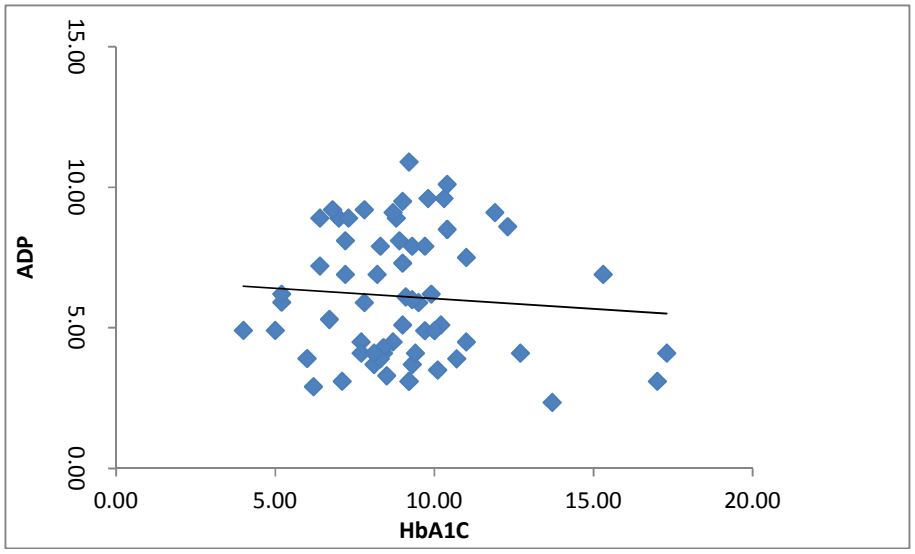

Fig. 1. Adiponectin is significantly negatively correlated with HbA1c (p<0.01)

Table 3. Pearson's product correlation coefficient (r) of adiponectin with anthropometric and metabolic parameters in all groups of the study

Variable	ADP		
	n	r	P
BMI	165	-0.26	<0.01
WC	165	-0.08	NS
SBP	165	-0.14	NS
DBP	165	-0.23	<0.05
Hb A1C	165	-0.25	<0.01
HOMA-R	165	-0.27	<0.05
Non HDL-C	165	-0.14	NS
TG	165	0.07	NS
HDL-C	165	0.14	NS

n= number of subjects studied, p<0.05 significant, p<0.01 highly significant, NS: non-significant

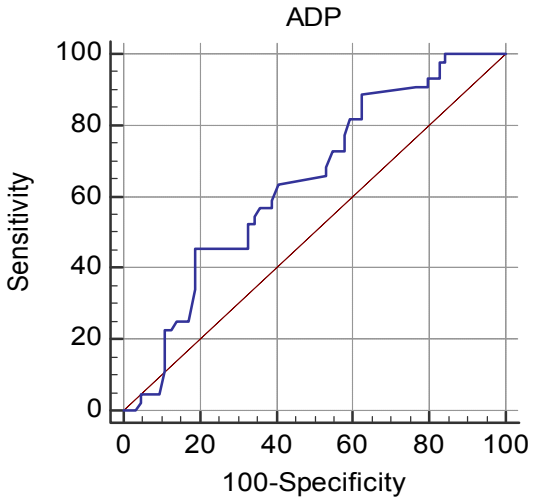

Fig. 2. Roc curve analysis for serum adiponectin (ADP) levels in patients with metabolic syndrome

On estimation of adiponectin level with analysis of group III according to the type of antidiabetic drug and the duration of treatment, the levels were significantly higher in the subjects started treatment with TZDs. Few studies assessed the impact of antidiabetic treatment type and duration on the adiponectin levels. Serum adiponectin levels may increase shortly after beginning of the hypoglycemic treatment. As in the present study, such an association was shown mainly for TZDs and was explained by the effect of these compounds on the peroxisome proliferator-activated receptor gamma (PPAR-G), as TZDs increase mRNA expression and adiponectin secretion, there transient increase in adiponectin levels after initiation of treatment and lasting for several months, after which, it return to base levels. The explanation of such phenomena is still unclear [28].

Studies have documented the significant relation between adiponectin concentrations and various measures of body fat and that significant weight loss leads to a rise in adiponectin levels. However, it is possible that the metabolic changes associated with obesity are implemented in the relationship between obesity and adiponectin. For example, insulin resistance and hyperinsulinemia are frequently associated with obesity, and both decline with weight loss [29]. Our results demonstrate that serum adiponectin levels had significantly negative correlation with BMI and non significant negative correlated with WC. Adiponectin has consistently been found to be negatively correlated with obesity in previous studies [30]. However, some studies did not find significant correlation [31].

Although adiponectin is secreted mainly from adipose tissue, its levels are in contrast to other adipokines i.e, lower in obese than in lean humans. This may be explained by feedback inhibition in its production that occur during development of fat mass due to increase in the production of other adipokines [32]. It has been suggested that with increasing grades of obesity, there may be a decrease in the metabolic functioning of adipocytes, along with hypertrophy and/or aging of these cells [33].

In this study, we showed a negative correlation between plasma adiponectin and blood pressure among the studied groups. Regarding to systolic blood pressure, this correlation did not reach the level of significance statistically ($p = 0.07$). However, the correlation of adiponectin levels with diastolic blood was significant negative correlation. So far, the data about the relation between adiponectin and blood pressure have been highly confusing. A negative association was reported between the systolic blood pressure and adiponectin levels in healthy female adolescents [34]. Adamczak et al. [35] described low adiponectin levels and a significantly negative correlation between adiponectin and blood pressure in hypertensive patients. On the contrary, Mallamaci et al. [36] reported elevated plasma levels in hypertensive men while they did not establish any association in women. However, in that study, 60% of patients were under anti-hypertensive drug

treatment which possibly caused divergent results.

The pathophysiological process linking the hypoadiponectinemia with elevated blood pressure are not known at present. Nevertheless, it has been documented that adiponectin affected the functions of endothelial cells and smooth muscle cells, two main cell types relevant to blood pressure regulation. For example, the recombinant adiponectin attenuated TNF-induced adhesion molecule expression in cultured human endothelial cells. The recombinant adiponectin also reduced platelet-derived growth factor induced proliferation and migration of cultured human smooth muscle cells [34].

Although various studies have demonstrated a significant relationship between serum adiponectin levels and insulin resistance in obese type 2 diabetic subjects [37], other studies have failed to observe this relationship [38]. This study, confirming some of the published findings, identified a significant inverse relationship between fasting serum adiponectin levels and insulin resistance. Our observation that adiponectin levels shows significant negative correlation with the status of glycemic control as represented by HbA1C among studied groups is supported by previous studies [39]. This could be explained by the fact that adiponectin stimulated AMP-activated protein kinase (AMPK) phosphorylation and activation; it also increases fatty acid combustion, glucose uptake, suppressing glucose production from lactate and pyruvate [40]. It has been proposed that adiponectin also increased fatty acid combustion and energy consumption, in part via Peroxisome Proliferator Activated Receptor alpha (PPAR(x) activation, which led to decreased triglyceride content in the liver and skeletal muscle [41]. To test the performance of serum adiponectin as a marker for the presence of cardiometabolic syndrome, the Roc curve analysis resulted in 4.9 mg/l as a cut off value of serum adiponectin to predict the presence of metabolic syndrome. Few previous studies have investigated the cut off value of serum adiponectin. A previous Japanese study established a level of 6.2 mg/l as the cut off value [42]. Another study on obese Japanese boys reported a level of 6.65 mg/l to discriminate metabolic syndrome [43]. In chinese, the patients with coronary artery disease reported an adiponectin level less than 4.0 mg/l [44]. The cut of value reported in the chinese study is comparable with our findings.

5. CONCLUSION

All measures should be taken to decrease the prevalence of cardiovascular diseases, known to have high morbidity and mortality. One of the important steps is to define new markers associated with cardiometabolic risks. Adiponectin could be used as a biomarker in metabolic syndrome because it is strongly associated with obesity and T2DM) having significant correlation with cardiometabolic risk factors.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard, patient's written consent has been collected and preserved by the authors. The study was conducted in accordance with current ethical considerations and meets with the Port Said university committee's approval.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
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