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Original Article

Evaluation of serum adiponectin levels in diabetic nephropathy

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ABSTRACT

Introduction: Diabetic nephropathy is one of the major microvascular complications of diabetes mellitus. Adiponectin is an adipose tissue-derived cytokine that was identified in a human adipose tissue cDNA library. Serum adiponectin levels are found to be reduced in various pathological states including obesity, diabetes mellitus, ischaemic heart disease and arteriosclerosis obliterans and elevated in end stage renal diseases. Objective: to assess the level of plasma adiponectin as an early predictor of microvascular complications in patients with type 2 diabetes mellitus.

Methods: 44 patients with type 2 diabetes recruited from outpatient diabetes clinic in Kasr Alainy hospital. All patients were subjected to full laboratory work-up including: Fasting blood glucose and Post prandial blood glucose, Glycated haemoglobin A1C, Serum creatinine, Serum total cholesterol, Triglycerides, Low density lipoprotein, High density lipoprotein, C-reactive protein titre, serum adiponectin and Urinary albumin/creatinine (UAC) ratio.

Results: The present study demonstrated that serum adiponectin concentrations had significant positive correlation with UAC ratio ($r = 0.534$, $p = 0.0001$). Adiponectin levels showed significant positive correlation in patients with diabetes and hypertension with microalbumiuria ($p = .001$) or normoalbumiuria ($p = 0.004$).

Conclusion: Serum adiponectin level can be a good predictor of diabetic nephropathy in patients with type 2 diabetes mellitus.

1. Introduction

Type 2 diabetes mellitus (T2D) is a wide-world health problem. It is estimated that the prevalence of T2D is going to be increasing in the following 2 decades [1]. Diabetes is a rapidly rising health issue in Egypt where the prevalence of T2D was tripled in the last 2 decades to reach around 15.6% of all adults above 20–79 years [2]. This may be related to a wide variety of factors like aging, overpopulation, sedentary life and western life style adoption [3]. T2D is characterized by multi-systems involvement caused by decreased sensitivity to insulin and subsequent hyperglycaemia. Diabetic complications often develop due to abnormalities in the vascular architecture leading to nephropathy, cardiomyopathy, retinopathy, neuropathy and other complications [4]. Diabetic nephropathy is a major microvascular complication of diabetes mellitus. One of the earliest clinical signs of diabetic nephropathy is an elevated urinary albumin excretion, referred to as microalbuminuria [5].

Increased vascular complications were found to be related to adipocytokines like adiponectin, leptin and tumor necrosis factor. They influence glucose and lipid metabolism and inflammatory processes. Studies have shown that different adipokines have different levels in each type of microangiopathy [6]. Adiponectin is an adipose tissue-derived cytokine and it is the most abundant adipokine. Adiponectin was found to have anti-atherogenic and anti-diabetic functions as it serves as insulin sensitizers [7]. It plays a vital role in metabolic syndrome and was found to have protective effect against cardiovascular diseases [8]. Several studies reported decreased adiponectin in obesity as fats accumulate and adipocytes enlarge and in insulin resistance and T2D as well. It has also been linked to occurrence of macrovascular complications and coronary artery disease [9].

On the other hand, despite the identification of the link between insulin resistance (IR) and adipose dysfunction, yet the direct effect and the serum levels of adiponectin on microvascular complications is controversial and still to be studied [10,11]. Several studies revealed increased levels of adiponectin in patients

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with diabetic nephropathy and others were done to investigate the possibility of depending on high serum levels of adiponectin as an early predictor of microvascular complications in patients with type 2 diabetes especially in diabetic nephropathy [10]. In addition, albuminuria and estimated glomerular filtration rate (eGFR) have been found to be insensitive biomarkers for chronic kidney disease (CKD) progression in patients with diabetic nephropathy and they were also unreliable as regards the accurate evaluation of the glomerulopathy occurring in T2D [12]. Furthermore; elevated adiponectin serum levels have been found to have a prognostic factor for end stage renal disease. For the above mentioned reasons, this study was done to evaluate serum adiponectin levels and investigate its role as a predictor biomarker in patients with diabetic nephropathy.

2. Methods

2.1. Subjects

Forty-four patients with type two Diabetes mellitus (T2D) both (male and female) were collected from outpatient diabetes clinic in Kasr Alainy hospital. All patients were subjected to full history including age, gender, diabetic duration and treatment. Clinical examination, Body mass index and waist to hip ratio assessment were done to all patients included in the study.

2.1.1. Inclusion criteria

1 All patients had type 2 diabetes.
2 Their ages ranged from 35 to 55 years old.

Exclusion criteria include patients with type 1 diabetes and secondary diabetes.

The purpose and nature of the study were explained to all patients. Informed consent form had been signed by each patient before participating in the study.

3. Statistical analysis

Results are expressed as mean ± standard deviation (SD). Comparison between variables in the studied groups was performed using unpaired t test. Statistical Package for Social Sciences (SPSS) computer program (version 19 windows) was used for data analysis. P value ≤ 0.05 was considered significant and <0.01 was considered highly significant.

4. Results

4.1. Clinical characteristics of the participants

The study was done on patients with their age range (35–55 years), 26 were males (59%) and 18 females (41%). As regards risk factors among the studied patients, 34% of participants were smokers (n = 15), hypertension in 70.5% (n = 31), dyslipidaemia in 45.5% (n = 20), positive family history of diabetes was found in 63.6% (n = 28) and no one of the studied group gave history of alcohol intake. Body mass index (BMI) of patients ranged from (25–42) kg/m^2, with mean of (30.92 ± 4.23) kg/m^2, waist to hip (W/H) ratio was ranging from (0.95–1.11) with mean of (1.02 ± 0.04) (Table 1).

4.2. Correlations between serum adiponectin level and clinical parameters

Adiponectin level showed a strong significant positive correlation with Albumin creatinine ratio (r = 0.534, p = 0.0001) shown in Fig. 1. Multiple regression analysis for adiponectin showed that microalbuminuria was an independent predictor of adiponectin as shown in Table 2.

Table 1
Laboratory data in the participants.

Laboratory test in 44 patients	Range	Mean ± SD
Blood sugar tests:		
• FBG (mg/dl)	77–258	144.9 ± 49.48
• PP blood glucose (mg/dl)	130–382	237 ± 62.4
• A1C	4.5–13.3	7.78 ± 2.01
Lipid profile:		
• Total cholesterol	81–299	207.2 ± 40.84
• TGS.	49–352	180.6 ± 62.11
• HDL.	15–165	46.19 ± 20.55
• LDL.	30.2–199	124.1 ± 36.84
Kidney function test:		
• Serum creatinine	0.50–1.23	1.03 ± 0.3
• A/C ratio	1.20–295	102.1 ± 101.04
Other tests:		
• CRP.	0.60–11.2	6.14 ± 3.81
• Serum uric acid	4–10.6	5.81 ± 1.11
BMI	25–42	30.92 ± 4.23
W/H ratio	0.95–1.11	1.02 ± 0.04

FBG, fasting blood glucose; PP glucose, postprandial glucose; HbA1c, glycated haemoglobin; TG, Triglycerides; HDL, high density lipoprotein; CRP, C-reactive protein; A/C ratio, albumin/creatinine ratio; BMI, body mass index; LDL, low density lipoprotein; W/H ratio, waist to height ratio.

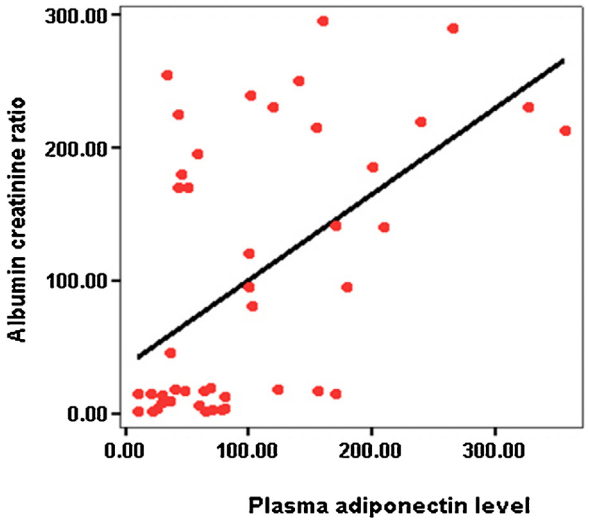

Fig. 1. Correlation of albumin creatinine ratio with plasma adiponectin level (μg/ml).

Adiponectin level showed significant positive correlation with hypertension in patients with T2D whether they were having microalbumiuria (p = .001) or normoalbumiuria (p = 0.004).

Patients were subdivided into two groups, according to the A/C ratio where normoalbuminuric (<23.0 mg/g) and microalbuminuric (23–300 mg/g). Plasma adiponectin levels in both groups showed significant difference where in patients with microalbuminuria, adiponectin mean of 140.74 ± 93.37 while in patients with normoalbuminuria group, adiponectin mean of 61.22 ± 44.18 (p = 0.002) Table 3, Fig. 2.

5. Discussion

In the present study, serum adiponectin concentration was significantly raised in patients with type 2 diabetes mellitus having micro-albuminuria. Adiponectin level showed a significant

Table 2
Correlations between serum adiponectin level and measured parameters in type 2 diabetic subjects.

Parameters	Correlation coefficient (r=)	P-value
Age	0.230	0.134
BMI	0.205	0.181
W/H ratio	0.186	0.228
Duration	−0.039	0.804
HBA1c	0.229	0.134
Fasting blood glucose	0.230	0.132
PP blood glucose	0.203	0.186
Total cholesterol	0.010	0.946
LDL	−0.065	0.677
HDL	0.203	0.185
TGS	0.062	0.688
CRP	0.086	0.577
serum creatinine	0.051	0.744
Uric acid	0.245	0.109
Albumin creatinine ratio	0.534**	0.0001
Hypertension (normoalbuminuria)	0.33	0.004
Hypertension (microalbuminuria)	0.55**	0.001

** Highly significant.

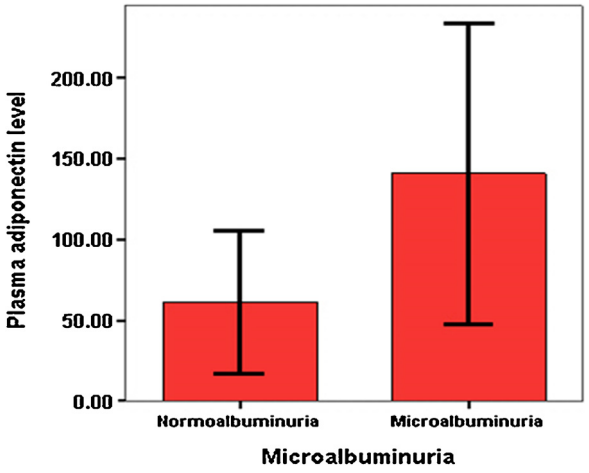

Fig. 2. Comparison of plasma diponectin level (μg/ml) between patients with normoalbuminuria and patients with microalbuminuria.

positive correlation with Urinary Albumin/creatinine ratio (UACR) and multiple regression analysis showed that micro-albuminuria was an independent predictor of adiponectin levels. Adiponectin level also was strongly correlated with hypertension in patients with diabetes with or without micro-albumiuria. There were also weak and statistically non-significant correlation between adiponectin levels and HDL **(r = 0.203)**, HbA1c (r=**0.229**), and FBG (r=**0.230)**.

Adiponectin is thought to be one of the adipocytokines with anti-oxidative and anti-inflammatory effects. Several studies have shown that adiponectin exerts its effect through the activation of adenosine monophosphate activated protein kinase in the renal glomerulus. Our study revealed that there is high serum adiponectin levels in cases of diabetic nephropathy and some studies stated that high adiponectin levels may predict mortality and chronic kidney disease progression to dialysis [13,14]. Renal insufficiency play a contributory role in the increased adiponectin levels may be due to increased degradation or enhanced production from adipose tissue. The increase in adiponectin in diabetic nephropathy might be a protective method aiming at improving endothelial function, reduction of oxidative stress and increased nitric oxide synthase [7].

This finding is in accordance with Fujita et al. who found a positive correlation between adiponectin and albumin excretion rate (AER) in patients with type 2 diabetes mellitus [15]. Moreover Fujita et al. found that adiponectin elevation in patients with diabetes may be physiological to avoid tubular injury and prevent infiltration of inflammatory cell into the tubulo-interstitial area which is a hall mark of diabetic nephropathy that may be developed if further complications occur. There was no correlation between plasma adiponectin and serum lipids in the form of TGs, LDL and total cholesterol [15].

Cha et al. found that plasma levels of adiponectin were significantly higher in patients with T2D and renal insufficiency and were inversely associated with eGFR. In addition, they identified significant associations between several of the measured adipokines and urinary albumin creatinine ratio (UACR). They also found that adiponectin was positively correlated with total cholesterol and HDL-C [16].

A study conducted on type 1 diabetes patients done by Bjornstad et al. showed that there was higher adiponectin levels in those patients than their peers who had no diabetes, and elevated adiponectin at baseline is independently associated with greater odds of developing early DKD over 6 years [17]. Another study stated that plasma adiponectin levels increased significantly with the severity of diabetic nephropathy (p value 0.002) [18]. Also, Moreno et al. found a strong association between increased adiponectin levels among T2D patients with micro and macroalbuninuria as compared with normoalbuminuria [19].

In contrast to our study, Jung et al. who reported Serum adiponectin levels were significantly lower in patients with nephropathy than in those without nephropathy (P = 0.017), and were significantly higher in patients with retinopathy or neuropathy than those without retinopathy or neuropathy (P = 0.01 and P = 0.002, respectively) [6].

Table 3
Laboratory characteristics for normoalbuminuric and microalbuminuric type 2 diabetic subjects.

Parameter	Normoalbuminuria (n = 21)	Microalbuminuria (n = 23)	P value
HBA1c	7.15 ± 2.14 (4.50-13.30)	8.35 ± 1.73 (5-11.10)	0.047*
FBG	135.33 ± 53.37 (91-258)	153.65 ± 45.04(77-215)	0.086
PP blood glucose	212.57 ± 72.95 (130-382)	259.35 ± 41 (177-330)	0.003*
Total cholesterol	205.19 ± 41.71(141-299)	209 ± 40.87(81-263)	0.761
LDL	129.19 ± 36.45 (73.20-199)	119.62 ± 37.41 (30.20-166)	0.396
HDL	43.83 ± 8.50 (27.60-64.20)	48.35 ± 27.38(15-165)	0.663
TGS	163.43 ± (55.88 (88-297)	196.39 ± 64.50(49-352)	0.078
CRP	5.33 ± 3.22(.60-11.10)	6.88 ± 4.21(.70-11.20)	0.181
Serum creatinine	.94 ± .28(.50-1.40)	1.11 ± 30 (50-1.60)	0.265
Uric acid	5.30 ± .96(4-7.50)	6.29 ± 1.05(5.30-10.60)	0.002*
Plasma adiponectin level (μg/ml)	61.22 ± 44.18(9.50-170)	140.74 ± 93.37 (34-358)	0.002*

Data are expressed as Mean ± S.D, range is stated between parentheses.
* Significant.

This positive association may represent an adaptive mechanism by which the oxidative stress associated with diabetes and renal dysfunction may be counteracted [20].

Another study done by Banerjee & Khemka, who assessed the levels of circulating adiponectin and their associations with insulin resistance in people with pre-diabetes and diabetes, they found that serum adiponectin levels were significantly lower in subjects with pre-diabetes and diabetes than in healthy controls [21].

As for the strong association we have found between hypertensive T2D patients regardless the presence of micro-albuminuria and higher levels of adiponectin, this can be explained by the role of adiponectin in cardiovascular protection. Yoshihisa Okamoto found that adiponectin provides cardiovascular protection in metabolic Syndrome. Okamoto and co-workers stated that adiponectin has protective properties against obesity-linked complications as hypertension, metabolic dysfunction, atherosclerosis, and ischaemic heart disease and that adiponectin exerts the beneficial effects on vascular disorders by affecting components of vascular tissue [8,9].

As regards obesity, our results showed that there was weak correlation between BMI and adiponectin levels yet not statistically significant (r=**0.205**). However, many studies have shown strong relation between adiponectin levels and higher BMI. Conversely, Wang et al. found stronger relation between adiponectin and T2D risk in higher BMI than their leaner counterparts [22]. A British [23] and a Japanese [24] study have shown that there was a strong association among obese when compared with non-obese. However, Kizer et al. found moderate negative correlation between adiponectin levels and BMI [25]. On the other hand, Heidemann et al. found no correlation between total or high molecular weight adiponectin and BMI [26].

Still there are many controversial issues as regards the role of adiponectin and its levels in serum of patients with diabetes and many questions are to be answered in the future especially in explaining its relation with diabetic kidney disease, insulin resistance and metabolic syndrome. According to the present study it was concluded that serum adiponectin level is higher in T2D patients with micro-albuminuria and can be used as a marker for early diabetic kidney disease in T2D patients. Also, adiponectin is found in high levels in hypertensive patients with T2D regardless their renal condition.

6. Conclusions

In the present study; it was found that:

- Serum adiponectin level is predictive for albuminuria in patients with type 2 diabetes.
- Plasma adiponectin concentration was significantly raised in patients with type 2 diabetes and microalbuminuria when compared to patients with normoalbuminuria.

Conflict of interests

All authors declare no conflict of interests.

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