The Correlation between Serum Total Adiponectin and Hemoglobin in Type 2 Diabetic Patients without Microalbuminuria

Ammar S. Khamis*, Shatha H. Ali,[1] and Khalid I. Al-Lehibi*****

* Department of Clinical Laboratory Science, College of Pharmacy, Al-Kufa University,Najaf, Iraq
**Department of Clinical Laboratory Science,College of Pharmacy,University of Baghdad,Baghdad, Iraq
***The Specialist Center for Endocrinology & Diabetes, Al-Kindy Teaching Hospital,Baghdad,Iraq

Abstract

Low serum total adiponectin is associated with a high incidence of type 2 diabetes or coronary artery disease in the general population. Paradoxically, serum total adiponectin is elevated in patients with chronic kidney disease (CKD), such as overt diabetic nephropathy. The current study aimed to investigate whether or not anemia to be dependently associated with serum level of total adiponectin in non-albuminuric male patients with type 2 diabetes . The study included 42 type 2 diabetic male patients. Anemia was defined as hemoglobin (Hb) below 14.0g/dL. All the patients were without microalbuminuria, to exclude diabetic nephropathy. The diabetic patients were divided into 2 groups according to the hemoglobin level in addition to 16 healthy control group. Serum total adiponectin levels were measured by a sandwich enzyme-linked immunosorbent assay. In all 42 patients with type 2 diabetes, serum total adiponectin levels were correlated positively with serum creatinine and age, whereas, negative correlations were found with Hb. A stepwise regression analysis demonstrated that among several significant variables, Hb had the strongest independent influence on total adiponectin (β = -0.512, at $P < 0.01$). In conclusion, anemia could be associated with a marked elevation in serum total adiponectin levels of diabetic patients without a detectable nephropathy (-ve microalbuminuria).

Key words: Type2 Diabetes, Adiponectin, Hemoglobin,Microalbuminuria.

العلاقة بين المستوى المصلي للاديبونكتين الكلي مع صباغ الدم في مرضى النوع الثاني من السكري غير المصابين بزلال البول الطفيف

عمار صباح خميس * و شذى حسين علي **،١ و خالد ابراهيم اللهيبي ***

* فرع العلوم المختبرية السريرية ، كلية الصيدلة ، جامعة الكوفة، نجف ، العراق .
** فرع العلوم المختبرية السريرية ، كلية الصيدلة، جامعة بغداد، بغداد ، العراق .
***المركز التخصصي الطبي للغدد الصم ومرضى السكري ، مستشفى الكندي التعليمي ،بغداد ، العراق .

الخلاصة

يرتبط المستوى المصلي للأديبونكتين الأجمالي مع نسبة عالية للاصابة بمرض السكري من النوع الثاني أو مرض الشريان التاجي في عموم المجتمعات. و لكن هناك مفارقة، بأن المستوى المصلي للأديبونكتين الأجمالي مرتفع في المرضى الذين يعانون من مرض الكلى المزمن ، مثل اعتلال الكلية السكري الواضح. والدراسة الحالية تهدف الى تقصي ما إذا كان فقر الدم مرتبطا بشكل مستقل مع المستوى المصلي للأديبونكتين في المرضى المصابين بداء السكري من النوع الثاني. قمنا بدراسة ٤٢ شخص من المصابين بمرض السكري من النوع الثاني من الذكور. وقد تم تعريف فقر الدم بمستوى خضاب دم أقل من ١٤غم/دل. و قد تم تعريف اعتلال الكلية الواضح بظهور الزلال في الأدرار. تم تقسيم مرضى السكري الى مجموعتين وفقا لمستوى خضاب الدم. تم قياس المستوى المصلي للاديبونكتين الاجمالي بتقنية الأنزيم المناعي المرتبط. في جميع المرضى المصابين بالسكري من النوع الثاني ، ارتبطت المستويات المصلية للأديبونكتين بإيجابية مع الكرياتينين في المصل والعمر ، في حين تم العثور على الارتباط السلبي مع خضاب الدم .ويشير تحليل الانحدار المتدرج الى أن من بين العديد من المتغيرات الهامة ، خضاب الدم كان له أقوى تأثير مستقل على المستوى المصلي للأديبونكتين الإجمالي (β = -0.512, at $P < 0.01$). و يمكن الاستنتاج بأنه، يرتبط فقر الدم مع ارتفاع ملحوظ في المستويات المصلية للأديبونكتين الإجمالي في مرضى السكري ، وهذا الارتفاع هو مستقل عن وظائف الكلى..

الكلمات المفتاحية : النوع الثاني من السكري ، الاديبونكتين وصباغ الدم (الهيموكلوبين) ، زلال البول الطفبف .

Introduction

Adiponectin [also known as Acrp30 -adipocyte complement related protein of 30 kDa- or AdipoQ] is a 244–amino acid protein secreted mainly by the adipose tissue. It was identified almost simultaneously by 4 different groups in the mid-1990s as an adipocyte-secreted hormone but remained in obscurity until the early 2000s (1). It circulates in multimers ; as full-length or high- molecular-weight (HMW), medium-molecular-weight (or hexamer), and low-molecular-weight (or trimer) adiponectin complexes(2). Additionally, full-length adiponectin may be cleaved to form a smaller, globular fragment, which has been proposed to have greater potency than full-length adiponectin (1). The HMW isoform was proposed to have a stronger association with insulin resistance , metabolic syndrome , and

[1] Corresponding author E- mail : hshathah@yahoo.com
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cardiovascular disease as the biologically most active form of the hormone[2]. However, several studies reported that the additional predictive value provided by HMW adiponectin in humans is minimal [2, 3]. Adiponectin is synthesized primarily in white adipose tissue and, at lower concentrations, in brown adipose tissue [4]. Much lower concentrations of expression have been reported in skeletal muscle, liver, colon, cardiac tissue, salivary glands, and placenta. Adiponectin is even detected in cerebrospinal fluid and breast milk at much lower concentrations [4,5]. Normal plasma adiponectin concentrations range between 5 and 30 µg/mL (depending on the assay used), and are inversely proportional to abdominal adiposity, insulin resistance, and type 2 diabetes [5].Adiponectin has also been shown to have distinct effects on lipid metabolism as well as antiinflammatory and antiatherogenic effects [6]. In addition to its peripheral actions, adiponectin may act centrally to modulate food intake and energy expenditure [7]. Women have higher adiponectin concentrations than do men (a measure that is independent of fat mass or distribution), which is possibly linked to differences in estrogen or androgen concentrations [8]. Reduced serum levels of adiponectin appears to play an important causal role in the development of insulin resistance, type 2 diabetes (T2D), and metabolic disease, thereby indirectly causing atherosclerosis.A recent meta-analysis of prospective studies with a total of 14,598 subjects and 2623 cases of type 2 diabetes indicated that higher adiponectin concentrations were associated with a lower risk of type 2 diabetes [9]. Moreover, reduced adiponectin levels also directly play a causal role in the development of atherosclerosis [10]. The present study aimed to investigate whether or not anemia is associated with serum level of total adiponectin in non-albuminuric type 2 diabetic males.

Materials and Methods

This study was carried out at The Endocrinology and Diabetes Center at Al-kindy Teaching Hospital for the period from October 2010-May 2011. The study included forty two male patients with type 2 diabetes mellitus (without overt nephropathy determined as negative microalbuminuria), twenty of the patients having anemia (i.e. Hb concentration less than 14gm/dl) ,the remainder of them(i.e.22) were considered as non anemic (Hb≥14gm/dl). All type 2 diabetic patients were maintained on oral hypoglycemic agents, and did not receive insulin therapy; all the patients were selected under supervision of a senior physician. Additionally sixteen apparently healthy male subjects matching the age and sex of the patients were included as a control group. Table (1) shows the baseline characteristics of the subjects included in the study. Serum adiponectin, and ferritin were measured by ELISA kits provided by Demeditec Diagnostics, Germany[11,12].Blood hemoglobin and serum urea were measured by kits provided from Cypress® Diagnostics, Belgium[13,14]. Whereas ,serum creatinine was measured by a kit provided from Spinreact ®, Spain [15]. Detection of microalbuminuria was performed by utilizing first morning urine specimens(turbidimetric test for quantitative determination) using kits purchased from Human® , Germany [16]. Statistical analysis was performed by Student t-test and analysis of variance ANOVA to examine the degree of significancy with p values *less than 0.05*. Correlations were tested by Regression Analysis using SPSS, version 17.

Table 1: Baseline characteristics of subjects.

Variable	Anemic Type 2 diabetic patients	Non anemic Type 2 diabetic patients	Controls
Number	20	22	16
Age (years)	55.35 ±2.231	53.23±1.869	50.33±5.20
Body Mass Index (kg/m2)	29.394±1.634	27.375±1.137	29.27±0.95
Duration of diabetes (years)	4.795±0.734	4.671±0.9	-
Fasting SerumGlucose (mmol/l)	11.022±0.878*	11.596±0.749*	6.353 ±0.165
Blood Hemoglobin (Hb gm/dl)	13.292±0.202*	14.938±0.139	14.795±0.551

The data are expressed as the numbers or mean ± standard error of mean (SEM).
* = significant difference from their control

Results

1. Serum total adiponectin

As shown in figure-1- data indicated that there was no significant difference in serum total adiponectin of the all type 2 diabetic patients (anemic and non anemic) when compared with the control group (P >0.05). While, there was a significant elevation (by about 8.7%) in serum total adiponectin of the anemic type 2 diabetic patients when compared to controls (P < 0.05). But, there was no significant difference in serum total adiponectin in non anemic Type 2 diabetic patients when compared to the control (P >0.05). Furthermore, a significant elevation (by about 7.2%) in serum total adiponectin of the anemic type 2 diabetic patients when compared to non anemic Type 2 diabetic patients (P <0.05).

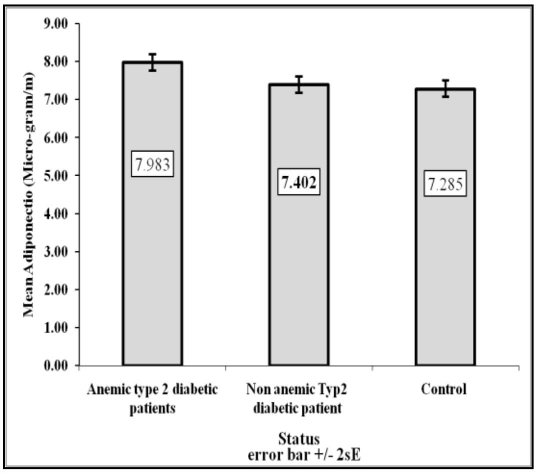

Figure 1 : Serum total adiponectin
Data are presented as: mean ± standard error

2. Blood hemoglobin

Table -2 demonstrated that there was no significant difference in Hb concentration between type 2 diabetic patients (anemic and non anemic) compared with controls (a decrease by 4.33% ,P >0.05). Data indicated that, there was a significant variation in blood Hb values of the anemic type 2 diabetic patients when compared to the control (lowered by 10.16%) with P < 0.05. But, there was no significant difference in blood Hb values between non anemic type 2 diabetic patients and the control group (P > 0.05). While, there was a significant difference in blood Hb of the anemic type 2 diabetic patients when compared to non anemic type 2 diabetic patients (by about 11%) P < 0.05.

3. Serum ferritin

As shown in table -2, there was a significant difference in serum ferritin levels (an increase by about 55%) of type 2 diabetic patients (anemic and non anemic) as compared with that of the control group (P <0.05). Data also indicated that, there was no significant difference in serum ferritin levels of the anemic type 2 diabetic patients when compared to the controls (P >0.05). While, there was a significant difference(an increase by about 36%) in serum ferritin level between non anemic Type 2 diabetic patients when compared to the control (P < 0.05). However, there were no significant differences have been observed in serum ferritin levels between that of the anemic diabetic patients as compared to non anemic diabetics(both of them without micoalbuminuria) ,p>0.05 .

Table 2: Blood hemoglobin & serum ferritin concentration among studied groups

	Whole Type 2 diabetics patients (n = 42)	Anemic Type 2 diabetic patients (n = 20)	Non anemic Type 2diabetic patients (n = 22)	Controls (n = 16)
Blood Hemoglobin (gm/dl)	14.154±0.175	13.292±0.202 [c, na]	14.938±0.139	14.795±0.551
Serum Ferritin (ng/ml)	116.792±14.25 [c]	99.139±19.355	132.1±20.493 [c]	60.919±9.720

Data are presented as: mean ± standard error of mean (SEM)
c: significant difference from control
na: significant difference from non anemic

4. Serum urea

As shown in table -3 , a significant increase (by about 16.6%) in serum urea concentration had been detected between type 2 diabetic patients (anemic and non anemic) and that of the control group (P < 0.05). Data indicated that, there was a significant difference (an increase by about 16.45%) in serum urea level between anemic type 2 diabetic patients and controls. (P < 0.05). Also there was a significant increase (by about 16.75%) in serum urea values in non anemic type 2 diabetic patients compared to the control values (P < 0.05). Furthermore, there was no significant difference in serum urea levels of the anemic diabetic patients as compared to non anemic diabetic patients(p > 0.05).

5. Serum creatinine

There was no significant difference in serum creatinine levels of type 2 diabetic patients (anemic and non anemic) when compared with the control group , (P >0.05), as illustrated in table -3. Meanwhile, there was no significant difference in serum creatinine values of the anemic Type 2 diabetic patients when compared to the control (P > 0.05). And there were no significant differences in serum creatinine between non anemic type 2 diabetic patients and controls. Also there was no significant difference in serum creatinine levels of the anemic type 2 diabetic patients when compared to non anemic diabetics both of them without micoalbuminuria (P >0.05).

Table 3: Serum urea & serum creatinine among studied group.

	Whole Type 2 diabetics patients (n = 42)	**Anemic Type 2 diabetic patients (n = 20)**	**Non anemic Type 2 diabetic patients (n = 22)**	**Controls (n = 16)**
SerumUrea (mg/dl)	43.64±1.696 ^{c}	43.559±2.395 ^{c}	43.715±2.452 ^{c}	36.392±2.094
Serum Creatnine (mg/dl)	0.668±0.048	0.676±0.056	0.661±0.077	0.680±0.042

Data are presented as: mean ± standard error of mean (SEM)

Discussion

The relatively high serum ferritin level in anemic type 2 diabetic patients (although it is lower than non anemic type 2 diabetic patients, but it is still higher than controls as shown in *table -2*) support the fact that the cause of anemia in type 2 diabetic patients is due to inflammation or so called anemia of chronic diseases rather than an iron deficiency anemia. Since the patients included in this study were non albuminuric diabetics, to exclude diabetic nephropathy and its relation to anemia through reducing erythropoietin (EPO) production [17].

The question is how precisely does iron overload exert its putative effects on the diabetic state?

1. Iron accumulation in hepatocytes may interfere with the liver insulin-extracting capacity. Supporting evidence comes from studies in noncirrhotic hemochromatotic patients. In these patients, insulin resistance and hyperinsulinemia appeared before pancreatic iron overload with selective B cell loss occurred.
2. Iron deposition may cause insulin resistance by interfering with the ability of insulin to suppress hepatic glucose production. This theory may explain the relationship found between insulin resistance and high ferritin level.
3. Iron tends to be auto-oxidized to form highly reactive, lipid soluble iron-oxygen complexes. In addition, ferrous iron also catalyzes the formation of glycosylated proteins derived free radicals. As a result, these highly reactive free radicals peroxidize lipids which change membrane properties and result in tissue damage. Increased oxidation of free fatty acids was also found to diminish glucose utilization in muscle tissue and to increase gluconeogenesis in the liver, leading to increased insulin resistance. Indeed, serum level of lipid peroxidation substances was high in patients with diabetes and diabetic microangiopathy.

The above suggestions and evidences lead to that hyperferritinemia may be associated with type 2 Diabetes Mellitus [18]. A significant association between serum ferritin levels [19, 20], high iron intake [21], and type 2 diabetes had been reported, but the association was not well understood. Low iron diets are not recommended, possible influences on ferritin levels were not excluded or taken into account in the statistical analyses of our study. They include burns, the recent use of aspirin and other nonsteroidal anti-inflammatory drugs, and recent blood donation, which lowers iron reserves and increases sensitivity to insulin [22].Concerning adiponectin , because of it's strong association with type 2 diabetes risks , preliminary data suggested that adiponectin may be moderately associated with cardiovascular morbidity and mortality. High adiponectin concentrations are associated with a favorable cardiovascular risk profile [23]. However, the relationship is more complex , some discrepancy may be related to the patient population studied (men versus women, older versus younger, prevalent cardiovascular disease). In addition, adiponectin may not directly affect cardiovascular risk but may be a marker of other risks, which may require further studies to clarify the relationship between adiponectin and cardiovascular disease [(24)].However ,it remains unclear why anemia is independently associated with an increased serum adiponectin levels, especially HMW adiponectin, in patients with type 2 diabetes. One possible explanation is the influence of tissue hypoxia(caused by anemia) on the expression of adiponectin in adipose tissue, through inducing the expression of hypoxia inducible factor (HIF) by cells of affected tissues [(25)].A recent study performed in mice has demonstrated that HIF-1 upregulates the expression of adiponectin in white adipose tissue, microvascular endothelial cells, or diabetic mouse hearts, presumably by acting on the presence of two putative HIF-1 response elements (HRE-1 and -2) in the promoter region of the murine adiponectin gene .Thus, it is possible that hypoxia may lead to increased adiponectin production either in adipose tissue or in the heart [(26)]. On one hand, local production of HMW adiponectin in cardiomyocytes and microvascular endothelial cells by HIF-1 may protect myocardium from hypoxia. On the other hand, production of EPO is also regulated by the tissue oxygen supply and the hypoxia-dependent gene expression of EPO is based on activation of the HIF-1 pathway. Thus, anemia may cause activation of the HIF pathway, resulting in the increased production of EPO, which suggests that activation of HIF pathway may result in an increase in serum concentrations of both HMW adiponectin and Epo[(27)].However, contrasting reports have indicated that hypoxia inhibits the expression of adiponectin in cultured adipocytes or mice adipose tissue [(28)]. Thus, there is controversy about the effects of hypoxia on the expression and metabolism of adiponectin. It is well known that a high serum adiponectin level is associated with a favorable lipid profile and improved glucose metabolism in both nondiabetic and diabetic subjects [(29,30)].Although blood urea concentrations increase as glomerular filtration declines, urea is a poor marker for kidney disease. Unlike creatinine, urea production rates are not constant, being dependent on the activity of the urea cycle enzymes and the protein load. An increased protein load may be due to diet, gastrointestinal bleeding, or catabolic states, including corticosteroid therapy [(31)]. In this study diabetics have higher blood urea levels as compared to non diabetic subjects. Furthermore , diabetic subjects could have significantly lowered serum total protein levels as compare to non diabetic subjects[(31)]. These biochemical changes may be related to the effect of having diabetes, where there is a depression of glycolytic enzymes and stimulation of gluconeogenic enzymes ,thus promoting gluconeogenesis in liver, which could further contribute to hyperglycemia, due to continuous catabolism of aminoacids leading to higher urea to be formed from urea cycle(our patients were selected to be free from liver disorders) .The current study demonstrated that Hb levels showed a strong negative correlation with serum total adiponectin levels in patients with type 2 diabetes (β = -0.512, at $P < 0.01$), as shown in figure -2-. Several previous studies, have shown that gender, age, TG, HDL- cholesterol, and renal function are independent determinants of the serum total or HMW adiponectin level in non diabetic and diabetic subjects [(32)]. In conclusion, the presence of anemia may contribute to the elevated serum levels of total adiponectin in male diabetic patients without chronic kidney diseases.

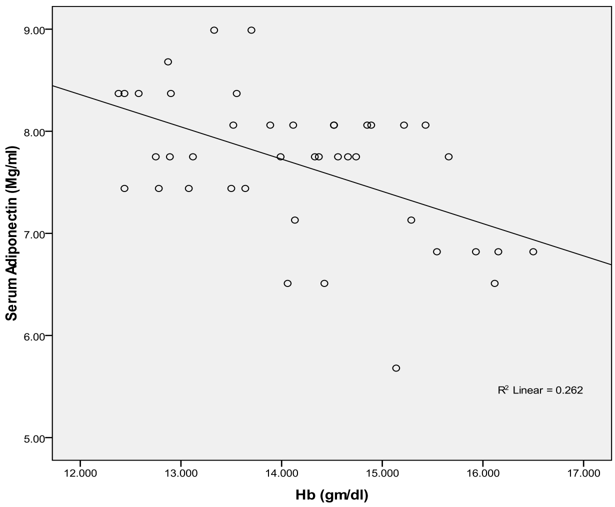

Figure 2: Correlation between serum total adiponectin and hemoglobin in type2 diabetic patients

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