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High AdiponectinHormone Modulation ofBlood Erythroid Parameters and its Relation with Erythropoietin in Patients with Diabetic Nephropathy

Zhian Sherzad Hayder*[1,2], Zrar Saleem Kareem[1]
[1]Department of Biology, Faculty of Science and Health, Koya University, Koya KOY45, Kurdistan Region – F.R. Iraq
[2]Department of Basic Science/College of Dentistry/ Hawler Medical University/ Erbil- Iraq

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Abstract
Background: Serum adiponectin is a hormone of adipose tissue that activateslipid metabolism and exertsphysiological functions. Its level usually fluctuates in several metabolic diseases,including renal insufficiency and diabetes; it loses its protective role against diseases and becomes a potentially risk factor for erythroid abnormalities.
Objectives: The study was designed to assess the association between adiponectin hormone, blood erythroid and various parameters in groups of patients.
Method: The study included 130 patientsand 42 healthy subjects. Parameters of serum adiponectin, erythropoietin (EPO), red blood cells (RBC), hemoglobin (Hb), hematocrit (Hct), renal function, serum insulin, fasting blood sugar (FBS), glycated hemoglobin % (HbA1c%) and homeostatic model assessment of insulin resistance (HOMA-IR) were estimated in all groups.
Result: Statistical analysis showed that high level of adiponectin was significantly associated with erythroid-related variables (EPO, RBC, Hb and Hct) in patients groups when compared with the control. Receiver Operating Characteristic (ROC) curve analysis showed that adiponectin is a significant risk factor for anemia progression in non-insulin dependent diabetes mellitus (NIDDM), end stage renal disease (ESRD)and diabetic nephropathy patients.
Conclusion: We suggest that high serum adiponectin level is dependently associated with EPO level and erythroid abnormalities in NIDDM, kidney failure and diabetic nephropathy patients. The present findings regarding ROC curve analysis of adiponectin suggested that this hormone could represent a risk factor for erythroid abnormality in diabetic nephropathy at ESRD.

Keywords: Diabetic nephropathy, adiponectin, EPO, erythroid abnormalities.

ارتفاع و تغيرات هرمون أديبونيكتين وعلاقتهبهرمون الاريثروبويتين وعوامل الدم الاخرى في المرضى الذين يعانون من إعتلال الكلى السكري

زيان شيرزاد حيدر[2،1]، زرار سليم كريم[1]
[1]قسم الأحياء ، كلية العلوم والصحة ، جامعة كويه ، Koya KOY45، إقليم كردستان .F.R – العراق
[2]قسم العلوم الاساسية ، كلية طب الاسنان، جامعة هولير الطبية، اربيل– العراق.

*Email:zhan.sherzad@hmu.edu.krd

الخلاصة

الخلفية: يعتبر هرمون أديبونيكتين المصلمن هرمونات الأنسجة الدهنية التي تنشط التمثيل الغذائي للدهون وغيرها من الوظائف الفسيولوجية. يتقلب مستوى الهرمون عادة في العديد من الأمراض الأيضية مثل قصور الكلوي ومرض السكري. يفقد دوره الوقائي ضد الأمراض ويصبح عاملاً محتملاً لخطر حدوث تشوهات في الكريات الحمر.

الأهداف: تهدف هذه الدراسة إلى تقييم العلاقة بين هرمون أديبونيكتين و الاريثروبويتين ، وكريات الدم الحمراء ومعلمات مختلفة في مجموعات من المرضى.

الطريقة: شملت الدراسة 130 مريضا و 42 حالة صحية. تم دراسة كل من أديبونيكتين المصل ، هرمون (EPO)الإريثروبويتين في المصل، خلايا الدم الحمراء (RBC) ، الهيموغلوبين (Hb) ، الهيماتوكريت (Hct) ، اختبار وظائف الكلى ، أنسولين الدم ، سكر الدم (FBS)، نسبة السكر الهيموغلوبيني المتراكم ٪ (HbA1c)٪كما و تم تقييم مستويات مقاومة الأنسولين (HOMA–IR) في جميع الفئات.

النتيجة: أظهر التحليل الإحصائي أن ارتفاع نسبة أديبونيكتين مرتبط بشكل كبير مع المتغيرات المرتبطة بالكريات الحمر (EPO ، RBC، Hbو Hct) في مجموعات المرضى بالمقارنة مع السيطرة. أظهر تحليل المنحنى خاصية التشغيل المتلقي (ROC) أن أديبونيكتين عامل مهم وخطر للإصابة بفقر الدم في داء السكري غير المعتمد على الأنسولين (NIDDM) ، ومرض الكلى في نهاية المرحلة (ESRD) ومرضى اعتلال الكلية السكري.

الخلاصة: نقترح أن يرتبط ارتفاع مستوى أديبونيكتين في المصل مع مستوى EPO وتشوهات الكريات الحمر في NIDDM ، الفشل الكلوي ومرضى اعتلال الكلية السكري. تشير النتيجة الحالية المتعلقة بتحليل منحنى ROCالهرمون الأديبونيكتين إلى أن هذا الهرمون يمكن أن يمثل عامل خطرا للإصابة بخلل في الكريات الحمر في اعتلال الكلية السكري في.ESRD

Introduction

Erythroid disorders, including anemia, are mostly encountered in the general clinical setting. Anemia is affected by hematopoietic growth factor erythropoietin (EPO)[1, 2]. Some people have anemia that is unrelated to nutrient deficiency or chronic metabolic diseases, but other factorsmay contribute to cause anemia [3]. Adiponectin is an adipokine secreted by adipocyte cells. Changes in adiponectin are a causative factor for diabetes and other diseases such as in patients with chronic renal failure undergoing dialysis, becauseof the decreased renal function[4-6]. It has also been stated that there is an association between serum adiponectin level and other risk factors for metabolic disorders, including traditional and new factors such as adipose tissue dysfunction and adipokinesabnormalities [7, 8]. Studies suggest that in patients with chronic renal failure,adiponectin is a predictor for progression of erythroid abnormalities and mortality [2, 5]. This suggests that the biological protective effect of adiponectin against cardiovascular and metabolic diseases is decreased in uremic and diabetic patients [8]. It is reported that suchchange in adiponectin level is associated with loss of energy and protein and increased fluid volume in this group of patients [2, 3]. Severalstudies [1, 9]suggest a negative correlation between adiponectinand growth of hematopoietic stem cells. According to some studies, it might also regulate mass of bone and mesenchymal stem cell migration in the bone marrow. Therefore, it probablyindirectly enhances erythropoiesis process rather than having a direct effect on erythrocytes[1, 9]. In chronic kidney disease (CKD) and diabetic patients, level of circulating adiponectin is paradoxically fluctuated and the role of adiponectin is complex to realize[1]. Therefore, we aimed to evaluate adiponectin level and blood erythroid parametersand determine whether adiponectinis associated with anaemia and Hb concentration in diabetic nephropathy patients, since such an associationseems to be unclear till now.

Materials and Methods

The study was conducted on 172 age and sex-matched subjects which were classified into 130 patients and 42 healthy persons. The studied population included four group subjects: Group 1 (Control Group) included 40 healthy people (20 males and 22 females) whose mean age range was 62.60 ± 6.4 years. They were selected based on a history of no arterial hypertensive, diabetic, cardiovascular, lung, renal, central nervous or endocrine system disorders. None of these subjects was

under any medical treatment. Group 2 (NIDDM patients group) included 50 adult patients with NIDDM under medical treatment (22 males and 28 females) with an age range of 60.65 ± 7.82 years. Group 3 (ESRD patients group) consisted of40 patients with end-stage renal disease under medical treatment and on hemodialysis(HD) (18 males and 22 females) withamean age range of 55.33 ± 6.43 years. Group 4 (NIDDM+ESRD Patients group) included40 patients with diabetic nephropathyunder medical treatment and on HD (20 males and 20 females) with amean age range of 53.90 ± 4.75 years, as illustrated in Table-1.All patients and control groups were subjected to personal interviews through a specially designed questionnaire form. Current standard criteria were applied for the diagnosis of NIDDM in differentiating the diabetic types. FBS, serum glycatedhaemoglobin (HbA1c %), insulin levels, and homeostatic model assessment of IR (HOMA-IR) were measured using conventional methods in order to identify Type I DM (IDDM), Type II DM (NIDDM) and gestational diabetes mellitus. Although we did not recruit obese patients, they had visceral fat accumulation because of the lifestyle and food quality. All the studied groups were neither obese nor overweight, but they had visceral adipocyte accumulation. All the groups showed an average urine output, varying from oliguria to normal, even when the GFR had been very low. There was also no protein excretion in the urine samples, and statistically, when compared with the control group, we did not observe any variations.

Blood samples were obtained after an overnight fasting and subjects were asked not to take their diabetes medications for 12 hours before the visit. Samples of venous blood (4 ml) were collected from the brachial veinby sterile disposable syringes in the morning and transferred into two disposable plastic test tubes; About 1 mlwascollected into anticoagulant ethylene diamine tetraacetic acid (EDTA) containing tubes(for haematological tests) and the remaining blood was added to biochemical gel and clot activator tubes in order to accelerate clotting for biochemical and hormonal studies. Serum wasseparated by centrifugation at 1000g for 20 minutes and divided into several equal aliquots;one was designated for the immediate assay of biochemical parameters in the serum, while the others were stored ina freezerat -70 Cº (Sony, Ultra-low, Japan) for subsequent assays. Hemolysed samples were discarded and repetitious freezing and thawing were avoided.Hematological, biochemical and hormonal evaluations includedRBC, hemoglobin (Hb), and hematocrit (Hct) which were analyzed by using coulter counter machine (Coulter counter/ Hitachi 211Q/ Japan).Serum creatinine, blood urea,fasting blood sugar (FBS), and serumglycatedhaemoglobin (HbA1c %) were determined by using the biochemical KENZA analyzer diagnostic kit (4 KENZA 240TX /Hitachi-USA) with a full automated biochemical analyzer. Insulin resistance (IR) was calculated by homeostatic model assessment of IR (HOMA-IR) formula. In each subject, the insulin resistance degree was estimated at the baseline by HOMA (Singh and Saxena, 2010), as follows:

$$\mathbf{HOMA-IR} = (\mathbf{fasting\ serum\ glucose} \times \mathbf{fasting\ serum\ insulin})/\mathbf{22.5}$$

Progression of kidney disease was evaluated by estimated glomerular filtration rate (eGFR) as in the followingCockcroft-Gault formula

$$eGFR = \{((l\,40 - age)\ x\ weight)/(72 x Serum\ creatinine)\} x\ 0.85\ (if\ female).$$

Serum adiponectin level was measured using an enzyme linked immunoassay kit (Biokit Corporation, Suite 103 Calsbad, CA, 93008, Spain). Serum EPOlevel was measured by ELISA Kit (Biokit Corporation., Carlsbad, CA 92006, Austria). Serum fasting insulin was measured by ELISA Kit (Cell biolabs INC., 5064 San Diego, USA).

Ethical considerations and written informed consent

Approval of the study was obtained from Koya University/ Faculty of Science and Health- Biology Department, Academic Ethical Committee office, with an ethics study number of 45. All patients were asked to sign an informed written consent for the acceptance of the study project.

Table 1-Schematic representation of the age and sex groups for the patients and controls

Subject	Sex and Age group/years		Total
	Male >40 yrs	Female >40 yrs	
Control	**20**	**22**	**42**
NIDDM	**22**	**28**	**50**
ESRD	**18**	**22**	**40**
NIDDM+ESRD	**20**	**20**	**40**

Statistical analysis

All values are presented as mean ± standard error (Mean ± SE). Statistical analyses were performed using one-way analysis of variance (ANOVA) by employingGraphpadPrism (Version 6). Person's correlation coefficient (r) was also used to find the association between adiponectin with EPO and mentioned parameters. Diagnosis of adiponectinlevel accuracy as a risk factor for anemia and progression in NIDDM, ESRD and diabetic nephropathy was presented in terms of sensitivity and specificity of Receiver Operating Characteristic (ROC) curve, which is a graphical display of sensitivity on y-axis and (100 – specificity) on x-axis for varying cut-off points of test values. Area under the curve (AUC) is a useful quantitative measure of accuracy. An area of 1 represents a perfect test; an area of0.5 represents a worthless test, while0.90-1= excellent (A), 0.80-0.90= good (B), 0.70-0.80= fair (C), 0.60-0.70= poor (D), and 0.50-0.60= fail (F).

Results

Selected laboratory data from the total study group (n = 172) are shown in Table-2. We observed significant differences in parameters in all studied ages. Serum adiponectin was significantly ($P<0.001$) increased in all groups when compared with the control subjects. Adiponectin was significantly ($P<0.001$) high in NIDDM+ESRD when compared with both ESRD and NIDDM groups. Adiponectin level in ESRD was significantly ($P<0.001$) high when compared with NIDDM. EPO level in all three patient subjects was markedly decreased ($P<0.001$) when compared with the control.Also,a significant ($P<0.001$) decrease in EPO was shown in NIDDM+ESRD when compared with NIDDM group, with no significance difference with ESRD. EPO level in ESRD was significantly ($P<0.001$) low when compared with NIDDM. Erythroid-related variables (red blood cells, Hb, and Hct) were significantly low ($P<0.001$) in all groups when compared with the control, whereasa significant ($P<0.001$) decrease in EPO was shown in NIDDM+ESRD when compared with NIDDM group, with no significance difference with ESRD. HOMA-IR showed significant elevation in NIDDM andNIDDM+ESRD subjects when compared with the control ($P<0.001$) and ESRD ($P<0.05$). HOMA-IR was significantly ($P<0.001$) high in NIDDM+ESRD when compared with both ESRD and NIDDM groups. Also, HOMA-IR of NIDDM was significantly ($P<0.001$) high when compared with ESRD. Renal function test showed a high decline in GFR, along with elevations in serum creatinine and urea levels in ESRD and NIDDM+ESRD patients ($P<0.001$) when compared to control subjects, while no significant change between NIDDM and control was observed when compared with ESRD and NIDDM+ESRD groups.

Statistical analysis revealed that serum insulin wasmarkedly elevated ($P<0.001$) in all groups when compared with the control subjects. There was a significant increase ($P<0.001$) in serum insulin ofNIDDM+ESRD group when compared with ESRD group. Also, serum insulin level in ESRD was significantly ($P<0.001$) low when compared with NIDDM. FBS was significantly ($P<0.001$) increased in all groups when compared with the control subjects. FBS was significantly ($P<0.001$) elevated in NIDDM+ESRD when compared with both ESRD and NIDDM groups. FBS level in ESRD was significantly ($P<0.001$) low when compared with NIDDM. Statistical analysis also revealed a significant elevation in HbA1c % ($P<0.001$) in NIDDM and NIDDM+ESRD groups when compared with the control subjects. There was a significant increase ($P<0.001$) in HbA1c % in NIDDM+ESRD when compared with ESRD group. Also, HbA1c level was significantly ($P<0.001$) high in NIDDM when compared with ESRD.

ROC analysis for serum adiponectin in NIDDM, ESRD and NIDDM+ESRD patients

Biomarker and risk factor analyses for NIDDM, ESRD and NIDDM+ESRD were performed by ROC curve. ROC curve analysis of adiponectin as a risk marker among the studied patients is shown in Figure-1, which demonstrated that the curve was significant ($P<0.001$),whereas the area under the curve (AUC) values were 0.828, 0.998 and 0.993 in NIDDM, ESRD and NIDDM+ESRD, respectively. The present observations revealed that adiponectin was an essential marker in NIDDM and ESRD patients.

Table 2-Mean ± S.E of the studied parameter changes in NIDDM, ESRD and diabetic nephropathy groups

Parameters	Control N=42	NIDDM N=50	ESRD N=40	NIDDM+ESRD N=40
insulin (pmol/L)	14.160 ± 1.524	40.040±1.919 *** +++	26.750±1.307 *** ###	45.900 ± 2.043 ***
FBS (mg/dl)	104.000±3.013	313.600±12.790 *** ### +++	123.300±3.110 *** ###	264.100 ±7.451 ***
HOMA-IR	0.6121±0.054	4.831±0.281 *** ### +++	1.496±0.067 * ###	7.344±0.290 ***
HbA1C (%)	5.000±0.100	7.354±0.090 *** +++	5.063±0.087 ###	7.100±0.130 ***
Hb (gm/dl)	13.460±0.168	10.020±0.169 *** ### +++	7.680±0.072 ***	7.232±0.056 ***
Hct(%)	40.630±0.368	29.420±0.421 *** ### +++	24.290±0.507 ***	22.620±0.758 ***
RBC (cell/mm^3)x10^6	5.033±0.115	3.902±0.053 *** ### +++	3.020±0.042 ***	2.870±0.061 ***
Urea (mg/dl)	37.220±1.338	41.240±1.811 ### +++	92.560±7.765 ***	97.050±3.932 ***
Creatinine (mg/dl)	0.996±0.037	1.404±0.097 ### +++	7.365±0.444 ***	7.517±0.624 ***
GFR (ml/min)	89.500±4.417	80.000±1.912 ### +++	15.810±1.817 ***	14.710±1.632 ***
Adiponectin (ng/ml)	6.213 ± 0.501	10.290± 0.866 *** ### +++	22.910 ± 0.756 *** ###	17.520 ± 0.548 ***
EPO (IU/ml)	49.380 ± 1.699	28.95±1.655 *** ### +++	2.054 ± 0.189 ***	1.674 ± 0.165 ***

Differences between **NIDDM, ESRD** and **NIDDM+ESRD** subjects compared to control subjects are shown with star sign (*P<0.05, **P<0.01, ***P<0.001), differences between NIDDM+ESRD with NIDDM and ESRD subjects are shown with hash sign (#P< 0.05, # #P<0.01, # # #P<0.001), while differences between NIDDM and ESRD subjects are shown with cross sign (+ P< 0.05, ++ P<0.01, +++ P<0.001).

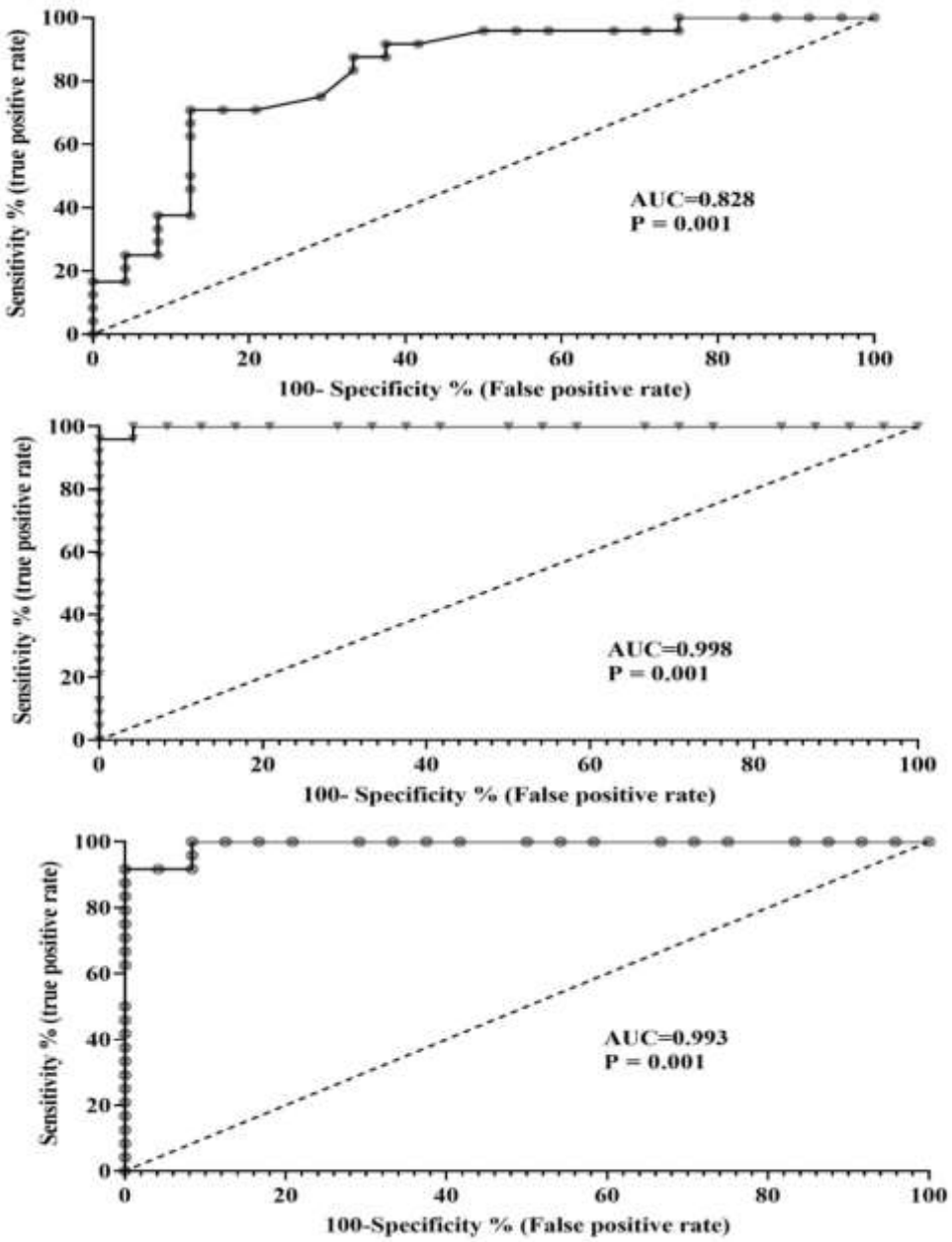

Figure 1-The ROC curve showingthe sensitivity and specificity of adiponectin concentration during A. NIDDM B. ESRD and C. diabetic nephropathy (NIDDM+ ESRD).AUC: Area under the curve.

Relationship between serum adiponectin and EPO with serum insulin and studied parameters in control with NIDDM subjects

Table-3showed that concentration of adiponectin negatively but not significantly related with Hb at (r= -0.084, p=N.S) and Hct at (r= -0.043, p=N.S), but significantly and negatively correlated with EPO level at (-0.395, p=0.001), RBC at (r=-0.270, p=0.05) and GFR at (r=-0.284, p=0.04). Adiponectin concentration was correlated significantly and positive with insulin (r=0.421, p=0.002), FBS (r=0.340, p=0.01), HOMA-IR (r=0.558, p=0.001), HbA1c (r=0.291, p=0.03), Serum urea (r=0.326, p=0.02) and creatinine (r=0.294, p=0.03).

Relationship of serum Adiponectin and EPO with serum insulin and studied parameters in control with ESRD subjects

Table-4 Pearson analysis indicated that adiponectin concentration was significantly related with EPO concentration (r=-0.923, p=0.001), RBC at (r=-0.432, p=0.002) and GFR was significantly negative (r=-0.407, p=0.004). Further Pearson analysis indicated that adiponectin concentration was

significantly related with insulin (r=0.691, p=0.001), FBS (r=0.500, p=0.001), HOMA-IR (r=0.642, p=0.001), HbA1c (r=0.417, p=0.003), serum urea (r=0.333, p=0.02) and creatinine (r=0.312, p=0.03). However, correlation between adiponectin and Adiponectin was related none significantly with Hb at (r= -0.243, p=N.S) and Hct at (r= -0.256, p=N.S).

Relationship of serum Adiponectin and EPO with serum insulin and studied parameters in NIDDM+ESRD with control subjects

Adiponectin level was significantly negatively related with EPO (r=-0.905, p=0.001), RBC (r=-0.413, p=0.004) and GFR (r=-0.454, p=0.001). Adiponectin concentration in Pearson analysis showed a positive relation with insulin (r=0.831, p=0.001), FBS (r=0.439, p=0.001), HOMA-IR (r=0.470, p=0.001), HbA1c (r=0.498, p=0.001), serum urea (r=0.432, p=0.002) and creatinine (r=0.385, p=0.006). Adiponectin was not related significantly with Hb (r= -0.225, p=N.S) and Hct (r= -0.187, p=N.S).

Table 3-Relationships of serum adiponectin and EPO with the studied parameters in NIDDM compared with the control.

Parameters		Adiponectin	EPO	Insulin	HOMA-IR	FBS	HbA1c	RBC	Hb	Hct	GFR	Urea	Creatinine
Adiponectin	r		-0.395	0.421	0.558	0.340	0.291	-0.274	-0.084	-0.043	-0.284	0.326	0.294
	p		0.005	0.002	0.001	0.01	0.03	0.05	N.S	N.S	0.04	0.023	0.03
EPO	r	-0.395		-0.629	-0.577	-0.508	-0.572	-0.434	0.194	0.179	0.207	-0.142	-0.184
	p	0.005		0.001	0.001	0.001	0.001	0.002	N.S	N.S	N.S	N.S	N.S

r = correlation

Table 4-Relationships of serum adiponectin and EPO with the studied parameters in ESRD compared with the control.

Parameters		Adiponectin	EPO	Insulin	HOMA-IR	FBS	HbA1c	RBC	Hb	Hct	GFR	Urea	Creatinine
Adiponectin	r		-0.923	0.691	0.642	0.500	0.417	-0.432	-0.243	-0.256	-0.407	0.333	0.312
	p		0.001	0.001	0.001	0.001	0.003	0.02	N.S	N.S	0.004	0.020	0.030
EPO	r	-0.923		-0.657	-0.575	-0.467	-0.478	0.244	0.263	0.225	0.382	-0.275	-0.334
	p	0.001		0.001	0.001	0.001	0.001	N.S	N.S	N.S	0.007	0.05	0.020

r = correlation

Table 5-Relationships of serum adiponectin and EPO with the studied parameters in NIDDM+ESRD subjects compared with the control.

Parameters		Adiponectin	EPO	Insulin	HOMA-IR	FBS	HbA1c	RBC	Hb	Hct	GFR	Urea	Creatinine
Adiponectin	r		-0.905	0.831	0.470	0.439	0.498	-0.413	-0.213	-0.187	-0.454	0.432	0.385
	p		0.001	0.001	0.001	0.001	0.001	0.004	N.S	N.S	0.001	0.002	0.006
EPO	r	-0.904		-0.826	-0.399	-0.423	-0.528	0.355	0.278	0.235	0.340	-0.380	-0.314
	p	0.001		0.001	0.004	0.002	0.001	0.013	0.055	0.107	0.017	0.007	0.029

r = correlation

Discussion

The results of the current study show elevations in serum adiponectin levels in NIDDM, ESRD and NIDDM+ESRD groups. A study by Mohammad*et al.*,[10]demonstrated that adiponectinexertsits effects on other organs via adiponectin receptors type I and II (AdipoR1 and AdipoR2), both have been identified in type 2 diabetes(NIDDM) and CKDpatients,which is consistent withthis study.The main causes for high adiponectin level in serum and urine in diabetic nephropathymay be either high biodegradation or elimination of adiponectin in the kidneys. Other causes might includeoverproduction of adiponectin in adipose tissue by amelioration of glomerular hypertrophy, through activation of adenosine 5'-monophosphate-activated protein kinase by AdipoR1 and activation of peroxisome proliferator-activated receptor (PPAR)-α signaling pathway by AdipoR2 (7). Several single nucleotide polymorphisms in the adiponectin gene are associated with increased risk of the development of diabetic nephropathy at ESRD[1,11]. A study by Zha *et al.*,[12]is in consistencewith the results of the presentstudyin terms of supportingthe notion that the association of adiponectin with diabetic nephropathy may be due to the expression and regulation by specific factors that regulate adiponectin gene (AdipoQ) transcription,such asCCAAT–enhancer binding protein A, forkhead box O1 (FOXO1), and specificity protein 1. It is intriguing that insulin might suppress the activity of FOXO1, which may negatively regulate the expression of adiponectin[11].

Based on the results of the current study, we revealed that high adiponectin levels cause reductions inthe levels of three erythroid-related variables (RBC counts , Hb levels and Hct %).Recent studies[5,12,13,14]showed that adipose tissue is not only an energy storage tissue, but also it is like an endocrine tissue that secretes essential hormones and a variety of adipocyte-derived factors which continually communicate with other tissues that affect metabolism [13]. Basic biological studies[8,15], consistent with thisstudy,suggest that adiponectin negatively and independently regulates the growth of hematopoietic cells because adiponectin and its receptors may affect components of the hemopoietic stem cell (HSC) niche. Nevertheless, it is still not clear that high adiponectin level was a prognostic factor for anemia. Determination ofthe relationship between anemia and adiponectin requires a prospective observational study, which has been long awaited and requires specific molecular studies [16]. Recent cross-sectional studiessuggested that adiponectin affects Hb levels along with EPO [3,15]. These findings also suggest that these factors are unrelated to renal or inflammatory anemia[4,17].

Conclusions: Adiponectin relevance to human diabetic nephropathy remains uncertain and controversial. From the obtained results,we suggest that adiponectinis implicated in the modulation of insulin sensitivity and,throughits unique signaling patterns, may be a significant factor in the

pathogenesis of insulin resistance and consequentdisorders,such aserythroid abnormalities. Further understanding is needed tothe relationship between independently associated high adiponectin and low EPO with erythroid variables, whichpredict the development of anemia.

Compliance with Ethical Standards

- No potential conflict of interest
- The research involved human participants with informed consent.
- Informed consent: All the patients were given an Informed consent form and the purpose of the study was explained to them.
- Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted with IRB and Ethics Committee approval has been obtained.
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References

1. Kim, H., Yun, H.R., Park, S., Jhee, J.H., Park, J.T., Yoo, T.H., Lee, K.B., Kim, Y.H., Sung, S.A., Lee, J. and Kang, S.W. **2018**. High serum adiponectin is associated with anemia development in chronic kidney disease: The results from the KNOW-CKD study. *Cytokine*, **103**: 1-9.
2. Milman, N. **2011**. Anemia—still a major health problem in many parts of the world!. *Annals of hematology*, **90**(4): 369-377.
3. Kohno, K., Narimatsu, H., Shiono, Y., Suzuki, I., Kato, Y., Sho, R., Otani, K., Ishizawa, K., Yamashita, H., Kubota, I. and Ueno, Y. **2016**. High serum adiponectin level is a risk factor for anemia in Japanese men: a prospective observational study of 1,029 Japanese subjects. *PloS one*, **11**(12): 0165511.
4. Lewerin, C., Johansson, H., Lerner, U.H., Karlsson, M.K., Lorentzon, M., Barrett-Connor, E., Smith, U., Ohlsson, C. and Mellström, D. **2015**. High serum adiponectin is associated with low blood haemoglobin in elderly men: the Swedish Mr OS study. *Journal of internal medicine*, **278**(1): 68-76.
5. Crawford, L.J., Peake, R., Price, S., Morris, T.C. and Irvine, A.E. **2010**. Adiponectin is produced by lymphocytes and is a negative regulator of granulopoiesis. *Journal of leukocyte biology*, **88**(4): 807-811.
6. Jasim, R. A., Umran, M. A. and Humadi, E. H. **2020**. Correlation Between Serum Interleukinslevels with Anthropometric Data and Lipid Profiles in Obese Iraqi Women With Polycystic Ovary Syndrome. *Iraqi Journal of Science*, **61**(1): 68-76.
7. DiMascio, L., Voermans, C., Uqoezwa, M., Duncan, A., Lu, D., Wu, J., Sankar, U. and Reya, T. **2007**. Identification of adiponectin as a novel hemopoietic stem cell growth factor. *The Journal of Immunology*, **178**(6): 3511-3520.
8. Matsubara, M., Namioka, K. and Katayose, S. **2004**. Relationships between plasma adiponectin and blood cells, hepatopancreatic enzymes in women. *Thrombosis and haemostasis*, **91**(02): 360-366.
9. Muhammed, T.R., Heidari, M., Deris, F. and Mardani, S. **2015**. Correlation of serum adiponectin level with some biochemical and metabolic factors in stable hemodialysis patients. *Journal of Parathyroid Disease*, **3**.
10. Yamauchi, T., Nio, Y., Maki, T., Kobayashi, M., Takazawa, T., Iwabu, M., Okada-Iwabu, M., Kawamoto, S., Kubota, N., Kubota, T. and Ito, Y. **2007**. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nature medicine*, **13**(3): 332.
11. Christou, G.A. and Kiortsis, D.N. **2014**. The role of adiponectin in renal physiology and development of albuminuria. *Journal of Endocrinology*, **221**(2): R49-R61.
12. Zha, D., Wu, X. and Gao, P. **2017**. Adiponectin and its receptors in diabetic kidney disease: molecular mechanisms and clinical potential. *Endocrinology*, **158**(7): 2022-2034.
13. Park, H.S., Lim, J.H., Kim, M.Y., Kim, Y., Hong, Y.A., Choi, S.R., Chung, S., Kim, H.W., Choi, B.S., Kim, Y.S. and Chang, Y.S. **2016**. Resveratrol increases AdipoR1 and AdipoR2 expression in type 2 diabetic nephropathy. *Journal of translational medicine*, **14**(1): 176.
14. Al-AttabyA. K. T.,& Al-LamiM. Q. D. **2019**. Effects of Duration and Complications of Type 2 Diabetes Mellitus on Diabetic Related Parameters, Adipocytokines and Calcium Regulating Hormones. *Iraqi Journal of Science*, **60**(11): 2335-2361.

15. Kammoun, H.L., Kraakman, M.J. and Febbraio, M.A. **2014**. Adipose tissue inflammation in glucose metabolism. *Reviews in endocrine and metabolic disorders*, **15**(1): 31-44.
16. Yu, L., Tu, Q., Han, Q., Zhang, L., Sui, L., Zheng, L., Meng, S., Tang, Y., Xuan, D., Zhang, J. and Murray, D. **2015**. Adiponectin regulates bone marrow mesenchymal stem cell niche through a unique signal transduction pathway: an approach for treating bone disease in diabetes. *Stem cells*, **33**(1): 240-252.
17. Kohno, K., Narimatsu, H., Shiono, Y., Suzuki, I., Kato, Y., Fukao, A., Kubota, I., Ueno, Y., Kayama, T. and Kato, T. **2014**. Management of erythropoiesis: cross-sectional study of the relationships between erythropoiesis and nutrition, physical features, and adiponectin in 3519 J apanese people. *European journal of haematology*, **92**(4): 298-307.