

ANEMIA IN DIABETIC PATIENTS WITHOUT MICROALBUMINURIA; IN RELATION TO TYPE OF DIABETES, GLYCEMIC CONTROL AND hs-C REACTIVE PROTEIN LEVELS

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Abstract

Recent studies have highlighted on association between anemia and the development and progression of diabetic nephropathy. There is also an increased cardiovascular risk in patients with diabetic nephropathy and a clear association between anemia and abnormal cardiac function, although most patients in the previous studies have type 2 diabetes mellitus. The present study focused on the possible variations in hematological parameters as well as hs-CRP levels in anemic type 1 and type 2 diabetics without microalbuminuria, in relation to their glycemic indices.

The study groups comprised of 50 diabetic patients (25 with type 1 and 25 with type 2) who had been selected to have haemoglobin levels below the gender specific normal range with negative microalbuminuria, in comparison to two control groups of 16 and 18 healthy subjects, respectively, whom are age and sex matching of type 1 and type 2 patients. For this the patients blood specimens were taken for testing blood levels of haemoglobin, red blood cells count, reticulocyte count, Hb_{A1C} levels; as well as fasting serum glucose, serum insulin, C-reactive protein levels.

The results indicated that anemia in both types of diabetes was not related to any of the RBC-indices (MCV, MCH, MCHC), results are not shown, but it's related to lowered total number of RBC as compared to their controls. Meanwhile, there was no evidence of an increased reticulocyte in the studied groups of either types of diabetes, indicating a defective erythropoiesis rate, although the selected patients were without detectable nephropathy (-ve testing for microalbuminuria). Furthermore, the reduction in RBC count was not significantly correlated with glycemic indices (FPG, FPI, Hb_{A1C}, QUICKI). However, hs-CRP levels were significantly elevated in diabetic patients, but CRP levels were significantly correlated with fasting serum insulin in type 2 diabetics, but not in type 1. Which may indicate a role for inflammation in type 2 diabetes in contribution to insulin resistance that may provide an additional risk factor for cardiovascular diseases in this type of diabetic whom have anemia as well.

Abbreviations: hs-CRP = high sensitive C-reactive protein, MCV = mean corpuscular volume, MCH=mean corpuscular haemoglobin, MCHC = mean corpuscular haemoglobin conc. FPG=fasting plasma glucose, FPI = fasting plasma insulin, QUICKI = quantitative insulin sensitivity check index, Hb_{A1c} = glycated blood haemoglobin.

Keywords: anemia, diabetes mellitus, microalbuminuria.

Introduction

Nephropathy is a frequent complication of both type 1 and type 2 diabetes mellitus. About 25- 40 % of patients with diabetes have kidney disease, where diabetes is considered as the primary cause of their kidney failure. ⁽¹⁾ Diabetic nephropathy is characterized by

excessive urinary albumin excretion, hypertension and renal insufficiency⁽²⁾.

An important complication of chronic kidney disease (CKD) is anemia, which is defined as haemoglobin values < 13 gm /dl for males, and < 12 gm/dl for females.⁽³⁾ Like many of the pathophysiological changes of diabetic nephropathy, such as albuminuria,

anemia may be apparent before a demonstrable decline in renal function. ⁽⁴⁾ Indeed a normochromic, normocytic anemia has observed in diabetic patients without overt renal disease⁽⁵⁾.

As the kidney plays a pivotal role in the control of hemopoiesis⁽⁶⁾, both in sensing small changes in tissue oxygenation and subsequently in stimulating hemopoietic precursors in the bone marrow through producing erythropoietin. Erythropoietin is manufactured by peritubular interstitial fibroblasts of the renal cortex and outer medulla. After that erythropoietin is secreted into peritubular capillary network from where it is delivered into systemic circulation via the renal vein. ⁽⁷⁾ although the decrease in the production of erythropoietin, mediated by renal insufficiency and the anti-proliferative effects of accumulating uremic toxins, contribute importantly⁽⁸⁾.

In addition, there are several evidence to suggest that anemia also independently contributes to the progression of microvascular complications⁽⁹⁾. Where, the majority of diabetic patients with anemia have functional erythropoietin deficiency, ⁽¹⁰⁾ when compared with non-diabetic patients (without overt renal disease) having similar decrease in haemoglobin (Hb)⁽¹¹⁾. However, degree of hyperglycemia and insulin resistance (specifically in type 2) represent the cornerstone in initiating and the maintenance of these complications, independently to other risk factors such as hypertension, high LDL-cholesterol, smoking, to develop cardiovascular diseases⁽¹²⁾.

Meanwhile, the production of specific inflammatory mediators by abdominal adipose tissues could link obesity to insulin resistance and diabetes later on. Emerging theories suggest that adipose-derived factors, produced in excess by adipose tissue, *adipocytokines* including interleukin-6, tumor necrosis factor-alpha and interleukin-18. C-reactive protein (CRP) was found to be significantly correlated with insulin sensitivity⁽¹³⁾.

The present study was designed to characterize the role of diabetes (both *type 1* and *type 2 diabetes*) in the pathogenesis of anemia in patients without nephropathy (negative microalbuminuria).

Material and Methods

This study was carrying out at the National Diabetes Center / Al-Mustansyria University and at the Center of Hematological Research / Al-Yarmook Teaching Hospital, from September/2008 to July/2009. The study included twenty five patients with type 1 (aged 22.28 ± 4.74 years) and another twenty five patients with type 2 diabetes mellitus (aged 47.48 ± 5.20 years) having anemia (i.e., Hb concentration < 13 gm/dl for males and < 12 gm/dl for females). Patients having type 2 DM were maintained on oral hypoglycemic agents, and did not receive insulin therapy, all the patients were selected under supervision of a senior physician. In addition to thirty four apparently healthy control subjects, 16 of them were matching the age and sex of type 1 diabetics and the reminder of the controls (18) were matching type 2 diabetics.

Venous blood specimens (20 ml) were withdrawn from each subject after an overnight (12 hours) fasting, after testing for microalbuminuria before including the subject in the study; utilizing first morning specimens. The obtained serum was utilized for analysing fasting serum glucose "evaluated according to the method of Barham and Trindoe (1972)"⁽¹⁴⁾, fasting serum insulin" using insulin ELISA kit which is a solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle"⁽¹⁵⁾, C-reactive protein (CRP)" using hc-CRP ELISA kit is based on the principle of a solid phase enzyme-linked immunosorbent assay"⁽¹⁶⁾. Whole blood (using EDTA-tubes) were used for assessing hematological parameters (Hb concentration "Based on Drabkin's solution"⁽¹⁷⁾, reticulocytes %". Simple technique for fluorescence staining of blood cells with Acridine orange"⁽¹⁸⁾, and automated RBC count by using Cell-DYN 3500 ⁽¹⁹⁾ within 1-2 hours and to estimate Hb_{A1C} concentration "was measured by automated ion-exchange high performance chromatography (Variant)"⁽²⁰⁾. The results were expressed as mean \pm standard error of mean (SEM). Student's t-test with p values less than 0.05 were considered significant. Person's correlation coefficient (r) was used to test for detecting statistical correlations between

studied parameters. The statistical analysis was performed using SPSS, version 11.5.

Results

1. Glycemic Indices in Anemic Type 1 and Type 2 Diabetic Patients:

Fasting Serum Glucose: Data presented in Table (1) indicates that fasting serum glucose levels are significantly different from their corresponding controls, in both type 1 and type 2 diabetic patients. Furthermore, fasting serum glucose levels were elevated significantly in type 1 diabetics as compared to type 2 patients.

Glycated Blood Haemoglobin (Hb_{A1C}): As presented in Table (1), the glycated blood haemoglobin levels were significantly higher in both types of diabetes (9.99 ± 2.05 % Hb, 8.66 ± 1.59 % Hb for type 1, type 2, respectively) as compared to their corresponding control groups (5.25 ± 0.46, 5.60 ± 0.52 for control 1, control 2, respectively). Glycated blood haemoglobin levels in type 1 diabetics were even statically greater than those of type 2 patients (p < 0.05).

The Quantitative Insulin Sensitivity Check Index (QUICKI): Insulin sensitivity was determined using the quantitative insulin sensitivity check index (QUICKI) which is calculated using the formula⁽²¹⁾.

$$\text{QUICKI} = \frac{1}{[\log (\text{FPI in } \mu\text{U/ml}) + \log (\text{FPG in mg/dL})]}$$

Insulin sensitivity index for both diabetic and control groups indicate a significantly lowered insulin sensitivity in diabetics when compared to their controls. Where type 1 diabetics expressed QUICKI values of 0.31 ± 0.02 Vs. 0.35 ± 0.001 for their controls (Table (1)). Whereas, type 2 diabetics QUICKI values were estimated to be 0.29 ± 0.01 Vs. 0.34 ± 0.02 for their controls. Furthermore, insulin sensitivity index values were significantly higher in type 1 as compared to type 2 (p < 0.05).

2. Haematological Parameters in Anemic Type 1 and Type 2 Diabetic Patients

Without Microalbuminuria:

Haemoglobin Concentration Hb: As shown in Fig.(1), the selected patients were anemic their haemoglobin concentration were significantly lower than that of their control

value. For type 1 diabetes the mean Hb value was 11.67 ± 0.75 g/dl, compared to the control 1 mean value of 15.11 ± 1.40 g/dl (p < 0.0001). For type 2 diabetes the mean Hb value was 11.26 ± 1.29 g/dl, compared to the control 2 mean value of 14.88 ± 1.52 g/dl (p < 0.0001). But their were no significant variations among the diabetic patients of the two types (P = 0.175).

Red Blood Cell Count: Fig.(2) indicates that red blood cell count values were reduced in type 1 diabetics (4.10 ± 0.27 M/μl) when compared to control 1 group (5.09 ± 0.50 M/μl) with p value=0.0001 for their t-test. Meanwhile, red blood cell count values for type 2 diabetics were 4.21 ± 0.25 M/ μl Vs. 5.14 ± 0.65 M/ μl, p < 0.0001. While, red blood cell count values were not significantly different among the diabetic patients of the two types (P > 0.05).

Reticulocyte Count: As shown in Fig.(3), the reticulocyte percentage was not altered in both of the patients groups as indicated by comparisons to their controls (1.30 ± 0.05 % Vs. 0.99 ± 0.51%, and 1.60 ± 0.65 % Vs. 1.27 ± 0.69% for type 1 and type 2, respectively). Meanwhile, there were no differences between the two types of diabetes.

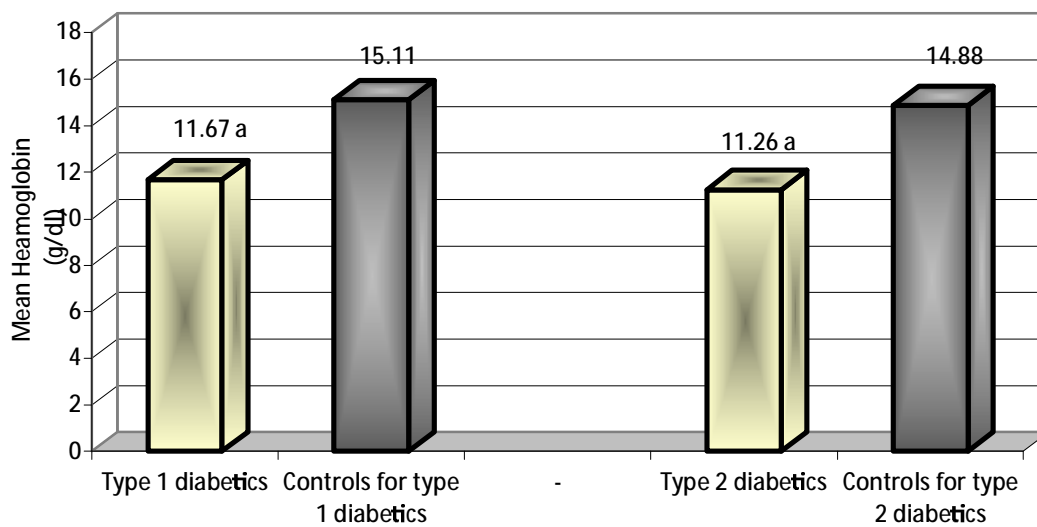
3. Serum High Sensitive C-Reactive Protein (hs-CRP) levels in Anemic Type 1 and Type 2 Diabetic Patients Without Microalbuminuria:

As presented in Fig.(4), the serum hs-C-reactive protein levels were significantly higher in both types of diabetes (3.94 ± 4.26 mg/L, for type 1, and 17.35 ± 7.50 mg/L type 2, respectively) as compared to their corresponding control groups (1.28 ± 0.61 mg/L for control 1, 9.13 ± 8.11 mg/L for control 2, with p value < 0.018, 0.001, respectively). Furthermore, hs- CRP levels in type 2 diabetics were even statically greater than those of type 2 patients (p < 0.0001).

Table (1)
Glycemic Indices.

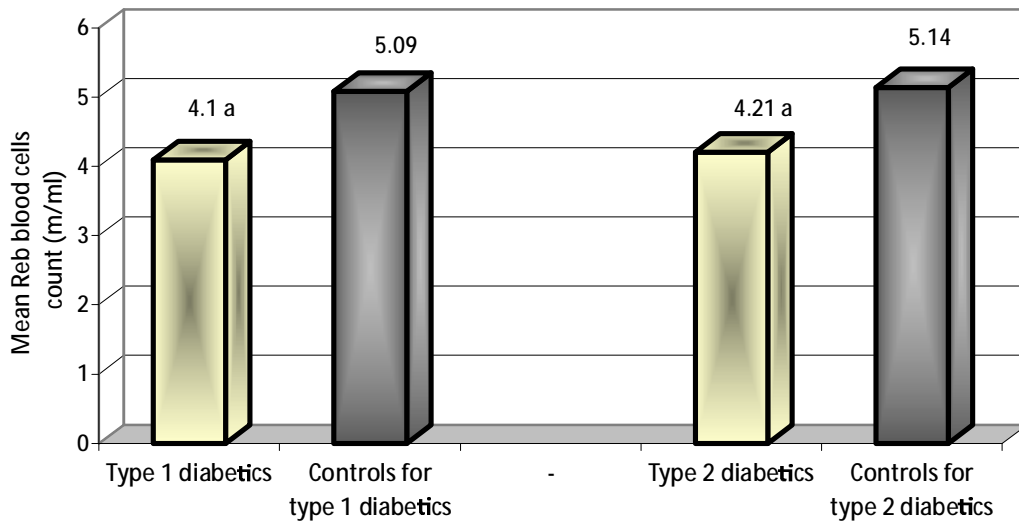
	<i>Type 1 diabetics (n=25)</i>	<i>Controls for type 1 diabetics (n=16)</i>	<i>Type 2 diabetics (n=25)</i>	<i>Controls for type 2 diabetics (n=18)</i>
Fasting Blood Glucose (mmol/l)	11.00±0.85 ^a	4.95±0.13	8.90±0.33 ^{ab}	5.45±0.13 ^c
Glycated haemoglobin %	9.99±0.41 ^a	5.25±0.12	8.66±0.32 ^{ab}	5.60±0.12 ^c
Fasting Serum Insulin µIU/ml	12.36±1.49 ^a	7.70±0.17	18.14±1.58 ^{ab}	10.57±0.98 ^c
Insulin Sensitivity Index(QUICKI)	0.31±0.001 ^a	0.35±0.001	0.29±0.001 ^{ab}	0.34±0.01 ^c

Data are presented as Mean±SEM, a = Significant difference from their control, b = Significant difference from diabetics type 1, c = Significant difference from control of diabetic type 1.



a = Significant difference from their control.

Fig. (1) : Blood Haemoglobin Concentration (g/dl).



a = Significant difference from their control.

Fig. (2) : Red Blood Cells Count (M/ml).

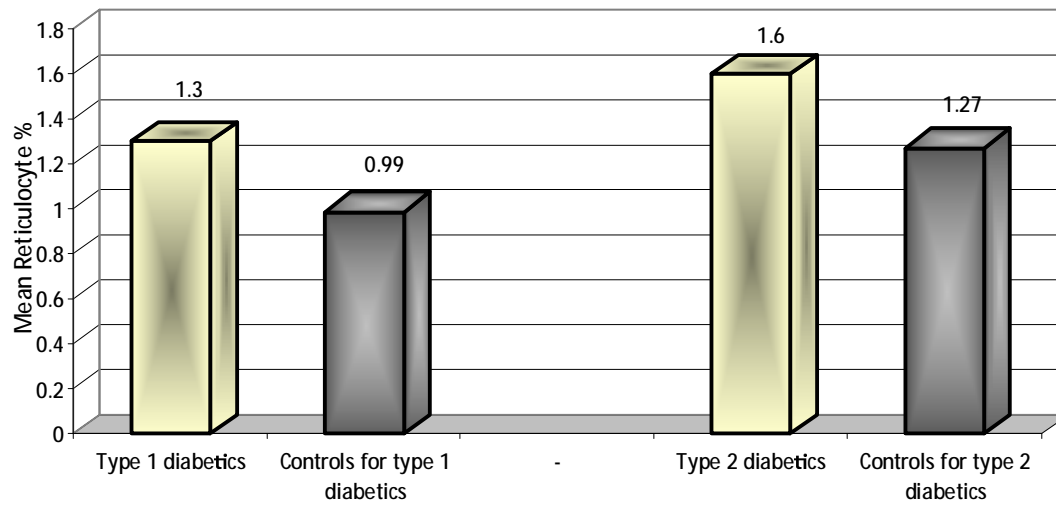
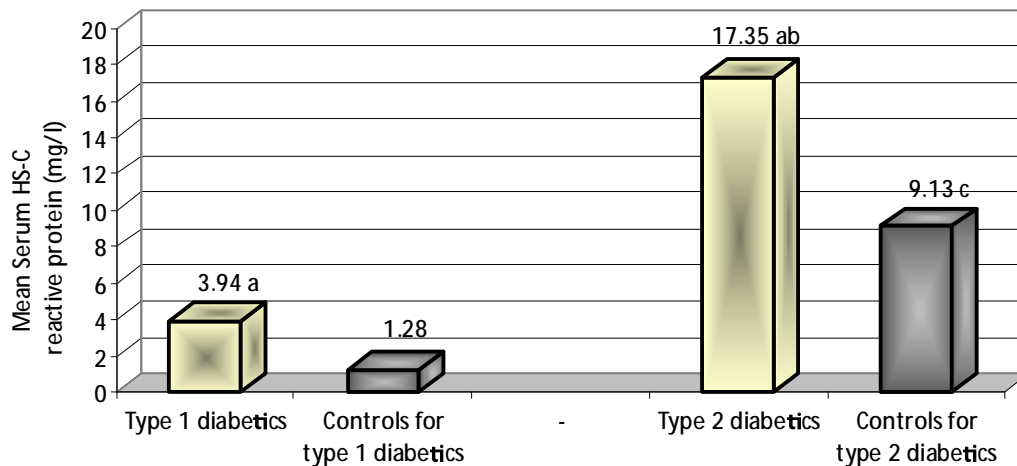


Fig.(3) :Reticulocyte Count in Studied Groups.



Data

are presented as Mean \pm SEM, a = Significant difference from their control, b = Significant difference from diabetics type 1, c = Significant difference from control of diabetic type 1.

Fig.(4) : Serum hs-C Reactive Protein (mg/L).

Discussion

Mildly impaired renal function is associated with cardiovascular morbidity and mortality. There are indications that several factors to be related to atherothrombosis, such as endothelial function and chronic inflammation, that are present in early stages of renal insufficiency⁽²²⁾⁽²³⁾. Meanwhile, it has been recognized recently that anemia is a common complication of diabetes, especially in those with diabetic nephropathy.⁽²⁴⁾

Data showed that in type 1 diabetes the Hb_{A1C} level is significantly elevated and positively correlated with RBC count ($r = 0.43$, $p < 0.05$), but not in type 2. Despite the significant variation in insulin sensitivity, presented by QUICKI values, between the two types of diabetes; there were no significant correlation between insulin sensitivity index and RBC count nor with reticulocyte count in either group. A recent survey had demonstrated that these patients had inappropriately low circulating erythropoietin levels which also implying a renal etiology to this disorder, however, patients with diabetes are still able to mount an appropriate response to acute hypoxia; suggesting that renal cells that produce erythropoietin are not simply lost in the process of interstitial damage that characterize diabetic renal disease⁽²⁵⁾. The reticulocyte count was not different between the patient groups with the lowest and highest

Hb levels and there was no relation between reticulocyte count and erythropoietin concentration⁽²⁶⁾. The reticulocyte count was significantly correlated with HbA1C level in diabetic subjects, independently of sex ($r = 0.68$, $p < 0.05$). Their reticulocyte count and Hb_{A1C} level showed parallel variations. Such correlation could be attributed to increased glycosylated haemoglobin in diabetic subjects which may cause sufficient chronic hypoxia to stimulate erythropoietin production and thus lead to an elevation in the reticulocyte count⁽²⁷⁾.

Patients with type 2 diabetes and low Hb level are said to have a 2- fold increased risk of diabetic retinopathy and a 5- fold increased risk of preproliferative or proliferative retinopathy, compared with those with higher Hb levels⁽²⁸⁾. Recent studies had suggested that reduced Hb levels, even within the normal range, identify patients with type 2 diabetes at increased risk for progressive renal disease. Which could be explained on the bases that anemia has direct mitogenic and fibrinogenic effects on the kidney and the heart, associated with the expression of growth factors, hormones, and vasoactive reagents, many of which are also implicated in diabetic microvascular diseases⁽²⁹⁾.

Although anemia is clearly associated with both micro- and macrovascular complications in patients with type 1 diabetes, it remains to

be established what role anemia may have in the development or progression of these complications because there is a direct relationship between anemia and diabetic kidney disease, anemia such as albuminuria may be a marker of more potent microvascular disease rather than being directly pathogenic⁽³⁰⁾.

The association between diabetes kidney disease and microalbuminuria is not as strong for patients with type 2 diabetes; only 30% of those with microalbuminuria demonstrated typical findings by kidney biopsy of diabetic nephropathy⁽³¹⁾. Where the studied anemic type 1 diabetic patients recorded creatinine clearance mean values of 99.31 ± 13.33 Vs 79.31 ± 15.12 for type 2 diabetics. Although patients with type 2 diabetes may show a slower rate of progression of renal diseases, with a cumulative incidence of nephropathy may be less than in type 1 diabetics⁽³²⁾.

It is now established that reduced haemoglobin levels in type 2 diabetics, even to a limited degree, identify patients at increased risk of progressive renal disease⁽³⁰⁾. Against this, patients with type 2 diabetes may have a slower rate of progression of diabetic renal disease, and the cumulative incidence of nephropathy may be less than in patients with type 1 diabetes⁽³²⁾.

Recent evidence suggests that poor glycemic control is significantly associated with the development of macrovascular complications of diabetes, CRP is an important risk factor for cardiovascular disease⁽³³⁾. Serum hs-CRP levels were significantly elevated in both types of diabetes; with a much greater elevation in type 2 diabetics; as compared to their controls, such variations in hs-CRP levels could be age related. Notably the elevated hs-CRP levels adds to the predictive values of dyslipidemia for premature coronary artery diseases in diabetics⁽³⁴⁾. Meanwhile, hs-CRP levels were significantly correlated with fasting serum insulin levels, specifically in type 2 diabetics ($r=0.423$, $p=0.035$). Elevated CRP concentrations increased with increasing Hb A1C levels, which strongly suggest an association between glycemic control and systemic inflammation in peoples with established diabetes⁽³⁵⁾. Inflammatory markers

as CRP have been related to the development of insulin resistance and type 2 diabetes. Additionally CRP levels are higher in people with diabetes and associated with HbA1C in people without diabetes.⁽³⁶⁾

The current study demonstrates that higher Hb A1C is significantly associated with elevation of CRP. These results simply a significant relation between inflammation and glycemic control in people with established diabetes. Prospective studies should be conducted to determine the direction of this association; such research would have important implications for the treatment of adults with diabetes.⁽³⁵⁾

Patients with type 1 diabetes and anemia were more than twice likely to have established macrovascular disease (25%) compared with patients without anemia 12%. This was largely determined by the increased risk of ischemic heart disease (IHD) in anemic patients. This effect was independent of the presence of renal disease, as twice as many patients with anemia had IHD with or without renal impairment.⁽³⁷⁾

Renal function was inversely associated with cardiovascular morbidity and mortality. The relative risk for cardiovascular mortality but not all –cause mortality associated with renal function decreased from 1.22 to 1.12 per 5 ml/min per 1.73 m² decrease of GFR after adjustment for markers of endothelial dysfunction. In conclusion, endothelial dysfunction was related to renal function and contributed to the excess in cardiovascular mortality in patients with mild renal insufficiency⁽³⁸⁾.

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الخلاصة

أشارت الدراسات الحديثة على وجود علاقة بين كل من فقر الدم وظهور وتطور أمراض الكلى لدى المصابين بداء السكري. إضافة إلى زيادة نسبة الخطورة في مرضى السكري الذين يعانون من اعتلال الكلى نتيجة السكري بسبب وجود علاقة واضحة بين كل من فقر الدم واختلال وظيفة القلب، على الرغم من إن معظم هذه الدراسات تمت على النوع الثاني من السكري. إن هذه الدراسة التي تركز على احتمالية ظهور اختلافات في بعض مؤشرات الدم و كذلك بمستوى البروتين – سي الفعال في مصلى المرضى لكلا النوعين الأول والثاني من السكري من المصابين بفقر الدم بدون اعتلال الكلى (عدم وجود آثار للألبومين في الأدرار).

تضمنت الدراسة 50 شخصا من المصابين بالسكري (25 منهم من النوع الأول و 25 من النوع الثاني) تم اختيارهم ليكون مستوى خضاب الدم لديهم أقل من مستواه الطبيعي حسب جنس المريض، من الذين اظهروا نتائج سلبية في فحص وجود آثار للألبومين في الأدرار. تم استحصا نماذج الدم بعد الصيام لقياس مستويات كل من

خضاب الدم وعدد الكريات الحمر وعدد الخلايا الشبكية في الدم اضافة الى مستوى الخضاب المرتبط بالسكر وكذلك مستويات كل من السكر والانسولين والبروتين - سي الفعال عالي الحساسية.

أظهرت النتائج ان فقر الدم في المجاميع المدروسة لم تبين اي اختلال في معايير الكريات الحمر (معدل حجم الكرية، معدل الخضاب فيها، معدل تركيز الخضاب فيها) - لم تبين النتائج هنا. ولكن كان فقر الدم يعزى بالدرجة الاساس الى انخفاض في تعداد الكريات الحمر لدى المرضى من كلا النوعين عند المقارنة بالأصحاء. على الغم من عدم وجود اي مؤشر لزيادة مستوى الخلايا الشبكية في الدم في اي من المجاميع المدروسة من مرضى السكري. مما قد يؤشر وجود خلل في عملية صنع الخلايا الحمر، على الرغم من اختيار المرضى غير المصابين باعتلال الكلي حسب الفحص السلي لأثار الالبومين في الاثرار. كما ان تناقص اعداد الكريات الحمر لم يكن مرتبطا احصائيا بأي من المؤشرات علي درجة سكرية الدم (فحص السكر، مستوى الانسولين، مستوى الخضاب المرتبط بالسكر، معدل التحسس للانسولين). في حين كان مستوى سي- بروتين الفعال عالي الحساسية شديد الارتفاع في المرضى حين المقارنة بالأصحاء، وكان ايضا مرتبطا بمستوى الانسولين في حالة الصيام لدى مرضى النوع الثاني من السكري فقط مشيرا الى احتمالية وجود دور لعملية الالتهاب في مقاومة الانسولين والتي قد تزيد عامل خطورة او مؤشرا اضافيا للاصابة بامراض القلب في مرضى النوع الثاني من السكري المصابين بفقر الدم.