J. of university of Anbar for pure science : Vol.7:NO.2: 2013
2nd Conference For Pure Science - university of Anbar 20-22/11/2012

ISSN: 1991-8941

Evaluation of vitamin C, uric acid, urea and creatinine levels in the blood of Type 2 diabetic Iraqi females

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Abstract:

Metabolic disorder of multiple causes characterized by chronic hyperglycemia and disorders of carbohydrate, fat, and protein metabolism… that have higher than normal serum creatinine and urea levels .The present study was carried out in patients with T2DM to evaluate the status of vitamin C, uric acid, urea and creatinine in total 51 (Iraqi females) patients and 31 control subjects matched for age, sex and ethnic background.Uric acid, urea and creatinine were measured by using commercially available kits. Serum vitamin C levels were measured by high performance liquid chromatography (HPLC). In type 2 diabetic patients serum creatinine and urea significantly elevated (P<0.001[HS]) and (P=0.021[S]) respectively while SUA and serum vitamin C were non significantly and significantly decreased (P=0.09 [NS]) and (P=0.005[S]) respectively as compared to control group.The normal levels of serum creatinine (0.76±0.15.1mg/dl) , urea (26.1±4.6mg/dl), uric acid (4.3±0.6mg/dl), and vitamin C (1.07±0.27mg/dl) recorded for the non-diabetic females were recorded in the diabetic females (0.94±0.17mg/dl) ; (28.8±5.3mg/dl) ; (4.1±0.7mg/dl) and (0.92±0.19 mg/ml)for serum creatinine, urea , uric acid and vitamin C respectively.In conclusion study shows significant increasing in urea and creatinine in type 2 diabetes mellitus patients when compared to control. Low levels of vitamin C and uric acid in diabetic patients indicating to an increased oxidative stress. Vitamin C level trying to fight against oxidative stress.

Key Words: S.vitamin C , S.uric acid , type 2 diabetes , S.urea , S.creatinine

Introduction:

Vitamin C is an important antioxidant in human[1] , capable of scavenging oxygen-derived free radicals[2]. Vitamin C is structurally similar to glucose and can replace it in many chemical reactions, and thus is effective in prevention of non-enzymatic glycosylation of proteins[3]. In addition, vitamin C acts as a regulator of catabolism of cholesterol to bile acid in guinea pig and has been demonstrated to be an important factor in lipid regulation[4]. Ness et al [5] showed beneficial effects of vitamin C on lipids in human. Many studies showed decreased basal vitamin C level in diabetic patients[6,7] and also it is suggested that oxidative stress is increased in diabetes[2,8,9].

Uric acid is the end product of purine metabolism in humans, excess serum accumulation can lead to various diseases, and most notably uric acid is causally involved in the pathogenesis of gouty arthritis [10-12].

Many prospective studies have suggested that hyperuricemia is associated with an increased risk of incident cardiovascular events and death in both nondiabetic and type 2 diabetic individuals[13–18].

Recent studies have shown that SUA level was significantly associated with Non-alcoholic fatty liver disease (NAFLD) and elevated SUA level was an independent risk factor for NAFLD [19-21] .

Low serum creatinine levels were associated with a higher risk of T2DM in a recent study of non-obese middle- aged Japanese men [22], leading the authors to speculate that low creatinine might reflect low muscle mass volume. In addition, glomerular hyperfiltration, which is associated with lower serum creatinine levels, may be associated with increased metabolic risk [23] and future diabetes [24].

Increased urinary protein excretion may be an early clinical manifestation of diabetic nephropathy [25-29].

However, there are clinical situations in which an acute renal failure may run with an increase in plasma creatinine keeping normal the urea level. Examples of the afore mentioned clinical situations are those patients who suffer from acute renal failure in the context of low protein intake, hepatic insufficiency, or/and diabetes insipidus [30-32].

Numerous studies have investigated the impact of multicomponent interventions on BP control in a variety of patient populations and settings, single studies of interventions aimed at both patients and providers have yielded mixed results with respect to improving BP control in patients with diabetes[33-38] .

PATIENTS AND METHODS:

The present study was carried out in the National Diabetes Center for Treatment and Research at Al-Mustansiriya University between April 2012-September 2012. A total of 51 patients of type2 diabetes mellitus (females of age group35→ 65 years.), who were already diagnosed to have type 2 diabetes mellitus based on the criteria of the expert committee on the diagnosis and classification of diabetes mellitus. 31 age and sex matched (females) healthy individuals served as controls who attended for routine health check up at the center. None of the healthy control was taking any medicine or dietary supplement; they were selected after detailed physical examination and laboratory tests. Samples collection: After 12 hrs fasting 5 ml. venous blood sample was collected in plain tubes, the samples were allowed to clot for half an hour following which a samples were centrifuged for 15 minutes at 2000 rpm. and serum was stored immediately at -20C until analysis.

Serum glucose was determined by a glucose oxidase method(Randox Company, U.K.) [39].Creatinine, uric acid and urea were measured by colorimetric method (LINER Chemicals /Spain).Vitamin C was determined by high-performance liquid chromatography (HPLC-UV)[40]. Systolic and diastolic blood pressure were recorded.

Statistical Analysis:

All data have been presented as mean ± SD. One-way analysis of variance (ANOVA) was performed on each variable and the Bonferroni statistics employed to compare the mean values from the different groups. Paired t-test was used to assess the effect between groups. Differences were considered significant at $P<0.05$. All statistical analyses were performed using SPSS statistical software (version 12).

RESULTS:

Table no.1 shows the average ages of the control and diabetic subjects were (49 ± 8.9) and (51 ± 6.9) years, respectively, (P =0.26[NS). It shows there were no group differences in BMI & Waist -hip ratio of the control and diabetic subjects were (30.8 ± 4.5) , (0.91 ± 0.04) and (32.7 ± 5.3), (0.91 ± 0.05) ;(P = 0.11[NS]) & (P = 0.99[NS]) respectively.

The table shows levels of Sys.BP, Dia.BP , FSG, S.urea, S.creatinine were elevated were as S.UA, S.vitamin C decreased in type 2 diabetic patients as compared to control group. The values were statistically significant, (P < 0.001[HS] for Dia.BP, FSG and S.creatinine);(P = 0.09[NS] for S.urea); (P = 0.001[HS]for SYS.BP). (P = 0.005[S] for S.VC); (P = .021[S]) for S.urea).

The normal levels of fasting serum glucose(96.3 ± 8.6 mg/dl), serum creatinine (0.76 ± 0.15 mg/dl) , serum urea (26.1 ±4.6 mg/dl), serum uric acid (4.3 ± 0.6mg/dl), Sys.BP (122.3 ± 10.7mmHg), Dia.BP (74.8 ±5.6 mmHg) and serum vitamin C (1.07 ± 0.27mg/dl) recorded for the non-diabetic females were recorded in the diabetic females (196.3 ± 56.1mg/dl); (0.94 ± 0.17mg/dl); (28.8 ± 5.3mg/dl); (4.1 ± 0.7mg/dl), (132.8 ± 15.5 mmHg), (82.9 ± 9.4 mmHg) and (0.92 ± 0.19 mg/ml) for fasting serum glucose, serum creatinine, serum urea , serum uric acid, Sys.BP, Dia.BP and serum vitamin C respectively.

Table no.2 shows the receiver operator curve (ROC) analysis of the forthcoming variations revealed the descending order of FPG (0.999), S.creatinine (0.801), S.VC (0.686), S.urea (0.660), S.UA (0.632) that showed significant variation.

Table no. 3 shows the validity parameters for selected indices when used as test to predict the new cut-off values for diagnosis of T2DM differentiating it from healthy controls.

Discussion:

Patients with diabetes should have their BP measured and recorded at each office visit with an instrument that has been recently calibrated[41] . Our results demonstrate that BP levels was elevated in T2DM subjects compared to control Subjects. our results agreed with different studies [42-44] that demonstrated decreased serum vitamin C levels in type 2 diabetic subjects.

Diabetes mellitus is a slow progressive disease characterized by hyperglycemia. Over time, high blood sugar levels damage million of nephrons -tiny filtering units with in each kidney. As a result, kidneys are unable to maintain the fluid and electrolyte homeostasis. Creatinine is filtered by the glomerulus; therefore, serum creatinine level is used as an indirect measure of glomerular filtration. As glomerular filtration rate (GFR) diminishes, there is a rise in concentration of serum creatinine and urea. Furthermore, the rise indicates progression of kidney disease and estimation of serum creatinine has greater prognostic ability compared with urea for predicting the adverse outcomes. The result of present study shows that diabetic subjects have significantly higher levels of blood urea (p=0.02) and serum creatinine (p=<0.001) as compared to non-diabetic subjects (Table 1). The above result corresponds with many studies [45-47] .

In humans, UA exists in blood at a concentration close to maximum solubility owing to the lack of the enzyme uricase, which oxidises uric acid to allantoin in other animals. Normally, UA is totally filtered in the renal glomerular and almost completely reabsorbed in the proximal tubular, while glucose competitively inhibits UA reabsorption and enhances its excretion at the same anatomic position, given normal renal function [48-50].

The results of this study demonstrate that serum Uric acid levels was decreased in T2DM subjects compared to control subjects (P=0.09 [NS]). The results of present study agreed with other studies [51-53] that demonstrated decreased serum Uric acid levels in type 2 diabetic subjects.

More recent studies suggest that oxidant stress could precede the development of endothelial dysfunction, and occurs when blood glucose concentrations are

moderately elevated above normal levels [54,55]. It was suggested that the serum UA acts as an antioxidant and antioxidative capacity in the early stages of the atherosclerotic process [56].

Urea is the major end product of protein catabolism in mammals. It is synthesized in the liver and excreted mainly by the kidney. Under basal conditions, this substance has a glomerular filtration of 100% although its final excretion is around 50%. This lower excreted amount respect to the filtrated one is a consequence of its reabsorption in the proximal tubules and in the very late part of the collecting ducts, close to the papillary tip. Moreover, since urea is also secreted in the S3 segment of proximal tubules, this substance suffers an intra-renal recycling process which contributes to reduce its excretion [57, 58].

In the present study, it was found that vitamin C deficiency and insufficiency was a great problem in our T2DM patients. The results showed that lower serum vitamin C level was associated with higher creatinine and higher serum glucose concentration in T2DM patients. These findings collectively suggest that vitamin C deficiency could be associated with the higher clinical serious status in our patients[59].

The oxidative products such as superoxide anion (O2-) and hydrogen peroxide (H2O2) could trigger inflammation in T2DM patients [60].

Type 2 diabetic subjects have multiple risk factors for cardiovascular disease, for example, hyperglycemia, insulin resistance, dyslipidemia, and hypertension. Each of these factors, separately, may be associated with increased free radical generation[61] .Diabetic patients may therefore have greater levels of oxidative stress than other groups of patients at risk of cardiovascular disease, these patients may also be more deficient in ascorbate than the general population. Previous studies in type 2 diabetes have revealed diminished tissue levels and impaired recycling mechanisms for ascorbic acid [62,63].

There are a number of mechanisms whereby ascorbic acid may increase nitric oxide bioactivity. Oxidative stress is increased in diabetes [64]. Free radicals such as the superoxide anion can degrade nitric oxide. Ascorbic acid is an extremely potent free radical scavenger and may thus protect nitric oxide from excessive degradation. However, it has recently been reported that supraphysiological concentrations of ascorbate are required to prevent the interaction of superoxide and nitric oxide [65] .

LDL particles are small and dense in type 2 diabetes and are susceptible to oxidation [66] .Oxidized LDL is directly toxic to endothelial cells and can impair the endothelial production of nitric oxide. α-Tocopherol is a lipid-soluble antioxidant and protects LDL particles from oxidative attack. Ascorbate is required for the regeneration of α-tocopherol [67]. Ascorbic recycling of α-tocopherol or by scavenging free radicals directly. Ascorbic acid may also enhance endothelial nitric oxide synthase activity. This may be secondary to the regulation of redox state but may also be due to an increase in the intracellular content of tetrahydrobiopterin [68] .Vascular smooth muscle is another potential site for the action of ascorbic acid. In vitro experiments have shown that guanylate cyclase sensitivity to nitric oxide may be enhanced after ascorbic acid administration [69]. Finally, ascorbic acid may reduce insulin resistance [70,71] .

Insulin can cause endothelium-dependent, nitric oxide–mediated vasodilation [72]. By improving insulin sensitivity, ascorbic acid may increase nitric oxide release from the endothelium. High blood pressure is very common in people with type 2 diabetes at diagnosis, which means that even small increases in blood pressure can be significant[73].

Our results demonstrate that serum vitamin C levels was decreased in T2DM subjects compared to control subjects, our results agreed with different studies [74-76] that demonstrated decreased serum vitamin C levels in type 2 diabetic subjects.

Conclusions:

Hypertension and diabetes are two common diseases. Increasing age, the presence of obesity, and worsening renal function all contribute to an increased likelihood of hypertension in people with diabetes. With increasing obesity, physical inactivity, and the aging of the population, diabetes and hypertension are crucial public health concerns for the 21st century.

High serum creatinine & urea are predictor of type 2 diabetes in Iraqi females. Low serum vitamin C is predictor of type 2 diabetes in Iraqi females. Low levels of vitamin C and uric acid in diabetic patients indicating to an increased oxidative stress. Vitamin C level trying to fight against oxidative stress, but low levels of serum uric acid in diabetic patients is not predictor of type 2 diabetes in Iraqi females.

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Table no.1 Showing the status of Age, BMI, W-Hr, SYS.BP, DIA.BP, FBS , S.UREA, S.CREATININE, S.UA and S.VITAMIN C in T2DM and Healthy Controls .

Parameters	Healthy controls (N=31)	Cases (T2DM) (N=51)	P (t-test)	Cohen's d (effect size)	SE controls	SE cases
Age (years)	(49 ± 8.9)	(51 ± 6.9)	($P=0.26_{[NS]}$)		1.6	0.97
Body mass index (BMI Kg/m^2)	(30.8 ± 4.5)	(32.7 ± 5.3)	($P=0.11_{[NS]}$)	0.38	0.81	0.74
Waist -hip ratio	(0.91±0.04)	(0.91±0.05)	($P=0.99_{[NS]}$)	0	0.007	0.007
Systolic blood pressure (mm Hg)	(122.3±10.7)	(132.8±15.5)	($P=0.001_{[HS]}$)	0.76	1.92	2.17
Diastolic blood pressure (mm Hg)	(74.8±5.6)	(82.9±9.4)	($P<0.001_{[HS]}$)	0.99	1	1.13
Fasting serum glucose (mg/dl)	(96.3±8.6)	(196.3±56.1)	($P<0.001_{[HS]}$)	2.24	1.55	7.85
Serum urea (mg/dl)	(26.1±4.6)	(28.8±5.3)	($P=0.021_{[S]}$)	0.53	0.82	0.74
Serum creatinine (mg/dl)	(0.76±0.15)	(0.94±0.17)	($P<0.001_{[HS]}$)	1.13	0.026	0.024
Serum uric acid (mg/dl)	(4.3±0.6)	(4.1±0.7)	($P=0.09_{[NS]}$)	-0.3	0.11	0.1
Serum Vitamin C (mg/dl)	(1.07±0.27)	(0.92±0.19)	($P=0.005_{[S]}$)	-0.68	0.049	0.027

Data presented as mean + SD.
HS-High Significantly different from control group by one-way ANOVA ;NS-Non Significantly different from control group ;S Significantly different from control group - FSG-Fasting serum glucose, Sys.BP- Systolic blood pressure, Dia.BP- Diastolic blood pressure, S.UA- Serum uric acid, S.VC- Serum Vitamin C, BIM-Body mass index, WHr - Waist -hip ratio.

Table no. 2: ROC area for selected parameters when used as test to predict a diagnosis of DM differentiating it from healthy controls.

Parameters	ROC area	P
Fasting plasma glucose (mg/dl)	0.999	<0.001
Serum. Creatinine(mg/dl)	0.801	<0.001
Serum Vitamin C (mg/dl)	0.686	<0.001
Serum Urea (mg/dl)	0.660	<0.001
Serum Uric Acid (mg/dl)	0.632	<0.001
Serum Triglycerides (mg/dl)	0.727	<0.001
Serum VLDL (mg/dl)	0.722	<0.001

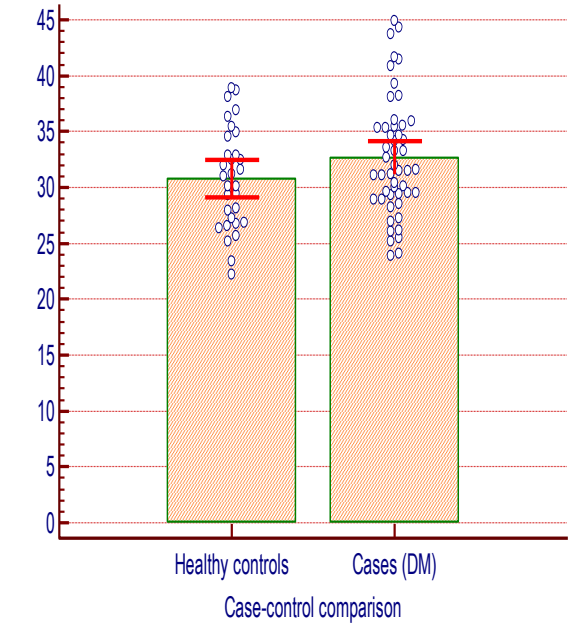

Fig. 1:The Body mass index in T2DM compared with control samples

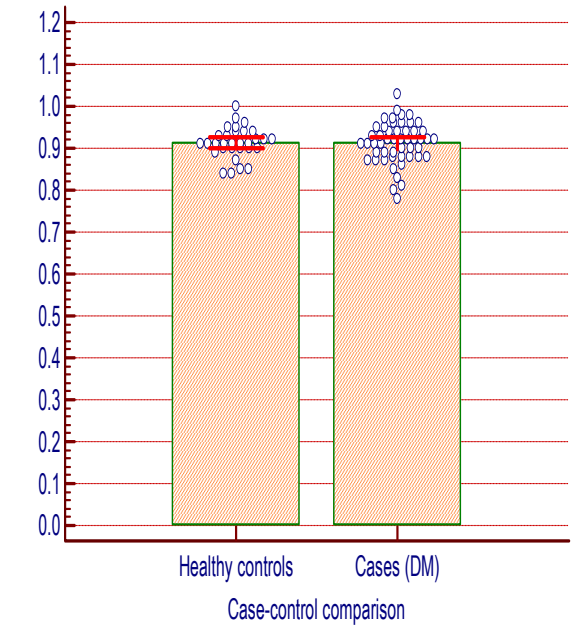

Fig. 2 :The waist-hip ratio in T2DM compared with control samples

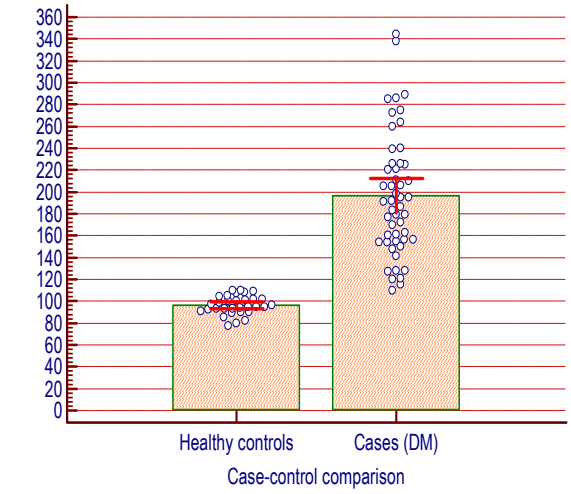

Fig. 3: The Fasting Plasma glucose levels in T2DM compared with control samples

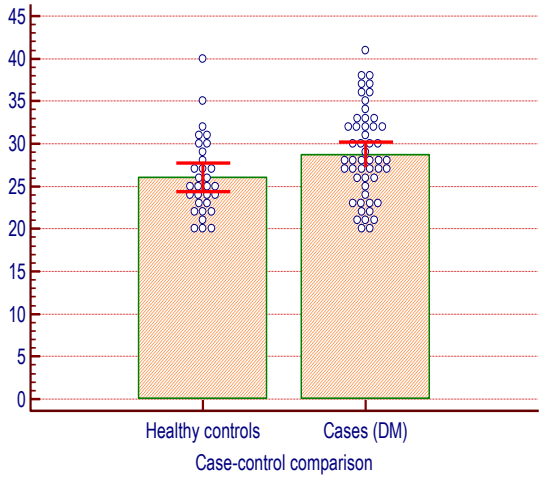

Fig. 4:The serum urea levels in T2DM compared with control samples

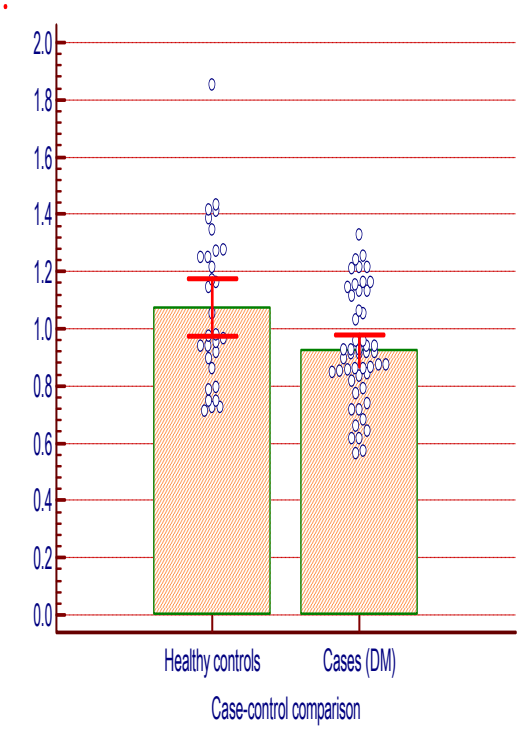

Fig. 4:The serum Vitamine C levels in T2DM compared with control

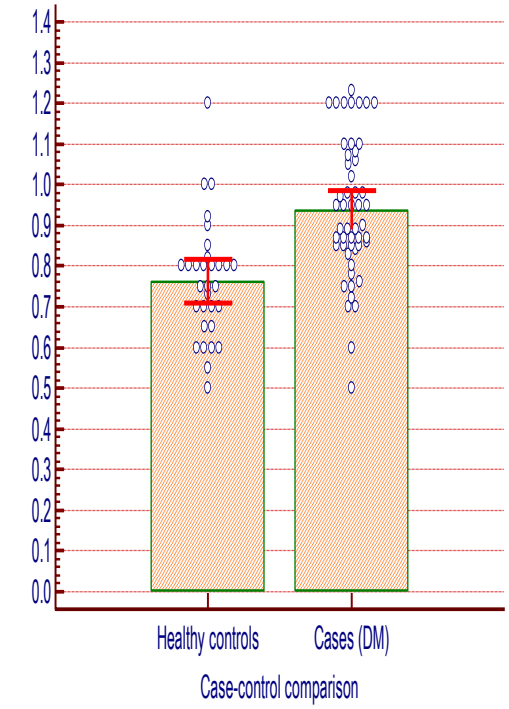

Fig. 4:The serum Creatinine levels in T2DM compared with control samples

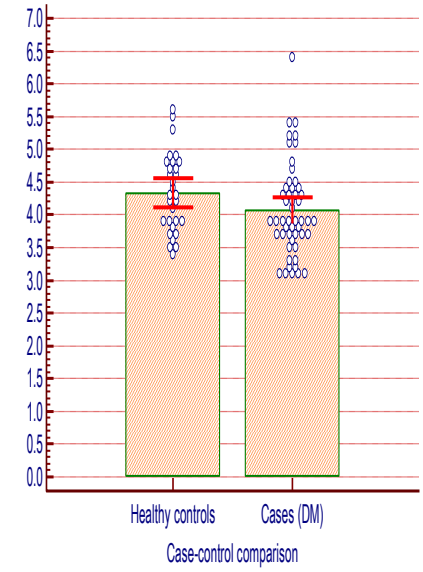

Fig. 4:The serum Uric Acid levels in T2DM compared with control samples

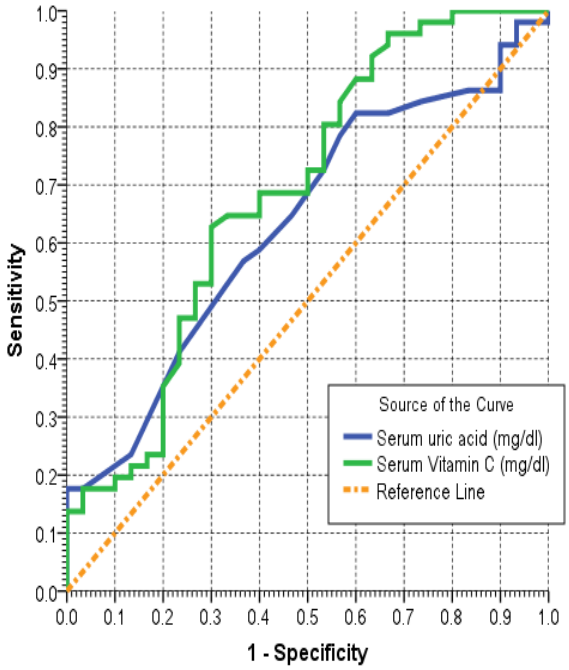

Figure 1: ROC curve showing the trade-off between sensitivity (rate of true positive) and 1-specificity (rate of false positive) for S.uric acid & vitamin C when used as test to predict a diagnosis of DM differentiating it from healthy controls.

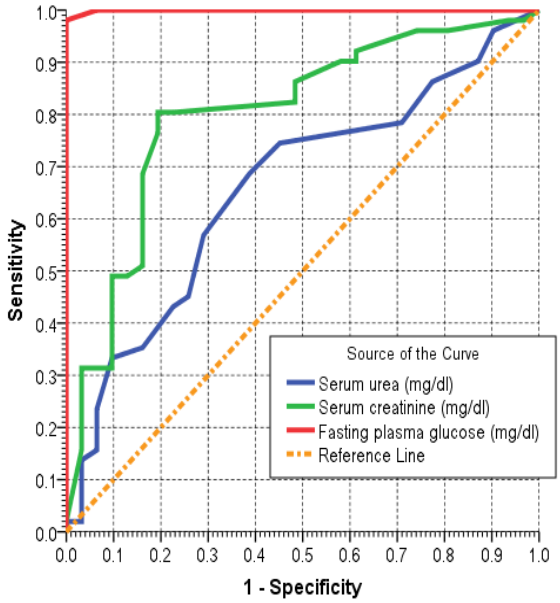

Figure 2: ROC curve showing the trade-off between sensitivity (rate of true positive) and 1-specificity (rate of false positive) for FPG ,S.urea & creatinine when used as test to predict a diagnosis of DM differentiating it from healthy controls.

J. of university of Anbar for pure science : Vol.7:NO.2: 2013
2nd Conference For Pure Science - university of Anbar 20-22/11/2012

تقييم مستويات فيتامين C, حامض اليوريك، اليوريا والكرياتينين في دم النساء العراقيات المصابات بداء السكري النوع الثاني.

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الخلاصة:

أجريت الدراسة الحالية بهدف تقييم المستوى المصلي لفيتامين C وحامض اليوريك واليوريا والكرياتينين لدى مرضى داء السكري النمط ألثاني وكان التقييم بواسطة كروموتوغرافيا السائل ذو الكفاءة العالية(HPLC) بالنسبة لفيتامين C اما المتغيرات الاخرى فتم تقييم مستوياتها عن طريق العدد المختبرية التجارية المتوفرة. أجريت الدراسة على 51 امرأة عراقية مصابة بداء السكري النمط الثاني من مراجعي المركز الوطني لعلاج و بحوث السكري التابع للجامعة المستنتصرية للفترة من نيسان 2012 ولغاية أيلول 2012، ولغرض المقارنة اعتمدت 31 امرأة من الأصحاء (السيطرة) المتوافقين بالعمر والجنس والعرق مع المرضى. كما وصف المرضى والسيطرة في ضوء عدد من ألمؤشرات العمر والجنس والتاريخ العائلي للسكري والسمنة (دالة كتلة الجسم) و نسبة الخصر الى الورك. وقيمت أيضا فترة الإصابة بالمرض وسكر مصل الدم الصائم.اظهر المستوى المصلي للدم لليوريا والكرياتنين زيادة معنوية وهي (28.8±5.3mg/dl) ; (0.94±0.17mg/dl) مقابل(26.1±4.6mg/dl) ; (0.76±0.15.1mg/dl)على التوالي في المرضى مقارنة بالسيطرة, بينما أنخفض معنوياً المستوى المصلي لحامض اليوريك وفيتامين C (4.1±0.7mg/ml) ;
(0.92±0.19 mg/ml) مقابل (4.3±0.6mg/dl) ; (1.07±0.27)على التوالي في المرضى مقارنة بالسيطرة0

للتمييز بين مرضى داء السكري النمط الثاني و مجموعة السيطرة استخدم تحليل Receiver Operator Curve (ROC) والذي أظهر الترتيب التنازلي بحسب الأهمية للمؤشرات التي أظهرت فروقآ معنوية وكان الترتيب لسكر بلازما الدم الصائم (0.999) و الكرياتينين (0.801) و فيتامين C (0.686) واليوريا (0.660) , وحامض اليوريك (0.632) 0 نستنتج من ذلك ان انخفاض مستوى فيتامين C وحامض اليوريك بشكل كبير مع زيادة مستوى اليوريا والكرياتينين في المصل يتزامن مع زيادة خطورة داء السكري النمط الثاني خصوصا مع البدينين منهم0