

Oxidant-Antioxidant Status and Some Related Parameters in Hypertension Diabetic (Type 1&2) Patients - in Thi-Qar /Iraq

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Abstract

Hyperglycemia is considered a major initiator of oxidative stress which lead to the formation of free radicals and consequently lipid peroxidation occurs that which lead to tissue damage and diabetes mellitus development. Therefore, the present study aims to investigate the relationship between antioxidant status and lipid peroxidation end products (malondialdehyde; MDA) and some trace elements in the plasma of 30 type 1 DM patients and 30 type 2 DM patients and 40 hypertension DM patients (20 type1 and 20 type2) and 30 non hypertension DM patients (15 type1 and 15 type2) and 40 non diabetic healthy control subjects.

Plasma MDA, chromium and ceruloplasmin concentrations was measured by manual methods, whereas glucose, iron, copper, transferrin and albumin concentrations were analyzed spectrophotometrically by kits in all patients with DM as well as in the control subjects. The results of type1DM were compared with type2DM and hypertension-DM were compared with a non- hypertension DM and control group using One way ANOVA-test to compare parameters in different studied groups.

The results show a significant elevation ($P \leq 0.05$) in levels of glucose, MDA, iron, copper and ceruloplasmin of type 2- diabetic patients in comparison type 1-diabetic patients and healthy subjects, also, it has been found a significant decrease ($P \leq 0.05$) in chromium, transferrin and albumin levels in type 2- diabetic patients in comparison with type 1- diabetic patients and control group. Also the results show a significant elevation ($P \leq 0.05$) in levels of glucose, MDA, chromium, iron, copper and ceruloplasmin of (type1 and type 2) hypertension- diabetic patients in comparison (type 1and type2) non hypertension-diabetic patients and healthy subjects, also, it has been found a significant decrease ($P \leq 0.05$) in transferrin and albumin levels (type1 and type 2) hypertension- diabetic patients in comparison (type1and type2) non hypertension-diabetic patients and healthy subjects.

Introduction

Diabetes mellitus is a group of metabolic diseases characterized by an elevated blood glucose level resulting from defects in insulin secretion, insulin action or both (Ian Murray, 2009) Also diabetes mellitus is characterized by hyperglycemia together with biochemical alterations of glucose and lipid peroxidation (Marshall, W. J., 2000) Lipid peroxidation is a free radical-related process, which is potentially harmful because its uncontrolled, self-enhancing process causes disruption of membranes, lipid and other cell components. It is also involved in oxidative stress, which plays a major role in the pathogenesis of diabetes mellitus (Jakus ,V., 2000) Hypertension is induced by oxidative stress so it is more prevalent in patients with diabetes than in the non-diabetic population (Oparil, S. et al 2003). In present study, the relationship between level of serum (MDA) an oxidant, as a marker of lipid peroxidation and some trace elements and some endogenous antioxidants in diabetic patients was investigated against no diabetic patients and healthy subject as controls.

Materials and Methods:-

Subjects

Forty normal healthy subjects with fasting plasma glucose (FPG) < 5.50 mmol/L were selected as control group. The ages ranged from 18 to 60 years. Thirty Type1 -diabetic subjects whose FPG > 11.99 mmol/L and thirty Type 2-diabetic subjects whose FPG > 16.95 mmol/L and twenty hypertension-type 1diabetic subjects whose FPG > 13.5 mmol/L and fifteen non hypertension-type 1diabetic subjects whose FPG > 11.96 mmol/L and twenty hypertension-type 2 diabetic subjects whose FPG > 16.98 mmol/L and fifteen non hypertension-type 2 diabetic subjects whose FPG > 14.95 mmol/L were selected from AL-Hussein Education Hospital and the Special Center of the Endocrine Glands and Diabetes in Thi-Qar. About (10 mL) of fasting venous sample all included subjects were taken and allowed to clot to get serum by putting it in empty disposable tube's centrifuge to separate it in the centrifuge at 3000 (rpm) for 10 min, the serum samples were separated, stored at (-20°C) for later measurement biochemical parameters, unless used immediately.

Measurements Biochemical Parameters

Serum glucose was determined by an enzymatic colorimetric test on basis of Trinder-Reaction (Greiling, H., 1995) (Trinder, P., Ann. 1989). MDA in plasma was performed as

described by Fong et al (Fong, K.L. et al 1973) Chromium in plasma was measured in the Italian hospital in Thi-Qar by manual procedure. Plasma iron was measured by a colorimetric (Ceriotti, F. 1980) Copper in plasma was measured by a colorimetric method (Abe. A., et al. 1989). Serum Tf is determined by adding an excess of inorganic iron to the plasma, any not bound to protein being removed. The concentration of iron remaining is assayed and the result expressed as TIBC (Short, L.F. et al. 1984). In colorimetric method an excess of iron is added to the serum to saturate the Tf. After centrifugation the iron in the supernatant is determined (Ceriotti, F. 1980) Ceruloplasmin in serum was measured by Menden et al (Menden, C.E. et al 1977). The concentration of albumin in serum sample was measured by the bromocresol green a colorimetric method (Webster, D., 1974).

Statistical analysis

Statistical analysis was carried out by One way ANOVA-test was used to compare parameters in different studied groups. P-values ($P \leq 0.05$) were considered statistically significant. The results were expressed as mean \pm standard deviations (mean \pm SD) by using SPSS version 10.0.

Results:-

Serum glucose concentrations were significantly higher ($P \leq 0.05$) in type2 diabetic group in comparison with type1 diabetic, also there is a significant increase in concentrations of serum glucose in all patients groups in comparison with control group ($P \leq 0.05$). However, an apparent increase was also observed in concentrations of serum MDA in type2 diabetic in comparison with type1 diabetic ($P \leq 0.05$) and there is a significant increase in concentrations of serum MDA in all patients groups in comparison with control group ($P \leq 0.05$). Chromium concentrations in serum were significantly lower in type2 diabetic group in comparison with type1 diabetic group ($P \leq 0.05$). Also, there is a significant decrease in concentrations of serum chromium in all patients groups in comparison with control group ($P \leq 0.05$). The iron concentration in type2

diabetic were a significantly higher in comparison with type1 diabetic ($P \leq 0.05$) and there is a significant increase in concentrations of serum iron in all patients groups in comparison with control group ($P \leq 0.05$). A significant increase was found in concentrations of serum copper in type2 diabetic in comparison with type1 diabetic ($P \leq 0.05$)

and there is a significant increase in concentrations of serum iron in all patients groups in comparison with control group ($P \leq 0.05$). A significant increase was found in concentrations of serum copper in type2 diabetic in comparison with type1 diabetic ($P \leq 0.05$) also there is a significant increase in concentrations of serum copper in all patients groups in comparison with control group ($P \leq 0.05$). A significant increase was found in concentrations of serum copper in type2 diabetic in comparison with type1 diabetic ($P \leq 0.05$) also there is a significant increase in concentrations of serum copper in all patients groups in comparison with control group ($P \leq 0.05$). The results show a significant decrease in concentrations of serum Tf in type2 diabetic in comparison with type1 diabetic ($P \leq 0.05$) and there is a significant decrease ($P \leq 0.05$) in concentrations of serum Tf in all patients groups in comparison with control group. A significant increase in concentrations of serum ceruloplasmin in type2 diabetic in comparison with type1 diabetic ($P \leq 0.05$). Also, there is a significant increase in concentrations of serum ceruloplasmin in all patients groups compared to control group ($P \leq 0.05$). A significant decrease ($P \leq 0.05$) in concentrations of serum albumin in type2 diabetic in comparison with type1 diabetic and there is a significant decrease ($P \leq 0.05$) in concentrations of serum albumin in all patients groups in comparison with control group.

A significant increase in serum glucose, MDA, chromium, iron, copper and ceruloplasmin in type1 and 2 hypertension-diabetic group in comparison with type 1 and 2 non hypertension-diabetic group ($P \leq 0.05$) and there is a significant increase in serum glucose concentrations in all patient groups in comparison with control group ($P \leq 0.05$). And a significant decrease in serum Tf and albumin in type1 and 2 hypertension-diabetic group in comparison with type 1 and 2 non hypertension-diabetic group ($P \leq 0.05$) All these results are shown in table (2).

Table (2):- Biochemical Parameters in Type 1&2 Diabetic Patients Related to Hypertension & Non Hypertension

Parameter	Mean \pm SD						
	Control	T1 DM	T2 DM	T1DM H	T1DM Y	T2DM H	T2DM Y
Glucose (mmol/L)	5.50 \pm 0.55 ^a	11.99 \pm 0.20 ^b	16.95 \pm 0.29 ^c	13.5 \pm 0.41 ^b	11.96 \pm 0.27 ^c	16.98 \pm 0.51 ^b	14.95 \pm 0.43 ^c
MDA (nmol/L)	6.89 \pm 0.07 ^a	65.41 \pm 0.08 ^b	67.38 \pm 0.59 ^c	66.87 \pm 0.08 ^b	64.29 \pm 0.13 ^c	69.15 \pm 0.09 ^b	67.23 \pm 0.14 ^c
Cr (mg/L)	0.69 \pm 0.01 ^a	0.33 \pm 0.01 ^b	0.24 \pm 0.01 ^c	0.58 \pm 0.08 ^b	0.40 \pm 0.01 ^c	0.37 \pm 0.09 ^b	0.26 \pm 0.01 ^c
Iron (μ mol/L)	19.09 \pm 0.07 ^a	32.01 \pm 0.06 ^b	34.81 \pm 0.07 ^c	33.57 \pm 0.05 ^b	31.89 \pm 0.10 ^c	36.58 \pm 0.07 ^b	34.71 \pm 0.12 ^c
Copper (μ mol/L)	23.16 \pm 0.06 ^a	28.02 \pm 0.08 ^b	30.63 \pm 0.08 ^c	29.46 \pm 0.07 ^b	27.90 \pm 0.12 ^c	32.39 \pm 0.09 ^b	30.47 \pm 0.15 ^c
Tf (g/L)	3.24 \pm 0.03 ^a	2.04 \pm 0.03 ^b	0.95 \pm 0.04 ^c	1.93 \pm 0.04 ^b	2.98 \pm 0.07 ^c	0.74 \pm 0.02 ^b	0.90 \pm 0.05 ^c
Cp (g/L)	2.94 \pm 0.02 ^a	5.49 \pm 0.09 ^b	7.68 \pm 0.11 ^c	6.89 \pm 0.08 ^b	4.39 \pm 0.13 ^c	9.38 \pm 0.13 ^b	7.52 \pm 0.20 ^c
Albumin (g/dL)	41.16 \pm 0.07 ^a	38.58 \pm 0.06 ^b	36.95 \pm 0.07 ^c	37.37 \pm 0.08 ^b	38.43 \pm 0.13 ^c	34.58 \pm 0.05 ^b	36.85 \pm 0 .0c

* Each value represents mean \pm SD values with non identical superscript (a, b or c ...etc.) were considered significantly differences ($P \leq 0.05$).

T1DM: Type 1 Diabetes Mellitus , **T2DM:** Type 2 Diabetes Mellitus, **T1DMH:** Hypertension patients with Type 1 Diabetes Mellitus, **T1DMY:** Non Hypertension patients with Type 1 Diabetes Mellitus, **T2DMH:** Hypertension patients with Type 2 Diabetes Mellitus, **T2DMY:** Non Hypertension patients with Type2 Diabetes Mellitus

Discussion

The results of this study shows a significant elevation in concentrations of serum glucose in T2DM in comparison with group T1DM . This finding is matched with the result of (Tan *et al* 2001)and(Annette *et al* 2003) and the reason of this state is that type 2 diabetes mellitus appears after age 40 and the increasing in glucose concentration in this type due to the weakness of β -cell , modicums of insulin production as well as responding and increasing of its resistance.

Where all this appears by aging so glucose concentrations increase with this type.

A significant increase in concentrations of serum MDA in group T2DM in comparison with group T1DM may be due to the increasing of oxidative stress in type2 diabetes because of the exposure to prolonged periods of hyperglycemia, which causes glucose to be in its highest concentrations. This study confers with the study conducted by (Jain *et al*, 1999)and (West *et al*, 2000) and similar finding was reported by (Dierckx *et al*, 2003). This results shows a significant decrease in concentrations of serum chromium in group T2DM in comparison with group T1DM. This result was matched with many considerable reports(Kornberg, A. 2004)(Ekmeckioglu, C. *et al*, 2001)(Stupar, J.*et al*, 2007) that tightly suggest the low concentrations of chromium in serum are significantly correlated with diabetes mellitus. Some studies(Rajpathak, S.*et al*, 2004)(Liu, J.*et al*,

2000) have reported a relation between type 2 diabetes and chromium concentrations in serum, where (Rukgauer, *et al* 2008) reported that type 2 diabetes patients have lower concentrations of serum chromium. (Davies, *et al*, 2004) compared the plasma chromium concentration in patients with type 2 diabetes and control and reported that decreased plasma chromium concentration play a major role in the development of diabetes. However, the decreasing in the concentration of chromium plays an important role in increasing concentration of glucose because it has an effective role on the insulin action. Elevated iron is more common in patients with diabetes (Merkel, P.A., *et al*, 2008) Excess iron may have a role in the development of diabetes (Wilson, J.G., *et al*, 2003) Type 2 diabetes patient has a higher concentration of serum iron because the iron is a catalyst in the formation of hydroxyl radicals, which are powerful pro-oxidants that attack cellular membrane lipids, proteins, and DNA. It has been hypothesized that the formation of hydroxyl radicals catalyzed by iron contributes initially to insulin resistance and subsequently to decreased insulin secretion and then to the development of type 2 diabetes (Ma, J., *et al*, 2002) This present finding was compatible with the finding of (Andrews N.C. *et al*, 2009) and (Kim N.H. *et al*, 2005) . This results are matched with the results of study of (Giwerzman, A. *et al*, 2003) whose reported that in diabetes mellitus, the mean values of serum concentration of copper are significantly increased, especially in type 2 diabetes. That is because copper is one of the trace elements that catalyzed free radical production and lipid peroxidation by its reacts with lipid

So, the increase in serum copper in patients with type 2 diabetes is a result of prolonged periods of hyperglycemia this result also reported by (Johnson, M. A. *et al*, 2006) and (Saari, J. T. *et al*, 2002) A significant decrease in concentrations of serum Tf in group T2DM in comparison with group T1DM , (Gonzalez AS, *et al*, 2006) reported that type 2 diabetic patients have a reduced concentration of Tf (McCullen, M.A., *et al*, 2004) the higher concentrations of iron in these patients made Tf saturated this leads to decrease its concentrations. This study is matched to many studies of (Zakin M.M. *et al*, 2002) and (Georgieff M.K., *et al*, 2005) . A significant increase in concentrations of serum ceruloplasmin in group T2DM in comparison with group T1DM

Ceruloplasmin is thought to be a scavenger (Jonsson, A., *et al*, 2006) (Kingston, IB. *et al*, 2007). So the increase in serum ceruloplasmin concentrations could be explained by an increase in oxidative stress in type 2 diabetes. Also, a high blood glucose concentration may cause an increase in serum ceruloplasmin in type 2 diabetes. This result was reported by (Korantzopoulos P., *et al*, 2003) which is similar to this results. A significant decrease ($P \leq 0.05$) in concentrations of serum albumin in group T2DM in comparison with group T1DM as shown in the results in concentrations of serum albumin in all patients groups in comparison with control group. In the present work, we focused on the antioxidant activity of albumin because oxidative stress is thought to play a significant role in the pathogenesis of many diseases, including diabetes. (Wolff S. P., *et al*, 2001) reported that the concentration of serum albumin decreases in type 2 diabetes because albumin is a carrier protein of copper and diabetic patients exhibit elevated concentrations of copper ions that have been shown to generate free radicals. These highly reactive species are able to induce oxidative degradation of protein (Pacifci, R. E. *et al*, 2001). (Vlassara H., *et al*, 2001) reported that these decreasing are due to the increasing in synthesis of lipid peroxide and elevation formation of free radicals which result in increasing of membranes permeability and leaking the proteins outside the vascular system. A significant increase in serum glucose concentrations in group T1DMH in comparison with group T1DMY. The study also shows a significant increase in concentrations of serum glucose in group T2DMH in comparison with group T2DMY . It has been suggested that hyperglycemia which cause diabetes may contribute to the pathophysiology for hypertension. This was similar to the result of (Cerillo *et al*, 2007). A significant increase in serum MDA concentrations in group T1DMH in comparison with group T1DMY and there is a significant increasing in concentrations of serum MDA in group T2DMH in comparison with group T2DMY. This study shows the effect of free radicals and lipid peroxidation on diabetes-hypertension patients which suggests that hypertension induced by an oxidative stress (Ylä-Herttuala ,S. *et al*, 1999) This finding was similar to the result of (Girotti A.W., *et al*, 2005). A significant increase in serum chromium concentrations in group T1DMH compared to group T1DMY with group T2DMY

($P \leq 0.05$). In a series of studies (Ferrannini, E. *et al*, 2003) (Jonsson, A. *et al*, 2006), the insulin system in diabetes-hypertension was based upon many accepted methods to evaluate glucose/insulin homeostasis. More recently, the ability of chromium (Preuss, M.B. *et al*, 2007) (Preuss, H.G. *et al*, 2009) ameliorate insulin action in diabetes-hypertension is one of these methods that strengthens the "insulin system" because each is known to influence on it so the diabetes-hypertension patients have a high concentration of serum chromium. The result of present study was similar to the result of (Gharib N., *et al*, 2001) and (Anderson R.A., *et al*, 2007). In this study, the significant increase in serum iron concentrations was observed in group T1DMH compared to group T1DMY ($P \leq 0.05$), also, there is a significant increase in serum iron concentrations in group T2DMH in comparison with group T2DMY have a high concentration of iron because of its stimulation role in free radical production and oxidative stress by the Fenton and Haber-Weiss reaction (Tilbrook, L., 2004). This finding was matched to this finding which was reported by (Paolisso G., *et al*, 2007) and (Ramakrishnan U., *et al*, 2006). In the present study, there is a significant increase in serum copper concentrations in group T1DMH compared to group T1DMY diabetes mellitus and hypertension have been shown to be states of increased free-radical activity, oxidative stress induced hypertension. Moreover, copper plays a major role in free radical production and lipid peroxidation. This result was matched with the results of (Julius S., *et al*, 2004) and (Bakris G., *et al*, 2002). A significant decrease in serum Tf concentrations in group T1DMH in comparison with group T1DMY is reported that oxidative stress induced hypertension and oxidative stress catalyzed by trace elements such as iron. In earlier finding, the highest concentrations of iron were found in hypertension-diabetic patients in these patients Tf becomes saturated and iron release (Arndt, T. *et al*, 1997) and the decreasing of Tf concentrations in these patients may be due to iron overload status. This result, the decrease in serum Tf in hypertension-diabetes patients was similar to de (Jong G., *et al*, 2000). A significant increase in serum ceruloplasmin concentrations in group T1DMH in comparison with group T1DMY in conform with the results of (Swain *et al*, 1994) and (Choi *et al*, 2000) suggested that during exposure to oxidative stress, free copper ions may be released.

Therefore, pathogenesis of many diseases such as diabetes and hypertension may occur. Ceruloplasmin is a scavenger of free radicals; so, the elevation of its concentration in hypertension-diabetes patients may be due to increasing in the formation of free radicals and oxidative stress which is promoted by iron and copper ions and this oxidative stress induced hypertension these findings are promoting this result. The result reflects the significant increase in serum albumin concentrations in group T1DMY in comparison with group T1DMH, a significant decrease in concentrations of serum albumin in group T2DMH in comparison with group T2DMY. Also, there is a significant decrease in serum albumin concentrations in all patient groups in comparison with control group. (Roberts A.B., *et al*, 2009) suggested that membranes permeability to albumin is increasing in hypertension-diabetes patients this is because of the high generation of free radicals and oxidative stress which decreases albumin concentrations in these patients.

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حالة أكسده- مضادات الأكسدة وبعض المعايير التي لها علاقه بمرضى داء السكري بنوعيه الاول والثاني و المصابين بارتفاع ضغط الدم في ذي قار

الملخص

يعتبر ارتفاع مستوى سكر الكلوكوز في الدم البادئ الرئيسي للإجهاد التأكسدي وقد يؤدي إلى تكوين الجذور الحرة و بالتالي حدوث عملية فوق الأكسدة التي تؤدي إلى تلف الأنسجة وتطور مرض السكري. لذلك هدفت الدراسة الحالية للتحقيق في العلاقة بين حالة مضادات الأكسدة و الناتج النهائي للأكسدة الفوقية للدهون (المالون ثنائي الألديهيد) وبعض العناصر النزرة في مصل ٣٠ مريض مصاب بالنوع الأول لداء السكري و ٣٠ مريض مصاب بالنوع الثاني لداء السكري و ٤٠ مريض مصاب بداء السكري و ارتفاع ضغط الدم (٢٠ نوع أول و ٢٠ نوع ثاني) و ٣٠ مريض بداء السكري ولا يعاني من ارتفاع ضغط الدم (١٥ نوع أول و ١٥ نوع ثاني) و ٤٠ شخص من الأصحاء غير المصابين بداء السكري و ارتفاع ضغط الدم للسيطرة. حُلت تراكيز المالون ثنائي الألديهيد، الكروم و السيرولوبلازمين في المصل بواسطة طرق يدوية، بينما قيست تراكيز الكلوكوز، الحديد، النحاس، الترانسفيرين، والألبومين طيفياً بواسطة عدة القياس لكل المرضى المصابين بداء السكري وكذلك مجموعة السيطرة. قورنت نتائج المرضى بالنوع الأول مع النوع الثاني وكذلك مرضى داء السكري المصابين بارتفاع ضغط الدم و مرضى داء السكري غير المصابين بارتفاع ضغط الدم ومجموعة السيطرة باستخدام اختبار ANOVA لمقارنة المعايير في المجاميع المدروسة المختلفة. أظهرت النتائج ارتفاعاً معنوياً ($P \leq 0.05$) في مستويات الكلوكوز، المالون ثنائي الألديهيد، الحديد، النحاس، السيرولوبلازمين لمرضى السكري النوع الثاني مقارنة بمرضى النوع الأول والأصحاء، كذلك وجد انخفاضاً معنوياً ($P \leq 0.05$) في مستويات الكروم، الترانسفيرين والألبومين لمرضى السكري النوع الثاني مقارنة بمرضى النوع الأول ومجموعة السيطرة. كذلك أظهرت النتائج ارتفاعاً معنوياً ($P \leq 0.05$) في مستويات الكلوكوز، المالون ثنائي الألديهيد، الكروم، الحديد، النحاس، السيرولوبلازمين لمرضى السكري (النوع الأول و النوع الثاني) المصابين بارتفاع ضغط الدم مقارنة بمرضى السكري (النوع الأول و النوع الثاني) غير المصابين بارتفاع ضغط الدم والأصحاء، كذلك وجد انخفاضاً معنوياً ($P \leq 0.05$) في مستويات الترانسفيرين والألبومين لمرضى السكري (النوع الأول و النوع الثاني) المصابين بارتفاع ضغط الدم مقارنة بمرضى السكري (النوع الأول و النوع الثاني) غير المصابين بارتفاع ضغط الدم ومجموعة السيطرة.