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Endothelin Level and Its Correlation with Uric Acid in Type 2 Diabetic Multiuse Patients

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ABSTRACT

This research aims to find the direct linkage among the Uric acid rates with Endothelin (ET-1), which is considered the indication of endothelial dysfunction or endothelial damage in patients with T2-DM. This study, included 96 patients with T2-DM and 96 controls, the mean age ranged (56.73 ± 9.14), (56.42 ± 8.74) respectively. Results showed a highly significant increase in Endothelin (ET-1) levels, uric acid, urea, and systolic blood pressure (SBP) was observed as compared with control group, while Diastolic blood pressure (DBP) and body mass (BMI) were not substantially increased. Additionally, significant positive correlation was found between ET-1 with uric acid, urea, SBP, DBP in patients with T2-DM ($p < 0.05$). Finally, elevated uric acid levels in older people who have chronic blood pressure are one of the factors influencing the increase release of ET-1, thus the development of cardiovascular disease.

KEYWORDS: Endothelin (ET-1); Hypertension, Uric acid.

INTRODUCTION

Elevated serum uric acid was accompanied sequentially with elevate hypertension, insulin resistance, dyslipidemia, chronic kidney disease. So high levels of serum uric acid may be a marker or a consequence of up-regulated or increased Xanthine Oxidoreductase (XOR) activity and increased oxidative stress, tumor necrosis factors, and both of them play important role in early T2-DM complication [1,2]. In patients with congestive heart failure found that high serum uric acid levels slightly production from the failing heart, considered as a prediction in patients with congestive heart failure and hypertension. Cardiovascular disease and increased mortality appear clear with elevate serum uric acid levels particular in the elder population, patients with T2-DM and in other high-risk patient groups [3,4]. In addition, Oxidative stress plays an important role in endothelial cell damage and functional changes and found that a significant increased oxidative stress level related to serum uric acid concentration, indicating that serum uric acid is involved in the formation of the early chronic kidney disease. On the other hand, bioavailability of nitric oxide reduced in present high levels of uric acid and this led to endothelial dysfunction and therefore, increased Endothelin-1 (ET-1) level, and decreased Nitric oxide /Endothelin-1 ratio. This could lead to several cardiovascular complications and even cardiovascular disease (CVD) related death precisely with (coronary heart disease, hypertension, and thrombosis) and cardiac insufficiency [5-8].

MATERIAL AND METHODS

Subjects

192 samples were included in this study, divided in two group (96 patients with T2-DM), and (96 healthy group). All information was taken for patients and healthful categories including weight, length, body mass index (BMI), age and family background of chronic kidney sickness. Furthermore, there was a person responsible for measuring blood pressure by the same scale. Venous blood samples have 10 ml volume taken using plastic disposable syringes, after coagulation, the serum was extracted by a

centrifuge at 3000 rpm for 20 minutes. 10μL of serum was taken to measure uric acid and urea.

Determination of Endothelin, Uric Acid, Urea

This assay utilizes the quantitative sandwich enzyme immunoassay (ELISA) technique was employed for valuation of Endothelin [9]. Uric acid [10], urea [11] was measured by enzymatic colorimetric method.

Statistical Analysis

Mean values and standard deviations (SD) utilized for continuous variables. Student T-test used to compare the importance of the variation in the mean control and cohort groups values. High significance: p-value ≤ 0.01 (HS), significance: p-value ≤ 0.05 (S). Correlation coefficient was used to determined relationship between studied parameters [12].

RESULTS

The prevalence of uric acid > 5.8 mg/dL (5.81 ± 0.89) mg/dL, was higher in patients with hypertension and T2-DM when compared with control group UA <5.8 mg/dL (5.02 ± 0.93) mg/dl ($P=0.004$). The higher uric acid category had marginally greater more BMI values (32.96 ± 5.63) confront to the lower uric acid category. (31.12 ± 2.98) kg/m², P= 0.138).

Table 1. Clinical characteristics of 96 patients with diabetes mellitus and 96 normal subjects.

Variable	Control		Patients		P-value
	Mean	SD	Mean	SD	
Age	56.42	8.74	56.73	9.14	P > 0.05 NS
BMI	31.12	2.98	32.96	5.63	0.138 NS
Blood pressure (High)	13.70	1.56	16.17	2.39	P < 0.0001 HS
Blood pressure (LOW)	8.57	0.94	8.90	0.80	0.217 NS
Uric acid	5.02	0.93	5.81	0.89	0.004 HS
Urea	27.30	4.49	31.60	5.22	0.004 HS

Data are expressed as mean ± SD, * Significance: P-Value ≤ 0.05,
** High significance: P-Value ≤ 0.01

Additionally, it was noted that there is a significant increase in urea in the blood in patients with T2-DM (31.60 ± 5.22) as compared with healthy control (27.30 ± 4.49). In this study, the prevalence of hypertension systolic blood pressure (SBP) was high significant increase (p-value ≤ 0.01) In T2-DM patients parallel to the control

condition, there was a showed no significant rise in diastolic pressure (DBP) ($p=0.217$) when compared to healthy control groups as shown in Table 1. The results in Figure 1 displays a positive and significant correlation between ET-1 as well as serum uric acid ($r=0.238$, $p < 0.05$ S), ET-1level was a highly significant positive correlation with the serum urea ($r=0.358$, $p=0.006$ HS). While, there was a Considerable favorable interconnection between ET-1 and SBP ($r=0.09$, $p=0.035$), significant negative correlation between ET-1 and DBP ($r= -0.265$, $p=0.045$). Table 3 shows the correlation coefficient (r) serum Endothelin (ET-1) and other parameters.
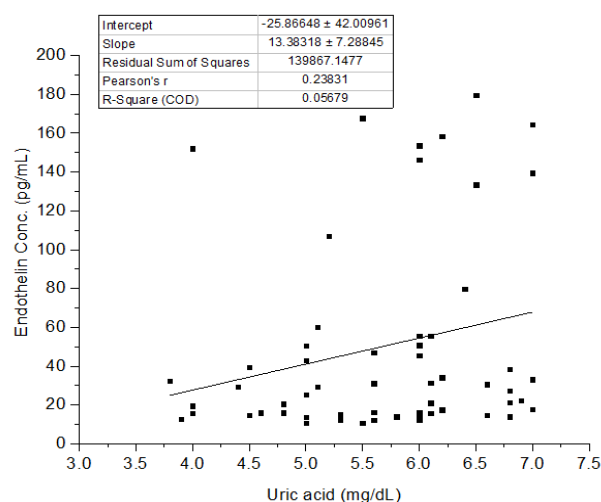

Figure 1. Correlation coefficient between ET-1 and Uric acid

Table 3. Correlation coefficient (r) serum Endothelin (ET-1) and other parameters.

Variables		Group of T2-DM (n=96)	
BMI (Kg/m²)	R	0.166	
	P	0.213	NS
Uric acid (mmol.L⁻¹)	R	0.238	
	P	0.027	S
Urea (mmol.L⁻¹)	R	0.358	
	P	0.006	HS
MDA (μmol.L⁻¹)	R	-0.006	
	P	0.962	NS
Systolic pressure (SBP)	R	0.09	
	P	0.035	S
Diastolic pressure (DBP)	R	-0.265	
	P	0.045	S

DISCUSSION

Association have also been found between plasma Endothelin and Hypertension happening serum uric acid rates, the results showed an important linkage between the rates of plasma endothylene and hypertension. (p<0.05).

An increased peripheral vascular resistance to blood flow associated with endothelial dysfunction and vascular remodeling characterizes essential hypertension. This increase is in a good agreement with Haak *et. al.*, who found that ET-1 levels was elevated in patients with primary hypertension were found [13]. The development of vascular complications in diabetes has been shown to significantly increase hypertension, because both high blood pressure and diabetes are working to change the endothelial cell structure and function of ET-1, and this leads to increased blood pressure and arteriosclerosis in patients with diabetes [14,15]. So, it has been suggested Uric acid is a significant cardiovascular factor particularly in patients with T2-DM so there must be a connection between Endothelin and rate of uric acid. The results show a highly increase uric acid proportion in patients with T2-DM detected in comparison with control groups. Large increase in serum uric acid are attribute linked with cardiovascular disease, is a prognostic predictor in patients with congestive heart failure. Study found that serum uric acid increased in patients with chronic Kidney disease and was associated with cardiovascular disease. The results showed a moderate positive with both of ET-1 and uric acid serum ($p < 0.05$). Which is consistent with study supports that ET-1 gene expression stimulate by uritric acid, partially by the activation of extracellular-signal-regulated kinase extracellular-signal-regulated kinase (ERK) pathway by through Reactive oxygen species Reactive Oxygen species (ROS) generation in cardiac fibroblasts, In heart fibroblasts exposed to uric acid, ET-1 peptide secretion also generally increases [16]. Alessandro *et.al.* [17], also agreement with these results after modification of age, duration of disease in T2-DM, chronic kidney disease (p=0.009). Additionally, we found that serum urea level was a very important strong correlation with the ET-1 (P < 0.0001), indicating that urea It has a link to endothelial cell cardiac failure and involves endothelial cell damage in the way earlier kidney disease.

CONCLUSIONS
High levels of uric acid in elderly people who have chronic blood pressure are one of the factors influencing the increase release of ET-1, thus the development of cardiovascular disease.

REFERENCES
[1] Kodama, S., Saito, K., Yachi, Y., Asumi, M., Sugawara, A., Totsuka, K., Saito, A. and Sone, H., 2009. Association between serum uric acid and development of type 2 diabetes. *Diabetes care*, *32*(9), pp.1737-1742.

[2] Bennett, M., Pandya, BJ., and Krishnan, E., 2009. Hyperuricemia as an early marker for type 2 diabetes among young adults. Arthritis Rheum-Us. 60:2033.

[3] Feig, D.I., Kang, D.H. and Johnson, R.J., 2008. Uric acid and cardiovascular risk. *New England Journal of Medicine*, *359*(17), pp.1811-1821.

[4] Zoppini, G., Targher, G. and Bonora, E., 2011. The role of serum uric acid in cardiovascular disease in type 2 diabetic and non-diabetic subjects: a narrative review. *Journal of endocrinological investigation*, *34*(11), pp.881-886.

[5] Khosla, U.M., Zharikov, S., Finch, J.L., Nakagawa, T., Roncal, C., Mu, W., Krotova, K., Block, E.R., Prabhakar, S. and Johnson, R.J., 2005. Hyperuricemia induces endothelial dysfunction. *Kidney international*, *67*(5), pp.1739-1742.

[6] Lehto, S., Niskanen, L., Ronnemaa, T. and Laakso, M., 1998. Serum uric acid is a strong predictor of stroke in patients with non–insulin-dependent diabetes mellitus. *Stroke*, *29*(3), pp.635-639.

[7] Choi, Y.J., Yoon, Y., Lee, K.Y., Hien, T.T., Kang, K.W., Kim, K.C., Lee, J., Lee, M.Y., Lee, S.M., Kang, D.H. and Lee, B.H., 2014. Uric acid induces endothelial dysfunction by vascular insulin resistance associated with the impairment of nitric oxide synthesis. *The FASEB Journal*, *28*(7), pp.3197-3204.

[8] Puddu, P., Puddu, G.M., Cravero, E., Vizioli, L. and Muscari, A., 2012. The relationships among hyperuricemia, endothelial dysfunction, and cardiovascular diseases: molecular mechanisms and clinical implications. *Journal of cardiology*, *59*(3), pp.235-242.

[9] Li, A., Yi, B., Liu, Y., Wang, J., Dai, Q., Huang, Y., Li, Y.C. and Zhang, H., 2019. Urinary NGAL and RBP Are Biomarkers of Normoalbuminuric Renal Insufficiency in Type 2 Diabetes Mellitus. *Journal of immunology research*, *2019*.

[10] Fossati, P., and Prencipe, L., 1982. Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. *Clinical chemistry*, *28*(10), pp.2077-2080.

[11] Ruppersberg, H.S., Goebel, M.R., Kleinert, S.I., Wünsch, D., Trautwein, K. and Rabus, R., 2017. Photometric determination of ammonium and phosphate in seawater medium using a microplate

reader. *Journal of molecular microbiology and biotechnology*, *27*(2), pp.73-80.

[12] Dean, J., Dean, DA., Coloumbier, D., Brebdel, KA., Smith, DC., Burton, AH *et al.,* Epi Info 6.04 c. A word processing, database, and statistic program for public health. Geneva, Switzerland: *Center for Disease Control and Prevention (Atlanta, USA), and World Health Organization,* (1997).

[13] Haak, T., Jungmann, E., Felber, A., Hillmann, U. and Usadel, K.H., 1992. Increased Plasma Levels of Endothelin in Diabetic Patients With Hypertension: An Alternative Viewpoint. *American journal of hypertension*, *5*(3), pp.161-166.

[14] Perfetto, F., Tarquini, R., Tapparini, L. and Tarquini, B., 1998. Influence of Non–Insulin-Dependent Diabetes Mellitus on Plasma Endothelin-1 Levels in Patients with Advanced Atherosclerosis. *Journal of diabetes and its complications*, *12*(4), pp.187-192.

[15] Tavares, A.M.V., Schaan, B.D.A., Terra, B.G., Duncan, B.B., Bavaresco, C.S., Leitão, C.B., Silva, D.D.F.D., Amado, D.M., Souza, D.S., Bianchini, I.M. and Sousa, J.S., 2013. Estratégias para o cuidado da pessoa com doença crônica: diabetes mellitus.

[16] Cheng, T.H., Lin, J.W., Chao, H.H., Chen, Y.L., Chen, C.H., Chan, P. and Liu, J.C., 2010. Uric acid activates extracellular signal-regulated kinases and the reafter Endothelin-1 expression in rat cardiac fibroblasts. *International journal of cardiology*, *139*(1), pp.42-49.

[17] Mantovani, A., Rigolon, R., Pichiri, I., Morani, G., Bonapace, S., Dugo, C., Zoppini, G., Bonora, E. and Targher, G., 2017. Relation of elevated serum uric acid levels to first-degree heart block and other cardiac conduction defects in hospitalized patients with type 2 diabetes. *Journal of Diabetes and its Complications*, *31*(12), pp.1691-1697.