Atherogenic Index of Plasma Levels in Patients with Diabetic and Neurodiabetic

مستويات مؤشر البلازما لتصلب الشرايين في مرضى السكري والسكري ذي الإعتلال العصبي

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الخلاصة

الهدف : تـهدف هذه الدراســة إلى تحديد مستويات (الكوليستيرول الكلي والدهون الثلاثية والبروتين الدهني ذي الكثافة العالية والبروتين الدهني ذي الكثافة الواطئة والبروتين الدهني ذي الكثافة الواطئة جدا) عند مرضى السكري والسكري ذي الاعتلال العصبي ومقارنة النتائج عند مجموعة السيطرة. وكذلك مقارنة مستويات مؤشر البلازما لتصلب الشرايين في هذه المجموعات والتي يمكن التنبؤ لهؤلاء المرضى بالتعرض لأمراض القلب والأوعية الدموية من خلاله.

المنهجية : استخدمت هذه الدراسة تســعين شخصا , تراوحت أعمارهم بين (40-65) عاما، ومؤشر كتلة الجسم (30-35) كغم /م^2. وتم تقسيمهم إلى ثلاث مجموعات على النحو الآتي :المجموعة الأولى (G1) وتتكون من ثلاثين شخصا من الأصحاء كمجموعة سيطرة , والمجموعة الثانية (G2) وتتكون من ثلاثين مريضا يعانون السكري , والمجموعة الثالثة (G3) وتتكون من ثلاثين مريضا يعانون السكري ذا الإعتلال العصبي. لقد تـم تعيين التوصيل الجلدي الكهروكيميائي (معدل القدم) والتوصيل الجلدي الكهروكيميائي (معدل اليد) والتوصيل الجلدي الكهروكيميائي (خطر الإصابة بالإعتلال العصبي) ومستويات وسكر دم الصائم والكوليستيرول الكلي والدهون الثلاثية والبروتين الدهني ذي الكثافة العالية وتم حساب البروتين الدهني ذي الكثافة الواطئة والبروتين الدهني ذي الكثافة الواطئة جدا ومؤشر البلازما لتصلب الشرايين لجميع المجموعات المدروسة.

النتائج : أوضحت النتائج أنه لا توجد زيادة معنوية كبيرة في الكوليستيرول الكلي والبروتين الدهني ذي الكثافة الواطئة في G2 مقارنة بـــ G1، في حين كانت هناك زيادة معنوية كبيرة في الكوليستيرول الكلي والبروتين الدهني ذي الكثافة الواطئة في G3 مقارنة بـــ G2 وG1. وكشفت النتائج أيضا زيادة معنوية كبيرة في الدهون الثلاثية والبروتين الدهني ذي الكثافة الواطئة جدا في G2 و G3 بـــ G1 , و G3 مقارنة بـــ G2. أظهرت النتائج أيضا إنخفاضا معنويا كبيرا في البروتين الدهني ذي الكثافة العالية في G2 و G3 مقارنة بـG1، في حين لم نلاحظ أهمية في الإنخفاض في G3 مقارنة مع G2. وأظهرت النتائج أيضا زيادة معنوية في مستويات مؤشر البلازما لتصلب الشرايين في G2 و G3 مقارنة بـــG1 ، في حين لم نلاحظ زيادة معنوية كبيرة في G3 مقارنة مع G2.

الإستنتاج : نستنتج من هذه الدراسة ان ارتفاع قيمة مؤشر البلازما لتصلب الشرايين في مرضى السكري والسكري ذي الاعتلال العصبي يمكن استخدامه كعلامة للتنبؤ بالأمراض القلبية الوعائية في مجموعات المرضى.

التوصيات : دراسة التحليل الجيني على مدى واسع عند مرضى السكري والسكري ذي الاعتلال العصبي والسيطرة بشكل شامل .

ABSTRACT:

Objective: To determined the levels of lipid profile (TC, TG, HDL-c, LDL-C, VLDL) in diabetic and diabetic neuropathy patients and compare the results with control group. Also, to compare Atherogenic Index of Plasma (AIP) levels in these groups that may be predict prone of patients to cardiovascular disease.

Methodology: Ninety subjects were enrolled in this study with aged ranged (40-65) years and BMI with (30-35) Kg/m^2 that divided into three groups as follows: group one (G1) consists of 30 healthy individuals as a control group, group two (G2) consists of 30 patients with diabetes and group three (G3) consists of 30 patients with diabetes and neuropathy as complication. Electrochemical Skin Conductance (Feet Mean), Electrochemical Skin Conductance (Hand Mean), Electrochemical Skin Conductance (Risk of neuropathies), FBS, TC, TG and HDL-c were determined. Also, LDL-C, VLDL and AIP were calculated.

Results: This study illustrated no significant increased were found in TC and LDL in G2 comparing to G1, while there was highly significant increase in TC and LDL in G2 comparing to G3 and in G3 comparing to G1. Results, also, revealed highly significant increase in TG and VLDL in G2 comparing to G1, G2 comparing to G3, and G3 comparing to G1. Data demonstrated highly significant decrease in HDL-c in G2 and G3 comparing to G1, while no significant decrease observed in G3 comparing to G2. Data, also, demonstrated highly significant increase in AIP levels in G2 and G3 comparing to G1, while no significant increased observed in G3 comparing to G2.

Conclusion: The study concluded that AIP is elevated in diabetic and neurodiabetic patients who could be used as a marker for predict CVD in patients groups.

Recommendation: Study the genetic analysis for wide range patients with diabetic, neurodiabetic and control as a comprehensive surrey.

Keywords: Diabetic Neuropathy, Lipid profile and AIP.

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INTRODUCTION

Diabetic autonomic neuropathy is frequent and can affect multiple systems, including cardiovascular, gastrointestinal and genitourinary. Cardiovascular system, the major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance and orthostatic hypotension. Also, silent myocardial ischaemia and sudden death have been found in diabetic autonomic neuropathy. Gastroparesis, constipation or diarrhoea, bladder dysfunction and erectile impairment are the most common types of the dysfunction of gastrointestinal and genitourinary systems [(1)].

Obesity increases the incidence (risk) of many diseases such as heart disease, type 2 diabetes, obstructive sleep apnea, cancers, and osteoarthritis [(2)]. There is a seven times greater risk of diabetes in obese people in contrast with healthy weight, with a threefold increase in risk for overweight people. Also, body fat distribution is an important determinant of increased risk of diabetes [(3)].

The atherogenic index of plasma (AIP), defined as logarithm [log] of the ratio of plasma concentration of triglycerides to high-density lipoprotein (HDL) cholesterol, has recently been proposed as a predictive marker for plasma atherogenicity and is positively correlated with cardiovascular disease risk. Also, AIP correlates with the size of HDL and LDL particles and with the fractional esterification rate of cholesterol by lecithin: Cholesterolacyl transferase in plasma. This ratio accurately reflects the presence of atherogenic small LDL and HDL particles, is a sensitive predictor of coronary atherosclerosis and cardiovascular risk and a useful surrogate for insulin resistance. Several studies established a direct relationship between insulin resistance, enhanced sympathetic nervous activity, hypertension (HTN) and type 2 diabetes [(4,5)].

The aims of this study is to determined the levels of lipid profile (TC, TG, HDL-c, LDL-C, VLDL) in diabetic and diabetic neuropathy patients and compare the results with control group. Also, to calculate AIP levels in these groups that may be predict prone of patients to cardiovascular disease.

MATERIALS AND METHODS

Ninety individuals with age ranged between (40-65) years and BMI with (35) Kg/m^2 were enrolled in this study. They were divided into three groups as follows: control group (G1) consists of 30 healthy individuals, diabetic group (G2) consists of 30 patients and diabetic Neuropathy group (G3) consists of 30 patients. Blood samples were collected from all groups after a period of fasting 12-14 hours. The study was conducted between

March 2015– October 2015 in the diabetic & endocrinology center in Al-sader medical city / Iraq.

Serum that obtained was used in determination of FBS, TC, TG, HDL-c. Electrochemical Skin Conductance (ESC) were determined by using Sudoscan™ instruments which based on different electrochemical principles (reverse iontophoresis and chronoamperometry) to measure sudomotor function than prior technologies, affording it a much more practical and precise performance profile for routine clinical use with potential as a research tool. The device consists of a simple desktop computer connected to two sets of large surface stainless steel electrodes: two for application of the palms, and two for the soles [6]. Serum glucose was measured by using kits from (Randox Company, United Kingdom) which based on the PAP enzymatic determination of glucose[7]. Total cholesterol[8], triglyceride[9] and HDL-c[10] were measured by enzymatic method from (Human Gesellschaft fur biochemical and Diagnostica mbH, Germany.). The levels of LDL-C and VLDL-C were analyzed by using Friedewald equation as follows[11]:

$$\text{LDL} - \text{C}\left(\frac{\text{mg}}{\text{dL}}\right) = \text{Total Cholesterol} - \text{HDL} - \frac{\text{TG}}{5}$$

Serum VLDL-C can be calculated by:

$$\text{VLDL} - \text{C}\left(\frac{\text{mg}}{\text{dL}}\right) = \frac{\text{TG}}{5}$$

The atherogenic index of plasma (AIP) was calculated according to Milada formula equation as display below [12]:

$$\text{AIP} = \log\frac{\text{TG}}{\text{HDL}_c}$$

Statistical Analysis:

The results expressed as mean ± SEM. Students t-test was applied to compare the significance of the difference between DN, Diabetic patient`s and control groups. P- Value with ($P \geq 0.05$) and ($P \leq 0.00001$) considered statistically no significant and highly significant respectively.

RESULTS:

Table (1) Descriptive parameters for all studied groups.

Parameters	Mean ±SEM(G1)	Mean ±SEM(G2)	Mean ± SEM(G3)	T-Test G1 vs G2	T-Test G2 vs G3	T-Test G1 vs G3
FBS (mg/dL)	92.57±1.7	191.13±9.7	284.43±10.3	H.S*	H.S	H.S
ESC (µS) Feet Mean	89.08±0.77	84.88±1.01	62.67±3.08	H.S	H.S	H.S
ESC Hand (µS) Mean	81.17±1.88	74.08±1.76	49.08±2.35	H.S	H.S	H.S
ESC (%) Risk of neuropathies	10.13±2.31	37.33±2.55	58.96±3.75	H.S	H.S	H.S

H.S: highly significant

Table (1) showed the levels of descriptive parameters FBS, ESC (Feet Mean), ESC (Hand Mean) and ESC (Risk of neuropathies). Results revealed highly significant differences in ESC (Feet Mean), ESC (Hand Mean) and ESC (Risk of neuropathies) between G2 and G3 comparing with G1 and in G3 comparing to G2.

Table (2) Lipid profile (TC, TG, HDL-c, LDL-c, VLDL-c) and AIP levels for all studied groups.

Parameters	Mean ±SEM(G1)	Mean ±SEM(G2)	Mean ± SEM(G3)	T-Test G1 vs G2	T-Test G2 vsG3	T-Test G1 vs G3
TC (mg/dL)	187.4±6.1	193.5±6.6	271.47±5.5	N.S	H.S	H.S
TG (mg/dL)	151.2±5.1	189.7±6.9	228.5±6.8	H.S	H.S	H.S
HDL-c (mg/dL)	42.88±1.1	28.57±1.0	29.82±0.8	H.S	N.S	H.S
LDL-c (mg/dL)	114.16±6.4	126.99±6.8	195.95±5.8	N.S	H.S	H.S
VLDL-c (mg/dL)	30.26±1.02	37.93±1.38	45.7±1.37	H.S	H.S	H.S
AIP	0.54±0.017	0.82±0.024	0.89±0.017	H.S	N.S	H.S

Table (2) shows the levels of lipid profile (TC, TG, HDL-c, LDL-c, VLDL-c) and AIP levels for G1, G2 and G3. Results illustrated no significant increase were found in TC and LDL in G2 comparing to G1,while there were highly significant increase in TC and LDL in G2 comparing to G3 and in G3 comparing to G1. Results, also, revealed highly significant increase in TG and VLDL in G2 comparing to G1, G2 comparing to G3, and G3 comparing to G1. Data in this table, also, demonstrated highly significant decrease in HDL-c in G2 and G3 comparing to G1, while no significant decrease observed in G3 comparing to G2. Data in this table, also, demonstrated highly significant increase in AIP levels in G2 and G3 comparing to G1, while no significant increase observed in G3 comparing to G2.

DISCUSSION

Electrochemical skin conductance (ESC) of hands and feet is decreased in G3 (diabetic neuropathy) diagnosed using the current Toronto classification of DPN (diabetic peripheral neuropathy), compared with G1 and G2. Feet ESC was significantly decreased in patients with painful DN compared with the value in patients with nonpainful neuropathy. These results suggest that sudomotor function, evaluated through reverse iontophoresis (Sudoscan), is a reliable option when evaluating diabetes patients for the detection of small fiber neuropathy and peripheral autonomic neuropathy. Combined with a simple bedside test as the NIS-LL (Neurologic Impairment Score—Lower Legs), Sudoscan may increase the effectiveness in detecting neuropathy[13]. As in the study by Casellini and collaborators, a number of projects have shown that ESC measurement may be a simple tool for early identification of autonomic neuropathy, and may be useful in screening for sub-clinical cardiac autonomic neuropathy(CAN) [6, 14].

The presence of correlation of some central neurological abnormalities with the serum total cholesterol and serum triglycerides suggests the importance of identifying these risk factors in the

assessment of central neuropathic affection. This might lead to risk-reduction strategies. There is evidence from in vitro and animal studies that lipid lowering therapy has multiple potentially neuroprotective effects through improvement in Schwann cell and polyol pathway function and improved neuronal blood supply[15].

Studies have shown that dyslipidemia is a significant contributor in the development of neuropathy via inducing oxidative stress in root ganglia sensory neurons [16]. In diabetes many factors may affect blood lipid levels, because of interrelationship between carbohydrates and lipid metabolism. Therefore, any disorder in carbohydrate metabolism leads to disorder in lipid metabolism and vice versa[17]. Diabetic dyslipidemia comprises a triad of raised triglycerides, reduced HDL-c and excess of small, dense LDL particles, which in agreement with the present study[18]. The lipid abnormalities are prevalent in diabetes mellitus because insulin resistance or deficiency affects key enzymes and pathways in lipid metabolism. In particular, the following processes are affected: apoprotein production, regulation of lipoprotein lipase, action of cholesteryl ester, transfer proteins and hepatic and peripheral actions of insulin[19]. Goldberg reported that hyperglycemia progressively increases the transfer of cholesterol esters from HDL-C to VLDL-C particles; hence, denser LDL particles acquire a large proportion of these HDL esters, further diminishing the HDL-C level[16].

Recent study demonstrated that AIP is significantly and positively correlated with weight, BMI and TG but inversely correlated with HDL these results are in agreement with the present study[20]. A report observed that an increasing atherogenic index is associated with an increase in BMI and this index is a significant independent predictor of CHD [21].

Accumulating evidence suggested that AGEs and their corresponding receptor activity are not only implicated in the complications of diabetes but also in the development of inflammation, atherosclerosis and neurodegenerative disorders, which may contribute to excess risk in cardiovascular and all-cause mortality[22]. Alternatively, PN may be a marker of sicker individuals with a greater prevalence of risk factors associated with CVD, including hypertension and higher levels of atherogenic lipids that might explain any excess risk. The excess mortality observed among patients with PN supports previous observations of increased mortality among patients with a history of diabetic foot ulceration compared with patients with diabetes and no history of ulceration. A meta-analysis of eight studies reporting on 17 830 individuals showed an excess risk of mortality among patients with a history of diabetic foot ulceration. However, it could not sufficiently separate the association of foot ulceration with cardiovascular versus non-cardiovascular end points, and to what extent a greater number of cardiovascular events were explained by the burden of conventional risk factors. Levels of advanced glycation end productss are higher in people with diabetes because hyperglycaemia and oxidative stress increase their accumulation. Advanced glycation end products have been shown to play a role in the development of neuropathy, and their presence in the skin correlates with both autonomic and sensory diabetic neuropathy [23,24].

Study suggested that preclinical stages of autonomic neuropathy may be associated with abnormalities in cardiac sympathetic function that can result in impaired coronary flow regulation, particularly in response to stress[25].

CONCLUSION

The study concluded that AIP is elevated neurodiabetic patients more than diabetic and control group that could be used as a marker for predict CVD in patients groups.

RECOMMENDATION

Study the genetic analysis for wide range patients with diabetic, neurodiabetic and control as a comprehensive surrey.

REFERENCES:

1. Callaghan B.C., Price R.S., and Feldman E.L., Distal Symmetric Polyneuropathy: A Review. JAMA. 2015; 314(20):2172-2181.
2. Lucia M., Sara M., Gabriella D'A., Antonio N., Eleonora P., Gabriella Di R., Eloisa G. and Teresa A. "Oxidative Stress in Obesity: A Critical Component in Human Diseases". Int. J. Mol. Sci. 2015; 16: 378-400.
3. Neeland IJ, Turer AT and Ayers CR. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. JAMA. 2012; 308(11):1150-1159.
4. C.C.Onyedun, E.E.Young, M.O.Iroezindu, C.J.Chukwuka and U.I.Nwagha, Atherogenic index of plasma in highly active antiretroviral therapy- naive patients with human immunodeficiency virus infection in south east Nigeria, *Indian Journal of Endocrinology and Metabolism*, 2014; 18(5): 631 – 635.
5. Essiarab F., Taki H., Lebrazi H., Sabri M., and Saıle R., "Usefulness of lipid ratios and atherogenic index of plasma in obese Moroccan women with or without metabolic syndrome". Ethn Dis. 2014; 24(2):207–212.
6. Vinik A.I., Nevoret M.L., and Casellini C. The new age of sudomotor function testing: a sensitive and specific biomarker for diagnosis, estimation of severity, monitoring progression, and regression in response to intervention. Frontiers in Endocrinology 2015; 6(94):1-12.
7. Barham D., and Trinder P. An improved colour reagent for the determination of blood glucose by the oxidase system. Analyst 1972; 97(151):5-142.
8. Richmond W. Proceeding in the development of an enzymatic technique for the assay of cholesterol in biological fluids. ClinSciMolMed 1974; 46:67.
9. Fossati P., and Prencipe L. Measurement of serum triglyceride calorimetrically with an enzyme that produce H_2O_2. Clin. Chem. 1982; 28(10):2077-2088.
10. Burstein M., Scholink H.R., and Morfin R. Measurement of HDL-c in the plasma with a sensitive calorimetric method .J Lipid Res 1970; 19:583.
11. Friedewald WT, Levy RI, and Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18:499-502.
12. Milada Dobia´sˇova. Atherogenic Index of Plasma [Log(Triglycerides/HDLCholesterol)]: Theoretical and Practical Implications. Clinical Chemistry. 2004; 50 (7).
13. Magdalena Z., Ewelina R., Barbara P., and Joanna M.: Mechanisms and pharmacology of diabetic neuropathy – experimental and clinical studies; Pharmacological Reports 2013; 65:1601-1610.
14. Manisaiah AR., Diabetic Autonomic Neuropathy: Biochemical Factors, Diagnosis, Treatment- Literature Review. Diabetes open 2015; 1(1): 1-5.

15. Ii M, Nishimura H, and Kusano KF,. Neuronal nitric oxide synthase mediates statin-induced restoration of vasa nervorum and reversal of diabetic neuropathy. Circulation 2005; 112:93-102.

16. Jyothirmayi B., Sanjayseth MR., Kaviarasi MS. S., and William E., "Study of serum GGT levels and lipid profile in diabetic peripheral neuropathy ". Int J Pharm Bio Sci 2012; 3(4): (B) 995 – 1000.

17. Uttra KM, Devrajani BR, Shah SZA, Devrajani T, Das T, and Raza S, Naseem: Lipid profile of patients with diabetes mellitus (A Multidisciplinary Study). World Appl Sci J 2011; 12(9):1382–1384.

18. Dixit et al. "The prevalence of dyslipidemia in patients with diabetes mellitus of ayurveda Hospital" *Journal of Diabetes & Metabolic Disorders*, 2014; 13:58.

19. Elinasri HA, and Ahmed AM: Patterns of lipid changes among type 2 diabetes patients in Sudan. Eastern Mediter Health J . 2008; 14:2.

20. Henry O.O., Ofem E.E., Emmanuel E.E., Okon E.E., and Patrick N.M., Comparative Analysis of Atherogenic Index of Plasma and Its relationship with Cardiovascular Risk among Patients with Diabetes Mellitus and Concurrent Diabetes Mellitus with Hypertension attending Endocrinology Clinic in A Tertiary Hospital South- South Nigeria. *IOSR Journal of Dental and Medical Sciences*. 2015; 14(8): 102-107.

21. (21) P.S. Kanthe, B.S.Patil, S.Bagali, A.Deshpande, G.B.Shaikh, and M.Aithala, Atherogenic index as a predictor of cardiovascular risk among women with different grades of obesity, *Intenational Journal of Collaborative Research on Internal Medicine and Public Health*, 2012; 4: 1767 – 1774.

22. Brownrigg J., Lusignan S., Govern A., Hughes C., Thompson M., Ray K., and Hinchliffe R., "Peripheral neuropathy and the risk of cardiovascular events in type 2 diabetes mellitus". Heart BMJ. 2014; 0:1–7.

23. Emin M.A. , Aysu T., Adalet O., Fatih O., Levent D., Adem G., and Nergis A., Association of uric acid, atherogenic index of plasma and albuminuria in diabetes mellitus. *Int J Clin Exp Med*, 2014; 7(12):5737-5743.

24. Wang Y, Yuan A and Yu C. Correlation between microalbuminuria and cardiovascular events. Int J Clin Exp Med 2013; 6: 973-978.

25. Marcelo F. Di Carli, Daniela Bianco-Batlles, Maria E. Landa, Andris Kazmers, Harvey Groehn, Otto Muzik, and George Grunberger," Effects of Autonomic Neuropathy on Coronary Blood Flow in Patients With Diabetes Mellitus" American Heart Association, Inc. 2015; 24(1):813-817.