Correlation between Uric Acid and Liptin with Its Ratio in a Sample of Iraqi Patients with Diabetes Mellitus

Zeina Ismael Ibraheam
Department of Chemistry, College of Science, Al-Nahrain University, Baghdad-Iraq.

Abstract

In this study the relation between uric acid and leptin hormone with its ratio, was investigated among sample of Iraqi diabetic patients. A case control study conducted in the National Diabetes Center, College of Medicine at Al-Mustansiryia University in Baghdad-Iraq. Hemoglobin A1c (HbA1c), fasting blood sugar, leptin and uric acid were measured. One hundred forty patients with DM was inhered in this study, and 100 subjects were healthy as a control revealed a highly significant increasing in serum (FBS), HbA1c, body mass index (BMI), Leptin and uric acid of diabetes patients than in healthy subjects($p < 0.0001$). While the ratio of glucose /leptin of diabetes patients was highly significant decrease compare to healthy subjects. As well as the present study indicate a positive relation between serum uric acid with HbA1c of diabetes mellitus patients and uric acid with leptin diabetes mellitus patients (($p < 0.0001$).

Keywords: Diabetes mellitus, Leptin, Uric acid, Glucose/leptin.

Introduction

Uric acid is the final oxidation product of purine catabolism. **S**erum uric acid is positively associated with serum glucose in healthy subjects.[1-7] However, this association is not consistent between healthy and diabetic individuals [8–10], as a low serum level of uric acid is reported in the hyperglycemic state [11].Hyperuricemia has been found to be associated with obesity and insulin resistance, and consequently with type 2 diabetes [12,13].

The association of high serum uric acid with insulin resistance has been known since the early part of the 20th century, nevertheless, recognition of high serum uric acid as a risk factor for diabetes has been a matter of debate. In fact, hyperuricemia has always been presumed to be a consequence of insulin resistance rather than its precursor [14-18]. However, it was shown in a prospective follow-up study that high serum uric acid is associated with higher risk of type 2 diabetes independent of obesity, dyslipidemia, and hypertension [19].Leptin is a peptide hormone encoded by the obesity gene. It is a 16-KDa food intake, reproduction, and immune function, plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism. It is one of the most important adipose derived hormones [20, 21].

Human leptin is a protein of 167 amino acids. It is manufactured primarily in the adipocytes of white adipose tissue, the major source of leptin, it can also be produced by brown adipose tissue, placenta, ovaries, skeletal muscule, stomach, mammary epithelial cell, bone marrow and liver [22]. The absence of leptin (or its receptor) leads to uncontrolled food intake and resulting obesity. Several studies have shown that fasting or following a very low caloie diet (VLCD) lowers leptin levels [23].It might be that on short-term leptin is an indicator of energy balance. This system is more sensitive to starvation than to overfeeding; leptin levels change more when food intake decreases than when it increases [24]. It might be that the dynamics of leptin due to an acute change in energy balance are related to appetite and eventually to food intake. Although this is a new hypothesis, there are already some data that support it [25, 26].

The finding of a positive correlation between serum leptin and uric acid levels suggests that leptin could be a pathogenic factor responsible for hyperuricemia in obesity [27].

Material and Method

A case-control study was conducted during the period from 1st August 2008 to the 25th of May 2010, in the National Diabetes Center,

College of Medicine at Al-Mustansiryia University in Baghdad Iraq. One hundred forty patients with diabetes mellitus (DM), male=52, female=88, type 1=74 and type 2=99, were enrolled in this study. Their age range was 30-55 years. None of that patient had cardiovascular diseases (CVD), liver disease, and renal failure. A 100 healthy non-diabetic subject were used as a control, 32 were males and 68 were females with the age rang from 30-55. ***Serum glucose*** was measured at biochemistry Laboratory at College of Science/chemistry Department at Al-Nahrain University from a fasting sample of participants 8-12 hr by enzymatic colorimetric method (GOD-PAP).***Serum uric acid*** was measured at the Biochemistry Laboratory at National Diabetes Center by enzymatic colorimetric method (Linear). ***HbA1c*** was measured by column chromatography method (Varna-Biurat /HPLC). ***Serum leptin*** was measured using high performance Liquid Chromatography (HPLC), Shimadzu (Kyoto, Japan) which consisted of a system controller model SCL-10 AVP,a degasser model DGU-12A, two liquid delivery pumps model LC-8 AVP, UV-Visible detector model SPD-10AVP, and injector model SIL-10A,equipped with 20 µl sample loop. The HPLC system has been interfaced with computer via a shimadzu class-VP5 chromatography data system program supplied by the manufacturer, Epson LQ-300 printer model P852A (Japan).

All samples and standard solution have been chromatographically analyzed with ODS column using gradient mobile phase30% acetonitrile,70% estimate water, flow rate 1 ml/min and UV-VIS detection at wavelength 233 nm in order to estimate serum leptin[28]. Normal reference ranges for leptin were [7.36±3.73 ng/ml] according to American Medical Association [29].Body mass index was calculated by dividing study subject weight (kg with their height (m^2) [30].

All data were analyzed by SPSS version 17. Descriptive statistics in terms of mean and Standard Deviation calculated for patients and healthy control. Pearson's correlation as well as linear regression equation was calculated to estimate the slope (B) in order to know the amount of change in dependent variables with per unit change in serum selenium concentration. A P-value of <0.05 was considered as significant.

Table (1)
Descriptive analysis including mean and stander deviation of Mean for DM patients and Healthy control.

	General	*Male*	*Female*	*Type I*	*Type II*
DM Patients	*(n=140)*	*(n=52)*	*(n=88)*	*(n=74)*	*(n=99)*
Age(years)	45.63±6.11	45.54±4.59	45.68±6.90	44.59±6.95	46.63±4.85
Fasting glucose(mg/dl)	171.91±62.92	187.86±77.43	154.03±34.22	187.86±77.43	154.03±34.22
HbA1c	8.65±2.18	8.664±1.90	8.64±2.34	9.15±2.28	8.09±1.93
BMI(Kg/m^2)	26.88±4.87	26.72±3.22	26.98±5.65	27.45±2.92	26.25±6.38
Leptin(ng/ml)	22.86±5.81	23.27±5.21	24.61±6.19	23.73±6.318	21.87±5.11
Uric acid(mg/dl)	5.86±1.73	6.06±1.60	5.74±1.81	6.32±1.76	5.35±1.57
Glugose/leptin ratio	7.85±3.06	7.69±3.08	7.95±3.09	8.08±3.09	7.59±3.17
Healthy control	*(n=100)*	*(n=32)*	*(n=68)*		
Age(years)	45.41±5.72	45.21±5.52	45.81±5.48	—	—
Fasting glucose(mg/dl)	86.58±4.22	87.7±4.29	85.45±3.94	—	—
(HbA1c)	6.44±0.436	6.36±0.48	6.53±0.38	—	—
BMI(Kg/m^2)	24.67±2.38	26.72±3.22	26.74±2.96	—	—
Leptin	8.34±1.55	9.51±0.63	7.17±1.30	—	—
Uric acid	3.59±1.35	3.72±1.40	3.24±1.45	—	—
Glugose/leptin ratio	11.20±4.13	9.21±4.22	12.30±4.61	—	—

Results and Discussion

Table (1) shows the basic characteristics of subjects included in this study. One hundred forty diabetic patients had mean age equal to 45.63±6.11 years [mean ± SD] and one hundred non diabetic healthy subjects aged (49.41±5.72) years were served as controls. Biochemical tests results exhibit that the levels of fasting glucose, HbA1c, BMI and leptin were highly significant increased in patients when compared to healthy control subjects ($p< 0.0001$) and this result confirmed the previous observation studies [3,7,35].

Patients BMI were (26.89±4.87) Kg/m^2 so the patients were over weight. The prevalence of hyperuricemia has been increasing in recent years, not only in advanced countries but also in developing countries, along with the development of their economies. It has been suggested that hyperuricemia is associated with metabolic syndrome [32], in this study serum uric acid was highly increased in patient as ageneral than in control ($p<0.0001$), as well as the significant increased in uric acid in type II diabetes than in type I diabetes which observed in this study is support the researchers proposed that hyperuricemia has been found to be associated with obesity and insulin resistance and consequently with type II diabetes [1] .While Nan H,Dong *et a*l in 2007 found that diabetic subjects have low serum uric acid than controls [33].

There are many ways to measure insulin resistance like Homeostasis Model Assessment

for Insulin resistance (HOMA-IR) and Quantitative Insulin-Sensitivity Check Index (QUICKI), hyperinsulinemic euglycemic clamp tests and insulin suppression tests [36].

Recently, a number of studies have suggested that the fasting glucose to insulin ratio (G/I) may represent another useful method for assessing insulin resistance [35]. However, unlike HOMA or QUICKI, which are based on the product of fasting insulin and glucose, G/I does not appropriately reflect the physiology underlying the determinants of insulin sensitivity. The potential problems with using the fasting G/I ratio as a physiologically appropriate index of insulin sensitivity become apparent when fasting glucose levels are abnormal, The potential problems with using the fasting G/I ratio as a physiologically appropriate index of insulin sensitivity become apparent when fasting glucose levels are abnormal [37]. Because of highly correlation between insulin and leptin in patient with diabetes and because of the potential problems with using the fasting (glucose/insulin) ratio as an index of insulin sensitivity ,a new ratio between fasting(glucose/leptin) was proposed to be used as an index for predicting diabetes mellitus when fasting glucose levels are abnormal by Raya Sulaiman et al [35], this study agreed with Raya Suliman as mentioned in Table (1), (glucose/leptin) found highly significant decrease in diabetes patients than in controls ($p< 0.0001$).

Multiple regression analysis showed that the estimates of total body obesity and serum uric acid concentration are independently associated with serum leptin concentration for both healthy and diabetes. The finding of a highly significant positive correlation between serum leptin and uric acid levels suggests that leptin could be a pathogenic for hyperuricemia in obesity [27], this study observed that in patients group as a general without sex and type classification, a highly significant positive correlation was found between fasting uric acid and fasting leptin ($p<0.001$) as shown in Table (2) and Fig.(1).

Table (2)
Correlation between fasting uric acid and HbA1c, FBS, leptin, BMI and ratio of Glucose/Leptin.

	r	*P value*
HbA1c	0.298*	0.012
FBS	0111	0361
Leptin(ng/ml)	0.482**	0.0001
BMI(kg/sqm)	0.176	0.145
Glucose/leptin	0.237	0.048

**** Significant correlation when p<0.05; ** highly significant correlation when p <0.01 and r= correlation.***

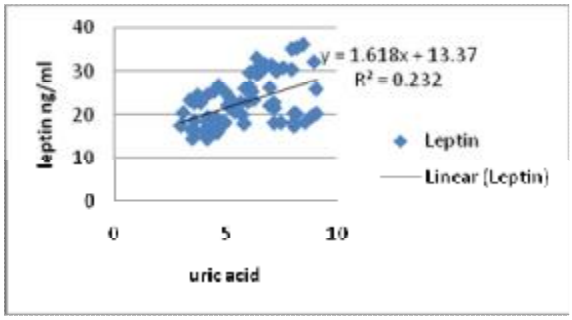

Fig.(1) Postive correlation with linear regression equation between fasting serum uric acid and leptin. (R^2= 0.232, r=0.482, p<0.0001).

The study of H. K. Choi and E. S. Ford found that Individuals with moderately elevated HbA1c levels (i.e. pre-diabetes) may be at a higher risk of hyperuricaemia and gout [38], the present study found a significant positive correlation between serum uric acid and serum HbA1c of patients ($p<0.05$) as shown in Table (2) and Fig.(2). In addition, a new correlation was proposed, this correlation is a significant negative correlation between serum uric acid and the ratio of (Glugose/leptin) of diabetes patients ($p<0.05$), Table (2) and Fig.(3).

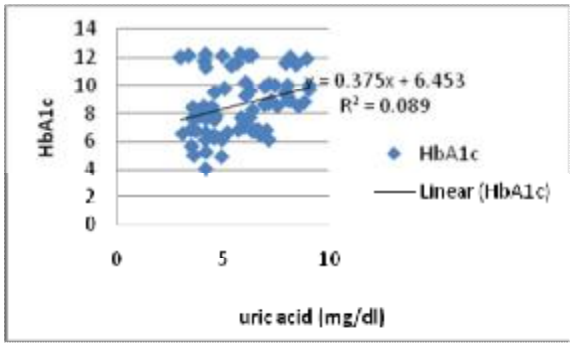

Fig.(2) Positive correlation with linear regression equation between fasting serum uric acid and HbA1c. (R^2= 0.089, r=0.298, p<0.05).

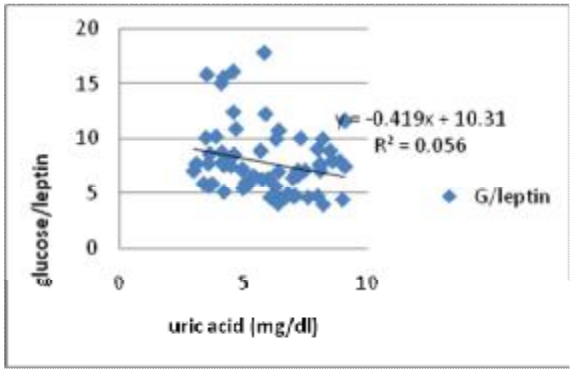

Fig.(3) Negative correlation with linear regression equation between fasting serum uric acid and ratio Glucose/Leptin. (R^2= 0.056, r=-0.237, p<0.05).

In conclusion, Serum Fasting blood sugar, body mass index, HbA1c, leptin and uric acid were significantly increased in diabetes mellitus patient. Serum uric acid tend to increase with increasing serum leptin, and with increasing serum HbAc1 of diabetes patients. But decrease with increase serum Glucose/leptin.

References

[1] Wolfgang Koenig and Christa Meisinger "Uric Acid, Type 2 Diabetes, and Cardiovascular Diseases: Fueling the Common Soil Hypothesis" *Clinical Chemistry, Vol.54*, pp.231-233, 2008.

[2] Becker BF "Towards the physiological function of uric acid" *Free Radic Biol Med*, Vol.14, pp 615-631, 1993.

[3] Strazzullo P, Puig JG. "Uric acid and oxidative stress: relative impact on cardiovascular risk" *Nutr Metab Cardiovasc Dis* Vol.17, pp.409-414, 2007.

[4] Becker BF, Reinholz N, Leipert B, Raschke P, Permanetter B, Gerlach E. "Role of uric acid as an endogenous radical scavenger and antioxidant" *Chest*;Vol.100, No.3, pp176S-181S. 1991.

[5] Strasak AM, Rapp K, Hilbe W, Oberaigner W, Ruttmann E, Concin H, . on behalf of the VHM & PP Study Groupet al. "The role of serum uric acid as an antioxidant protecting against cancer: prospective study in more than 28 000 older Austrian women" *Ann Oncol*, Vol. 18, pp1893-1897, 2007.

[6] Modan M, Halkin H, Karasik A, Lusky A"Elevated serum uric acid: a facet of hyperinsulinaemia" *Diabetologia*, Vol. 30, pp 713–718, 1987.

[7] 7- Facchini F, Chen YD, Hollenbeck CB, Reaven GM" Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasmauric acid concentration" *JAMA*, Vol. 266, pp 3008– 3011, 1991.

[8] Wun YT, Chan CSY, Lui CS" Hyperuricaemia in type 2 diabetes mellitus" *Diabetes Nutr Metab* Vol.12,pp286 –291, 1999.

[9] Nakanishi N, Okamoto M, Yoshida H, MatsuoY, Suzuki K, Tatara K" Serum uric acid and risk for development of hypertension and impaired fasting glucose or type II diabetes in Japanese male office workers" *Eur J Epidemiol* Vol. 18, pp 523–530, 2003.

[10] Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S, Okada K "Serum uric acid and the risk for hypertension and type 2 diabetes in Japanese men" *the Osaka Health Survey. J Hypertens* Vol.19, pp 1209–1215, 2001.

[11] Nan H, Dong Y, Gao W, Tuomilehto J, Qiao Q "Diabetes associated with a low serum uric acid level in a general Chinese population."*Diabetes Res Clin Pract* 2006.

[12] Baker JF, Krishnan E, Chen L, Schumacher HR "Serum uric acid and cardiovascular disease: recent develop-ments, and where do they leave us" *Am J Med*; Vol. 118, pp 816-826, 2005.

[13] Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC. "High serum uric

acid as a novel risk factor for type 2 diabetes mellitus" *Diabetes Care* Oct 31. 2007.

[14] Kanellis J, Kang DH. "Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease" *Semin Nephrol*, Vol. 25, pp 39-42, 2005.

[15] Waring WS, McKnight JA, Webb DJ, Maxwell SR. "Uric acid restores endothelial function in patients with type 1 diabetes and regular smokers" *Diabetes*,Vol.55,pp3127-3132, 2006.

[16] Gersch MS, Johnson RJ. "Uric acid and the immune response" *Nephrol Dial Transplant*; Vol. 21, pp 3046-3047, 2006.

[17] Sanchez-Lozada LG, Nakagawa T, Kang DH, Feig DI, Franco M, Johnson RJ, et al. "Hormonal and cytokine effects of uric acid" *Curr Opin Nephrol Hypertens*, Vol.15, pp30-33,2006.

[18] 18-25 Cappuccio FP, Strazzullo P, Farinaro E, Trevisan M. "Uric acid metabolism and tubular sodium handling. Results from a population-based study" *JAMA* Vol. 270, No. 3, pp 354–359, 1993.

[19] Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC (February 2008). "High serum uric acid as a novel risk factor for type 2 diabetes". *Diabetes Care* Vol.31,No.2,pp 361–362,2008.

[20] Farook IS,O Rahilly S. "leptin:a pivotal regulator of human energy homeostasis"*Am J clin Nutr*, Vol. 89, pp 980S-984S, 2009.

[21] Brennan AM, Mantzoros CS "Drug Insight: the role of leptin in human physiology and pathophysiology--emerging clinical applications". *Nat Clin Pract Endocrinol Metab*, Vol.2 No.6, pp 318–27, 2006.

[22] Margetic S, Gazzola C, Pegg GG, Hill RA "Leptin: a review of its peripheral actions and interactions" *Int. J. Obes. Relat. Metab. Disord.* Vol. 26, No.11, 2002.

[23] Dubuc G, Phinney S, Stern J, Havel P "Changes of serum leptin and endocrine and metabolic parameters after 7 days of energy restriction in men and women". *Metab. Clin. Exp.* Vol. 47, No.4, pp 429–34, 1998.

[24] Chin-Chance C, Polonsky K, Schoeller D "Twenty-four-hour leptin levels respond to cumulative short-term energy imbalance and predict subsequent intake". *J. Clin. Endocrinol. Metab*. Vol. 85, No.8, pp 2685–91, 2000.

[25] Keim N, Stern J, Havel P. "Relation between circulating leptin concentrations and appetite during a prolonged, moderate energy deficit in women". *Am. J. Clin. Nutr.* Vol. 68, No. 4, pp 794–801, 1998.

[26] Mars M, de Graaf C, de Groot C, van Rossum C, Kok F (2006). "Fasting leptin and appetite responses induced by a 4-day 65%-energy-restricted diet". *International journal of obesity (Lond)* Vol. 30, No.1, pp 122–8, 2006.

[27] Bernd fruehwald schultes,Achim peters, Werner Kern,Jurgen Beyer and Andreas pfutzner. "Serum leptin is associated with srum uric acid concentration in humans" *Metabolism.* Vol. 48, pp 677-680, 1999.

[28] Bushra H. "Biochemical and clinical study of polycystic ovary syndrome and the effect of clomiphene citrate on hormones ,leptin and trace elements".MSC.Thesis. College of science.AL-Nahrain University. 2002. PP. 39.

[29] IversonCL,Christinsen S,Flanagin, AF, Fontanarosa PB, Glassn RM, Gregoline B, Lurie SJ,Meyer HS,Winker MA,Young RK. AMA Manual of Style: A Guid for Athuthors and Editors. 10 th ed.New yourk,NY: Oxford University press; 2007. PP 798.

[30] Pratley R, Nicolson M, Bogardus C, Ravussin E "Plasma leptin responses to fasting in Pima Indians". *Am. J. Physiol.* Vol. 273, No. 3 E644–9, 1997.

[31] H.K.choi and E.S. ford. Haemoglobin A1c,fasting glucose,serum c-peptide and insulin resistance in relation to serum uric acid levels –the third national health and nutrition examination survey.Rheumatology 2008; 74; 713-717, advance access publication.

[32] CHEN Li-ying, ZHU Wen-hua, CHEN Zhou-wen, DAI Hong-lei, REN Jing-jing, CHEN Jian-hua, CHEN Lei-qian, FANG Li-zheng. "Relationship between hyperuricemia and metabolic syndrome" *Chen et* 594 *al. / J Zhejiang Univ Sci B*, Vol. 8, No.8, pp 593-598, 2007.

[33] Nan H, Dong Y, Gao W, Tuomilehto j,Qiao. " Diabetes associated with a low serum uric acid level in a general Chinese

population.Diabetes Res Clin pract". Vol. 76, No. 1, pp 68-74, 2007.

[34] J.Mohiti,F.Talebi and M. AFKani-ardekani. "circulation free leptin in diabetic patients and its correlation to insulin level" *Pakistan Journal of Biological Sciences*,Vol.12, No.4, pp397-400,2009.

[35] Rayah sulaiman Baban,Khawla Abdul Kareem Kasar,isam Noori AL-Karawi "fasting Glugose to Leptin ratio as new Diagnostic Marker in Patient with Diabetes Mellitus"Oman medical Journal,Vol.25, No.4., pp 296-272,2010.

[36] Farooq AK, Sikandar HK, Amir I, Abdus S, Mohammad D, Rizwan H. "Common Anthropometric Indices and Insulin Resistance" *Pak J Med Res*. Vol. 48, No.2, 2009.

[37] Hui Chen, Gail Sullivan, Lilly Q. Yue, Arie Katz, and Michael J. Quon. "QUICKI is a useful index of insulin sensitivity in subjects with hypertension" *Am J Physiol Endocrinol Metab*. Vol.284, No7, pp 804-812, 2003.

[38] H. K. Choi andE. S. Ford. " Haemoglobin A1c, fasting glucose, serum C-peptide and insulin resistance in relation to serum uric acid levels the Third National Health and Nutrition Examination Survey ".*Rheumatology* ,Vol.47 , No.5, pp 713-717,2008.

الخلاصة

الهدف من هذه الدراسة كان لمقارنة مستوى مصل الدم من حامض اليوريك و هرمون اللبتن و مقارنة مستوى مصل الدم من حامض اليوريك مع نسبة كلوكوز /اللبتن. تم اجراء الدراسة في المرركز الوطني لمرض داء السكر ي في كلية الطب-الجامعة المستنصرية في الاول من شهر اب ٢٠٠٨ ولغاية الثلاثين من شهر كانون الثاني ٢٠١٠. وكان عدد المرض ١٤٠،بينما كان عدد الاصحاء ١٠٠ مع مراعاة تقارب الاعمار والجنس بين المجموعتين .تم قياس كمية السكر الصائم ، وحامض اليوريك في مصل الدم بطريقة بطريقة المطياف في حين تم قياس هرمون اللبتن بتقنية الفصل بالسائل العالي الاداء HPLC.

وتم حساب كتلة الجسم (BMI) وحساب نسبة السكر الصائم/اللبتن الصائم.وقد وجد انه مستوى حامض اليوريك، السكر الصائم ، هرمون اللبتن،هيموكلوبين السكر الصائم وكتلة الجسم (BMI) يرتفع بشكل ملحوظ عند المرضى المصابين بالسكري مقارنة بالأصحاء.في حين ان نسبة (السكر الصائم/اللبتن الصائم) ينخفض عند المرضى مقارنة بالاصحاء.

كما وجد ان هناك ارتفاع في مستوى حامض اليوريك في مرضى السكري النوع ٢ (السكر غير المعتمد على الانسولين).

وبغض النظر عن عن تقسم المرضى حسب الجنس ونوع السكر وجدت علاقة ان هناك علاقة خطية مع ارتباط موجب بين كل من حامض اليوريك وهرمون اللبتن وكذلك بين حامض اليوريك وهيموكلوبين السكر الصائم.بينما وجدت علاقة خطية سالبة الارتباط بين حامض اليوريك مع نسبة (السكر الصائم/اللبتن).