Medical Journal of Babylon
Vol. 12- No. 3: 618-624, 2015
http://www.medicaljb.com
ISSN 2312-6760©2015 University of Babylon

Original Research Article

Study The Relationship of IL-33 with Adiponectin in Postmenopausal Female with and without Type 2 Diabetes Mellitus

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Accepted 20 May,2015

Abstract

Postmenopausal women influence by several physiological changes such as coronary artery disease, obesity and insulin resistance. Interleukin-33 (IL-33) a cytokine which have a protective effect to cardiovascular disorders and regarded either pro- or anti-inflammatory. Adiponectin is a hormone with anti-inflammatory properties, associated with hyperlipidemia and insulin resistance. The aim of this study is to investigate the relationships of IL-33, adiponectin with atherogenicity as considered risk factor for heart disease in postmenopausal women with and without type 2 diabetes mellitus.

Ninety women age between (54-62) years were enrolled in this study. Fasting blood glucose (FBG), glycated hemoglobin (HbA1c), body mass index (BMI), lipid profile, atherogenic index of plasma (AIP), IL-33 and adiponectin levels were determined in patients and control groups.

The results revealed highly significant increase in FBG, HbA1c, BMI, TCh, TG, LDL-c, VLDL-c and AIP. While reduce HDL-c, adiponectin and IL-33 levels were founded in postmenopausal women when comparing to control group. Furthermore, a positive correlation was observed in IL-33 with HbA1c, also with AIP, but a negative significant correlation between IL-33 and adiponectin, also between IL-33 and BMI in diabetic postmenopausal women group. Conclusion from the results of present work lead to suggest that higher reduction in IL-33 and adiponectin levels in diabetic postmenopausal women may be useful in predict action of cardiovascular disorders.

Key words: Interleukin-33, Adiponectin, postmenopausal, atherogenicity.

دراسة علاقة مستويات الانترلوكين -٣٣ مع الاديبونكتين لدى نساء سن اليأس من المصابات وغير المصابات بداء السكري من النوع الثاني

الخلاصة

ان النساء في مرحلة سن اليأس يتعرضن للاصابة بامراض القلب والسمنة اضافة للحساسية تجاه الانسولين نتيجة لتأثير مجموعة من التغيرات الفسيولوجية التي تحدث في هذه المرحلة. الانترلوكين-٣٣ ينتمي لعائلة الانترلوكين-١ ويعتبر كدالة تنبؤية لانواع متعددة من امراض القلب , اما الاديبونكتين فهو هرمون بروتيني يمتلك خصائص مضادة للالتهاب وخصوصا تلك المتعلقة بأرتفاع نسبة الدهون والحساسية تجاه الانسولين. أن هدف الدراسة الحالية هو ايجاد العلاقة بين مستويات الانترلوكين-٣٣, الاديبونكتين ومؤشر البلازما المعصد بأعتبارهم عامل خطورة للاصابة بأمراض القلب لدى نساء سن اليأس من المصابات وغير المصابات بداء السكري من النوع الثاني.

شارك في هذه الدراسة (٩٠) أمراءة تراوحت اعمارهن بين (٥٤- ٦٢) سنة حيث تم لجميعهن قياس مستوى الكلوكوز الصائم (FBG) ,الهيموغلوبين المسكر(HbA1c), مؤشر كتلة الجسم(BMI), مؤشر البلازما المعصد(AIP) , أضافة الى مستويات الاديبونكتين والانترلوكين- ٣٣ (IL-33) .

اظهرت نتائج هذه الدراسة زيادة معنوية عالية في كل من FBG, HbA1c, BMI, TC, TG, LDL-c, VLDL-c و AIP . بينما كان هنالك انخفاض ملحوظ في تراكيز كل من IL-33 ,HDL-c والاديبونيكتين في مجموعة نساء اليأس المصابات بداء السكري عند مقارنتها مع المجموعة الضابطة. بألاضافة الى وجود علاقة موجبة ملحوظة بين HbA1c وIL-33 وكذلك بين AIP وIL-33 في مجموعة المريضات . بينما كانت هناك علاقة سالبة او عكسية بين الاديبونكتين وIL-33 وكذلك بين IL-33 و BMI وبالاعتماد على نتائج هذه الدراسة نتوقع ان النقصان الحاد في تراكيز الانترلوكين-٣٣ والاديبونكتين لدى نساء اليأس المصابات بمرض السكري من النوع الثاني من الممكن الاعتماد عليه للتنبؤ بخطر الاصابة بأمراض القلب لهذه الفئة من النساء.

Introduction

Menopause is a natural distinguish of the reproductive years end with cessation of cyclic ovarian functions which manifested by cyclic menstruation [1]. Menopause is associated with elevation in follicle- stimulating hormone and luteinizing hormone levels with a decrease in estrogens [2]. The levels of hormones show a significant effect on the metabolism of lipids and lipoproteins [3]. Antiatherogenic effect of estrogen and the protection of females against heart disease are signifies during the premenopausal period [4]. Several physiological changes that develop during menopause may prone to the risk of cardiovascular disease (CVD), increase obesity or low metabolic rate resting and physical activity [5]. During premenopausal period insulin resistance become more prevalent and many women have increasing in blood sugar levels, due to sex hormones effect, also when women reach menopause the body becomes more sensitivities to insulin like it was prior to premenopausal period [6].

Interlukin-33 (IL-33) is a cytokine related to IL-1 super family [7]. IL-33 is a protein which has a role in signaling damage of the cell pathogenesis of the inflammatory disease by releasing from necrotic or damaged cell [8]. Other research demonstrated that IL-33 is distributed throughout different organ systems in the body, which expressed in non hematopoietic cell, including fibroblasts, adipocytes, smooth muscle cell, endothelial and intestinal epithelial cells [9]. IL-33 has been demonstrated to have a potent protective role in various experimental chronic heart failure studies through inhibition of the nuclear factor kappa B cascade. So that, IL-33 plays a role in various cardiovascular disorders [10]. IL-33 could act earlier in artery inflammatory cells and modulate the innate immune responses by regulation macrophage effecter function [11]. From the other side, IL-33 has protected effect against atherosclerosis, obesity and type2 diabetes (T2D). Therefore, IL-33 considered pro- or anti-inflammatory based on the model of disease [12].

Adiponectin is a novel collagen like protein synthesized by adipocytes and acts as a hormone with anti- inflammatory and insulin sensitizing properties through decrease the risks of T2D, including suppression of hepatic gluconeogenesis, or stimulation of fatty acid oxidation in the liver and glucose uptake in skeletal muscle [13]. Adiponectin which have antiatherogenic properties [14] and inversely associated to hyperlipidemia and insulin resistance [15]. Adiponectin enhances glucose utilization and the oxidation of fatty acid in muscle. Also increase endothelial nitric oxide secretion, inhibits monocyte adhesion and smooth muscle cell proliferation in the vascular wall [16].

Data in IL-33 levels and correlate it with adiponectin in menopausal women with and

without T2DM are not available. So that from this point the present research aimed to investigated the association between the IL-33 levels, adiponectin and atherogenicity as consideration risk factor for CVD in postmenopausal women with and without T2DM.

Materials and Methods

Ninety women age ranged between (54-62) years were selected from those attending to Baghdad Teaching Hospital from October 2013 to March 2014. They were recruited as 50 postmenopausal women with T2DM and 40 apparently healthy postmenopausal women as control group. Menopause was confirmed by the absence of menstruation for more than two years [17]. Exclusion criteria consisted of those haring a history of menstrual disorders, thyroid abnormalities, inflammatory or infection disease, autoimmune and rheumatic's disease, fever, cancer as well as those who under treatment with steroidal anti-inflammatory drugs were excluded. BMI was measured based on world Health Organization (WHO) procedure [18].

Fasting blood samples from all subjects were collected to analyzed glycated hemoglobin (HbA1c) [19], fasting blood sugar [20], total cholesterol [21], triglyceride [22], HDL-c [23]. AIP was estimated: log TG/HDL-c [24] in both groups. Serum IL-33 and adiponectin levels were measured by an enzyme immuno assay (ELISA) [25].

Statistical Analysis

Student T-test was used to compare the significance of the difference in the mean values of two groups. The results were expressed as mean ± SD. The P-value ≤ 0.05 was considered significant. Pearson coefficient (r) was applied to describe the relation between the different studied variables P-value <0.0001 was considered significant.

Results

Table (1) shows the mean of age, BMI, HbA1c, FBG, TCh, TG, HDL-c, LDL-c, VLDL-c, AIP, adiponectin and IL-33 levels in diabetic postmenopausal group and control group. The results showed a highly significant elevation in BMI level, HbA1c, FBG, TCh, TG, LDL-c, VLDL-c and AIP in diabetic postmenopausal group comparing to control group. Also a high significant reduction was observed in the levels of LDL-c, adiponectin and IL-33 in patient group than control group.

Table 1 : Descriptive characteristic of parameters in patients and control groups.

Variable	Control group	Patients group	P-value
Age (Yrs)	55±6.1	56±4.2	>0.01
BMI (Kg/m^2)	26.13±1.20	33.21±4.8	<0.001
HbA1c %	4.57±1.43	9.13±1.49	<0.001
FBG (mg/dl)	91.27±13.09	283.53±92.95	<0.001
TCh (mg/dl)	180.93±16.86	229.40±10.71	<0.001
TG (mg/dl)	91.50±6.95	145.50±112.21	<0.001
HDL-c (mg/dl)	42.80±4.78	28.97±4.76	<0.001
LDL-c (mg/dl)	119.90±17.04	194.67±18.58	<0.001
VLDL-c (mg/dl)	18.6±1.39	60.87±32.08	<0.001
AIP	0.33±0.07	0.94±0.17	<0.001
Adiponectin (µg/ml)	10.49±1.46	4.64±0.69	<0.001
IL-33 (ρg/ml)	25.29±1.31	18.21±1.71	<0.001

Data in table (2) indicate presence a correlation in IL-33 with HbA1c, BMI, adiponectin and AIP in diabetic postmenopausal women. A highly significant positive correlation was observed in IL-33 levels with HbA1c (r =0.165, P<0.001) and with AIP (r=0.632, P<0.001) in diabetic postmenopausal women but, a negative significant correlation was founded in IL-33 with adiponectin (r= -0.791, P<0.001) and BMI (r = -0.815, P<0.001).

Table 2 : Correlation of IL-33 with HbA1c, AIP, adiponectin and BMI.

	r	P-value
IL-33 & HbA1c	0.165	<0.001
IL-33 & AIP	0.632	<0.001
IL-33 & adiponectin	- 0.791	<0.001
IL-33 & BMI	- 0.815	<0.001

Discussion

The results in the present investigation showed significant elevation in levels of HbA1c, FBG, TCh, TG, LDL-c, VLDL-c and AIP in diabetic postmenopausal women compared with that in participants without diabetic, which agreement with other studies [26] [27] [28]. Probably, that related to the changes in hormones and follicular failure development in these ages. AIP has been used a risk factors for CVD [29], to based on our findings diabetic and non diabetic postmenopausal women at a high risk of developing cardiovascular disease [30]. The mean value of BMI was significantly higher increase in diabetic postmenopausal women when compared with control group and that agree with previously demonstrated [31]. Hyperglycemia associated with increase protein glycation which led to the high levels of HbA1c are commonly in this situation and that responsible for many chronic complication such as increase in body weight, dyslipdemia and increase the risk for atherosclerosis [32].

This study also, showed that the serum adiponectin levels in patients group were lower than levels of control group significantly. Adiponectin secreted by adipocytes and act as hormone contribute in homeostatic control of glucose and lipid

levels so that in T2DM patients adiponectin levels well reduce [33]. Hypoadiponect-enemia has many adverse clinical consequences as adiponectin has antiatherogenic and anti-inflammatory properties [34]. Al-Zubadi *et al* suggested that adiponectin may have important role in the CVD pathogenesis in both gender with T2DM [35]. Low concentration of adiponectin associated with atherosclerosis development which led to anti-inflammatory effect of adiponectin as protective agent against atherogenic vascular change [36, 37]. So that, adiponectin becomes beneficial in the prevention of.

Serum IL-33 levels in diabetic postmenopausal women were significant decrease than those non-diabetic postmenopausal women. In patients group there was a highly significant positive correlation in IL-33 with HbA1c and AIP were founded. Also, there was a highly significant negative correlation was observed in IL-33 with BMI and adiponectin level. No such correlation existed between IL-33 and HbA1c, AIP, BMI and adiponectin in diabetic postmenopausal women. IL-33 play important role in many heart disorders. The reduction in IL-33 levels in diabetic mellitus patients may due to the protective effect of IL-33 by reducing adiposity and improving glucose tolerance and insulin resistance [38]. To our knowledge, this is the first study that high lights on levels of IL-33 and related with adiponectin concentration in menopausal women with and without diabetic mellitus. Therefore, the finding of the present work lead to suggest that higher reduction in IL-33 and adiponectin levels in diabetic post-menopausal women may be useful in predict action of cardiovascular disorders.

References

1. Burger E.F., Kustin A.A., Baron D.C. "Endocrinology and metabolism". Ann Int Med (2002), 251:872-942.
2. Blake J. "Menopause: evidence-based practice". Best Pract Res Clin Obstet Gynaecol (2006), 20(6): 799- 839J
3. Usoro C.A., Adikwuru C.C., Nsonwu A.C. "lipid profile of postmenopausal women in Calabar, Nigeria". Pakistan Journal of Nutrition (2006), 5(1):79-82.
4. Manju B, Seth S, Seth R. "Lipid profile in various phases of menstrual cycles and its relationship with percentage plasma volume changes". Clinica Chimica Acta (1988), 273:201-7.
5. Chang C.J.,Wu C.H., Yao W.J., et al. "Relation of age, menopause and central obesity on cardiovascular disease risk factors in Chinese women". International Journal of Obesity (2000), 24:1699-704.
6. Aufaira S. Nsaif."Study the effect of sex hormones in diabetic women". Iraqi J. Commm. Med. (2014), 1:18:20.
7. Liew F.Y., Pitman N.I., Mclnnes I.B. "Disease associated functions of IL-33: the new kid in the IL-1 family". Nat Rev Immunol (2010), 10:103-110.
8. Nile C.J., Barksby E., Jitprasertwong P. et al. "Expression and regulation of IL-33 in human monocytes". Immunology (2010), 30:172-180.
9. Moussion C., Ortega N., Girard J.P. "The IL-1 like cytokine IL-33 is constitutively expressed in the nucleus of endothelial cells and epithelial cells in vivo: a novel 'alarmin". Plos One (2008), 3:e3331.
10. Kunes P., Holubcova Z., Kolackova M., Krejsek J. "IL-33 a novel member of the IL-1/IL-18 cytokine family in cardiology and cardiac surgery". Thorac Cardiovasc Surg (2010), 58:443-449.
11. Ciccia F., Alessandro R., Rizzo A., Raimondo S. et al. "IL-33 is overexpressed in the inflamed arteries of patients with

giant cell arteritis". Ann Rheum Dis (2013), 72:258-264.
12. Kakkar R., Hei H., Dobner S., Lee RT. "IL-33 as a mechanically responsive cytokine secreted by living cells". J Biol Chem (2012), 9:6941-6948.
13. Kadowaki T., Yamauchi T., Kubota N., Hara K., Tobe K. "Adiponectin and adiponectin receptors in insulin resistance, diabetes and the metabolic syndrome". J Clin Invest (2006), 116 (7):1784-1792.
14. Matsubara M., Maruoka S., Katayose S. "Inverse relationship between plasma adiponectin and leptin concentrations in normal-weight and obese women". Eur J Endocrinol (2002), 147: 173-180.
15. Yamamoto Y., Hirose H., Saito I., Tomita M. et at. "Correlation of the adipocytes derived protein adiponectin with insulin resistance index and serum high density lipoprotein-cholesterol, independent of body mass index, in the Japanese population". Clin Sci (2002), 103:137-142.
16. Diez J.J., Iglesias P. "The role of the novel adipocytes-derived hormone adiponectinine human disease". Eur J Endocrinol (2003), 148:293-300.
17. Nwagha U.I., Ikekpeazu E.J., Ejezie F.E., Maduka I.C. "Atherogenic index of plasma as useful predictor of cardiovascular risk among postmenopauasal women in Enugu, Nigeria". African Health Sciences (2010), 10 (3):248-252.
18. Garrow J.S., Webster J. "Quetelet's index (W/H2) as a measure of fatness". Int J Obes (1985), 9:147-153.
19. Jeppson J.O., Kobold U., Barr J., Finke A., Weykamp C. "Approved IFCC reference method for the measurement of HbA1c in human blood". Clin Chem Lab Med (2002), 40(1):78- 89.
20. Bartham D., Trrinder P. "An improved color reagent from the determination of blood glucose by the oxidation system". Analyst (1972), 97:142-145.
21. Richmond W. "Proceeding in the development of an enzymatic technique for the assay of cholesterol in biological fluids". Clin Sci Mol Med (1974), 46:67.
22. Fossati P., Prencipe L. "Measurment of serum triglycerides calorimetrically with an enzyme that produce H_2O_2". Clin Chem (1982), 28(10):2077-2088.
23. Burstein M.,Scholink H.R.,Morfin R. Measurment of HDL-c in the plasma with a sensitive calorimetric method. J Lipid Res (1970), 19:583.
24. Ikewuchi C.J., Ikewuchi C.C. "Alteration of plasma lipid profile and atherogenic index of cholesterol loaded rats by tridax procumbens linn: implications for the management of obesity and cardiovascular diseases". Biokemistri (2009), 21(2): 96.
25. Voller A., Bidwell O., Bartlell A. "Enzyme immune assay in diagnostic medicine". Bull Wllo (1976), 53:55-56.
26. Milagrose T., Jocson M.D. "Dyslipidemia in Filipino postmenopausal women. Its associated risk factors". Philippine Journal of Obstetrics & Gynecology (2007), 31(4):183-95.
27. Madhavi D.K., Kammar K.F. "Lipid profile in postmenopausal women of Hubli city". J Pub Health Med Res (2014), 2(1):25-28.
28. Saline A., Jeyanthi G.P. "Cardac biomarkers and atherogenic indices in hypertensive postmenopausal women with co-morbidites". IJPRBS (2014), 3(4):389-406.
29. Tan M.H., Johns D., Glazer N.B. "Pioglitazone reduces atherogenic index of plasma in patients with type 2 diabetes". Clin Chem (2004), 50:1184-88.
30. Dobiasova M. "AIP-atherogenic index of plasma as a significant predictor of cardiovascular risk: from research to practice". (2006), 52(1):64-71.
31. Al-Mukhtar S.B., Fadhil N.N., Hanna B.E. "Serum lipid profile in subjects

with type 2 diabetes mellitus and hypertension in relation to metabolic syndrome: a case control study". Duhok Med J (2012), 6(2):29-44.
32. Stanaway S.E., Gill G.V. "Protein glycosylation in diabetes mellitus, biochemical and clinical considerations". Practical Diabetes International (2000), 17:21-25.
33. Manal F.E., Samar M.S., Marwa M. E., Nahed E. "Adiponectin: an adipocytes-derived hormone and its gene encoding in children with chronic kidney disease". BMC (2012), 5:174-179.
34. Dunajska K., Milewicz A., Jedzejuk D., Szymczak J. et al. "Plasma adiponectin concentration in relation to severity of coronary atherosclerosis and cardiovascular risk factors in middle-aged men". Endocrine (2004), 25:215-221.
35. Hanan A.M. Al-Zubaidi, Abdul hussien M.K. Al-Jebory. "Serum level of adiponectin as a risk marker for cardiovascular and type 2 diabetes patients". Medical Journal of Babylon (2013), 10 (2):517-529.
36. Yuji M., Tohtu F., Shinji K., Iichiro S. "Adiponectin and metabolic syndrome". Arterioscler Thromb Vasc Biol (2007), 27:1267-82.
37. Amir E., Amira S., Tarek A.G., Marwan A. "Association between low adiponectin level and cardiovascular complications in diabetic and non diabetic patients with end stage renal disease". Arab Journal of Nephrology and Transplanation (2010), 3:15-21.
38. Miller A.M., Asquith D.L., Hueber A.J., Anderson L.A., et al. "IL-33 induces protective effects in adipose tissue inflammation during obesity in mice". Circ Res (2010), 185:1222-1229.