IGF-1 , Leptin & AIP in relation to Osteoarthritis with and without Diabetes Mellitus Type2

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Abstract

IGF-1 is a protein produced by the liver in response to growth hormone stimulus.One important key in effectively preventing and treating osteo arthritis, is establishing a healthy balance of IGF-1. Leptin is a hormone produced by adipose tissue, acting as a sensor of fat mass in part of a negative feedback loop that maintains a set point for body fat stores. Leptin plays an important role in the progression of Osteoarthritis (OA), prompting some to classify OA as a metabolic disease. it, has been found in synovial fluid from patients with OA , and are thought to have local effects on joint tissues . Atherogenic index of plasma (AIP) is newly marker of atherogenectiy provide prediction to accelerated development of atherosclerosis in diabetes mellitus patients. **Objective** This study was designed to find out the variation of some parameters in OA with & without T_2DM.

Patients and methods This study included (88) subjects aged between (40-60) years (all females , newly diagnoses and obese) who were attending the Al- Kadhimiya Teaching Hospital . Baghdad and Al-Mustansiriya University . The enrolled patients were divided to four groups: OA(24) , T2DM (20), OAwithT2DM (24) and control (20) . Venous blood samples from women were taken for laboratory investigation which included : Fasting plasma glucose , lipid profile (TC ,TG , HDLc and LDLc) , IGF-1 , Leptin were measured and Atherogenic index of plasma calculated as molar ratio of log (TG/ HDL-C).

Results The current study shows a significant increased atherogenic index , Leptin value , in three patients groups diabetes , osteoarthritis and OAwith DM when compared with control. But IGF-1 level was significantly decreased in the three patients groups T2DM, OA , T2DM with OA when compared with control .

Conclusion Osteoarthritis has a direct effect on dislipidemia ,Leptin & AIP value in Diabetes mellitus type2

Key Words: osteoarthritis , AIP , Leptin , T2DM , IGF-1

Introduction

Osteoarthritis (OA), is a chronic disease, resulted in patient suffers from harmful changes in cartilage, bone, ligaments and muscles. Osteoarthritis is not a single, well-define disease condition but is best described as a final stage failure of the joints that presents similar symptoms and radiographic findings regardless of the original cause [1],.The question that arises is does diabetes inhibit osteoarthritis pain? It was proved that neuropathy caused by impaired glucose tolerance / diabetes mellitus inhibit the expression of pain due to osteoarthritis in the lower extremities among a portion of patients displaying radiographic osteoarthritis [2].

Both OA and DM can be viewed as chronic disease processes characterized by earl, undetected levels of biological change. Some of the studies of the association between OA and DM, examined a variety of relevant factors, such as Leptin, AIP, Insulin-like growth factor 1 (IGF-1)…etc[3,4,5]. Atherogenic index of plasma (AIP) defined as log (TG/HDL-C), has been proposed as a marker of plasma atherogenicity because it is increased in people at higher risk for coronary heart disease and is correlated with LDL particle size.[6] Although HDL in fact may be directly antiatherogenic, it also is a marker for the presence of other lipid and nonlipid risk factors. however, the presence of a low HDL level carries strong predictive power for development of atherosclerotic cardio vascular disease ASCVD. [7] The serum TC and HDL-C levels in knee OA were inversely correlated with disease activity, suggesting a potential role of inflammation in the atherogenic profile and the higher atherosclerotic risk in arthritic patients.[8] IGF-I levels play a role in the development of the vascular complications of type 2 diabetes. IGF-I may also play a role in the regulation of cardiovascular function and development of myocardial infarction in subjects without type 2 diabetes, IGF1 is regulated by multiple mechanisms that are known to regulate systemic growth.[7] IGF-1 and diabetes has a strong physiological basis. Its level was reduced in diabetes mellitus and oxidation stress, [9] IGF and insulin are linked hormones that diverged in evolution.[10] IGF-1 provides important information about the body's levels of this crucial hormonal mediator in osteo arthritis, and also helps assess the general functioning integrity and homeostasis of the nervous system.[7] Leptin regulates energy homeostasis and interferes with several neuroendocrine and immune functions. A higher amount of leptin is secreted by subcutaneous adipocytes than by the visceral adipocytes. Leptin is generally synthesized and secreted by gastric chief cells in the stomach.[11] Leptin circulating levels are directly proportional to the body fat. .[12] It has a fundamental role in the control of appetite and also in regulating energy expenditures.[13] osteoarthritis is a metabolic disease induced by local abnormal leptin activity . A proinflammatory effect of leptin on cartilage would be in keeping with the fact that, in comparison with men, women have both higher circulating leptin levels and a greater propensity to develop osteoarthritis.[14]

Materials and Methods

The study was conducted at Al- Kadhimiya Teaching Hospital. Baghdad, and Department of National Diabetes Center for Treatment Research at Al-Mustansiriya University. (88) patient subjects were enrolled osteoarthritis and type 2 diabetes mellitus (T2DM) patients,(all females, newly diagnoses and obese), the age range was within (40-60 years),(68) Divided into three groups. and control group (20) subjects. Blood samples taken for laboratory investigation which included , Fasting blood sugar , Lipid profile (Total Colesterol, Triglyceride, high density lipoprotein and Low density lipoprotein),Insulin like growth factor -1 determination by (RIA) Kit (IMMUNOTECH), Leptin level determination by ELISE Kit (IMMUNOTECH) and Atherogenic index of plasma (AIP) calculated by

molar ratio of log(TG/ HDL-C). Data processing and statistical analysis ware done by the computer SPSS- 15 System (Statistical Package for Social Science – version 15).

Results and Discussion

Tables(1,2,3) revealed the levels of Atherogenic index and related clinical parameters investigated throughout the recent study . Their levels were estimated as Mean ± SD. The result reflects significant elevation in AIP ($P< 0.05$) in all patient groups compared with that of control . The result also reflects significant elevation in Leptin ($P< 0.05$) compared with that of control . Patient groups suffer from T2DM as confirmed in tables(1,2) . Atherogenic index of plasma (AIP) is defined as log (TG/HDL-C), has been proposed as a marker of plasma atherogenicity because it is increased in people at higher risk for coronary heart disease and is correlated with LDL particle size.[6] Atherogenic index of plasma(AIP) provides prediction to accelerated development of atherosclerosis in diabetes mellitus patients.[4]Osteoarthritis (OA) is a process of progressive destruction of articular cartilage which makes the OA patients physically inactive and increases the probability to develop (CVD).[16] The probability of OA patients to develop future risk of CVD are more as characterized by elevated antherogenic index, systemic inflammation and oxidative stress and reflect the need of antioxodants supplementation along with drug as choice to reduce CVD risk in OA patients. [17] Although precise etiology of this debilitating disease (OA) is poorly understood, probability of OA patient to develop future CVD risk is more due to involvement of some common CVD risk factors such as high body mass index, aging, genetic factor and nutritional factors. Previous studies have also shown an excess of cardiovascular risks, morbidity and mortality in patients with arthritis compared with the general population[17,18]. In type 2 diabetes ,insulin resistance and obesity together cause to moderate hypertriglyceridemia and also cause reduction of HDL-c ; usually , this dyslipidemia pattern is involved with excessive production of very low density lipoproteins (VLDL). Excessive production of TG- rich lipoprotein . TG levels inversely are associated with HDL-C , and are considered as the carrier protein for cholesterol ester in transferring cholesterol from HDL-C to VLDL. Some study showed lipid profile is abnormal , and is characterized by modestly elevated LDL-C, high triglyceride levels , and is associated with markedly increased cardiovascular risk among diabetic patients. [19] Leptin is a 16 kDa adipocyte-derived hormone. It has recently been recognized as a modulator of inflammatory and immune responses**.** Leptin has a dual role in inflammation. [20] It is a hormone produced by adipose tissue, acting as a sensor of fat mass in part of a negative feedback loop that maintains a set point for body fat stores.. The role of leptin in the pathogenesis of OA via synthesis of IGF-1**.** Leptin over expressed Transcription IGF-1**.** Leptin either alone or with IL-1 significantly reduced collagen release from cartilage by up regulating colagenolytic and colagenolytic activity in chondrocytes , and acts as pro inflammatory adipokine with a catabolic role on cartilage metabolism via the up regulation of proteolysis enrages . this suggests that fat red in arthritic joints is local producer of leptin . [21] Several studies have demonstrated the effects of leptin on articular cartilage .[22,23] And its role in chondrocyte function and skeleton, as well as in inflammatory and degenerative cartilage joint diseases[24] some studies have shown a role of Leptin as pro inflammatory mediators in rheumatoid arthritis. Therefore, approaches that reduce adipose tissue depots may reduce the severity of their resultant pathologies.[25] hormone that has been shown to be involved in pathways influencing the risk of diabetes. Also, it has been suggested that the association between plasma leptin and diabetes may be a manifestation of an underlying leptin resistance mediated by obesity.[26] IGF-1 shows decreases levels in patient groups when compared with control .The decreases were shown to be significant on comparing IGF-1 with control. Insulin like growth factor-1 (IGF-1) is a hormone similar in molecular structure to insulin. It plays an important role in

childhood growth and continues to have anabolic effects in adults. A synthetic analog of IGF-1 is used for the treatment of growth failure.[27] One important key in effectively preventing and treating osteo arthritis, is establishing a healthy balance of IGF-1).[28] (IGF-1), the most abundant growth factor in the bone matrix, regulates bone mass in adulthood.[29] they found that the level of bone marrow IGF-1 was decreased during aging in rats and closely associated with the bone volume whereas serum levels of IGF-1 were relatively steady[30] it was postulated that a primary function of IGF-1 in the bone matrix is to maintain bone mass and skeletal homeostasis during bone remodeling.[31] IGF-1 has been shown to enhance chondrocyte proliferation , proteoglycan and collagen synthesis by chondrocytes in normal cartilage, both *in vivo* and*in vitro* [32] also during cytokine exposure, which drives most predominating catabolic processes in cartilage. Furthermore, IGF-1 inhibits cytokine-stimulated degradation of proteoglycans directly in normal cartilage *in vitro* .[33] Association between serum IGF-1 levels and OA is very important, because this could increase our understanding of the pathogenesis of OA, which subsequently could lead to development of new treatment options.[34] In patients with type 2 diabetes, serum IGF-1levels are dependent on the degree of metabolic control, with near normal IGF-1 levels in well- controlled diabetics, whereas they tend to be decreased in poorly controlled diabetics. It has also been suggested that lowered serum IGF-1concentration predict worsening of insulin-mediated glucose uptake in older people, Although the mechanism for the progressive reduction of circulating serum IGF-1level with ageing in patients with type 2 diabetes has remained obscure, it has been suggested that this decreased level is at least in part a result of decreased IGF-1 production through lowered growth hormone (GH) concentration or uncoupling of the GH induction of IGF-1generation by insulin resistance .[35] IGF-I concentrations may be important in the development of osteoarthritis IGF-I receptors are abundant in bone and cartilage, and in vitro work has suggested an anabolic effect of IGF-I on chondrocytes. [33]

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Table (1): Levels of AIP in different patient groups compared with control

Variables	AIP value			
	DM	OA	DM + OA	Control
Sample No.	20	24	24	20
Mean ± SD	0.27±0.19	0.21±0.17	0.34±0.20	0.19±0.11
Range	0.010-0.600	0.021-0.711	0.030-0.720	0.051-0.376
P against control	0.096	0.028	0.014	
P against total	0.019			

P value < 0.05 represents significant.

Table (2) Levels of Leptin in different patient groups compared with control

Variables	Leptin level (ng/ml)			
	DM	OA	DM + OA	Control
Sample No.	20	24	24	20
Mean ± SD	37.1±23.10	22.4±12.93	37.4±25.64	14.23±7.53
Range	3.9-49.7	7.5-82.0	5.6-86.6	7.5-39.1
P against control	0.092	0.001	0.0001	
P against total	0.0001			

P value < 0.05 represents significant.

Table (3): Levels of IGF-1 in different patient groups compared with control

Variables	IFG-1 level (ng/ml)			
	DM	OA	DM + OA	Control
Sample No.	20	24	24	20
Mean ± SD	127.8±24.07	138.0±31.86	98.71±17.05	298.2±56.14
Range	94-195	95-166	79-141	208-395
P against control	0.0001	0.0001	0.0001	
P against total	0.0001			

P value < 0.05 represents significant.

علاقة هرمون النمو الشبيه بالانسولين واللبتين ومؤشر معصد البلازما في مرضى سوفان المفاصل المصابين وغير المصابين بداء السكري من النوع الثاني

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الخلاصة

هرمون النمو الشبيه بالانسولين هو بروتين ينتج من الكبد كرد فعل لهرمون النمو وهو المفتاح المؤثر في منع وعلاج سوفان المفاصل. وهناك توازن بين هرمون النمو الشبيه بالانسولين واللبتين الذي ينتج من النسيج الدهني ويعمل كمؤشر لكتلة الدهون , واللبتين له دور مهم في تطور مرض سوفان المفاصل . وقد تضمنت هذه الدراسة (88) عينه من النساءكلهم في باية التشخيص تتراوح اعماره مبين(40-60) سنه, تم جمع العينات من مستشفى الكاظمية التعليمي والمركز الوطني لعلاج وبحوث السكري / مستشفى اليرموك وقد قسمت هذه العينات الى اربعة مجاميع وهي مجموعة مرضى السكري20عينة) , (مجموعة مرضى سوفان المفاصل 24 عينه) ,(المجموعة التي تحمل كلا المرضين24 عينه) و مجموعة السيطرة (20) عينه وقد تم اجراء الفحوصات المختبرية التالية : قياس مستوى الكلوكوز بالدم و قياس مستوى الدهون وهرمون النمو الشبيه بالانسولين ومستوى اللبتين وايضا حساب قيم مؤش ر معصد البلازما. في هذه الدراسة لوحظ زيادة معنوية في قيم مؤشر معصد البلازما واللبتين في كافة المجاميع اعلاه بالمقارنة مع مجموعة السيطرة. لكن لوحظ انخفاض معنوي في هرمون النمو الشبيه بالانسولين في نفس المجاميع اعلاه بالمقارنة مع مجموعة السيطرة . ومن الدراسة نستنتج ان لمرضى سوفان المفاصل تاثير مباشر على زيادة اختلال الدهون ومستوى هرمون اللبتين وقيم مؤشر معصد البلازما في مرضى السكري.

الكلمات المفتاحية: سوفان المفاصل, مؤشر معصد البلازما , داء السكري,هرمون النمو الشبيه بالانسولين