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VITAMIN D AND RISK OF OSTEOARTHRITIS AMONG IRAQI PATIENTS WITH AND WITHOUT METABOLIC SYNDROME

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Abstract

Vitamin D is considered as a regulator of mineral metabolism and bone homeostasis, also it has non-skeletal actions. Several studies have proposed that vitamin D3 deficiency has a vital role in the pathogenesis of metabolic syndrome. The study aimed to evaluate the metabolic and hormonal factors in osteoarthritic Iraqi patients with and without metabolic syndrome, also study the effect of gender.

Eighty patients who attended to the National Diabetic Center, Al-Mustansiryah University between February 2019 to August 2019 at the age of (48–60) years were included in this revision. They were equated with 30 healthy subjects as control group. Glycemic tests, serum insulin, lipid profile, serum luteinizing hormone, follicle stimulating hormone, and vitamin D3 were determined in this study.

There was a substantial rise in glycemic tests in osteoarthritic patients with metabolic syndrome and without metabolic syndrome as paralleled the control. Also, there was a substantial rise in serum insulin and homeostasis model assessment for insulin resistance-2 in osteoarthritic patients with metabolic syndrome as paralleled to the controls ($p < 0.5$). Additionally, there was a substantial rise in serum total cholesterol, triacylglycerol, and low density lipoprotein cholesterol in osteoarthritic patients with metabolic syndrome as paralleled to those without metabolic syndrome and controls. A decrease in luteinizing hormone/ follicle stimulating hormone ratio in osteoarthritic patients with metabolic syndrome as paralleled with the two groups was found, but it was not substantial. There was a substantial reduction ($p= 0.01$) in vitamin D3 in osteoarthritic patients with metabolic syndrome as paralleled to controls (11.68±6.43 ng/ml vs. 35.7±1.41 ng/ml). Females patients had the higher percent for hypovitaminosis D (71% with metabolic syndrome and 59% without metabolic syndrome) as compared to males.

The present revision shown elevated levels of fasting serum glucose, insulin, and lipids accompanied with hypovitaminosis D. Hypovitaminosis D is common in osteoarthritic patients with metabolic syndrome which is revealing of irregular bone homeostasis and mineral metabolism among individuals with insulin resistance.

Key words : Osteoarthritis, Metabolic syndrome, Vitamin D, Insulin resistance, Luteinizing hormone/ follicle stimulating hormone ratio.

Introduction

Osteoarthritis (OA) is the most corporate and disabling rheumatic disorder. It is a multifarious disease whose pathogenesis, alters the tissue homeostasis of articular cartilage and subchondral bone, and evaluate the prevalence of damaging courses (Cross *et al.*, 2010). A vital role in the pathophysiology of articular cartilage is shown by cell/extracellular matrix interactions. It has been indicated that pain, gender, age, joint stiffness, joint impairment, decreased the motion, and donate to improved debility (Goldring and Goldring, 2016). Though this defeat of OA, it is generally putative that all the joint structures are exaggerated counting synovium, periarticular ligaments, subchondral bone, meniscus in the knee, and adipose tissue (Mobasheri *et al.*, 2017).

Structural modifications of these joint tissues disturb the biomechanics and homeostasis of the synovial joint,

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foremost to the loss of its functional integrity (June *et al.*, 2016).

Individuals with a raised body mass index (BMI) has a positive relationship between OA and obesity results in overburdening and damage to the joint (Toivanen *et al.*, 2010).

Nevertheless, it is documented that the relationship between OA and obesity might be due to dysregulation of lipid homeostasis. Evolving indication establish that OA was strictly related with obesity and other metabolic associated diseases, such as type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, and metabolic syndrome (MetS) for identifying metabolic OA as a subtype (Bliddal *et al.*, 2014).

Obesity and insulin-resistant situation are moreover related with higher free fatty acids (FFAs), which may affect OA development. Insulin role's on OA stills debated, mainly because the higher levels of insulin are related with insulin resistance (IR), so that it is difficult to differentiate between the effects of insulin linked to IR and the effects per se (Askari *et al.*, 2017). Human chondrocytes express functional insulin receptors that respond to physiologic insulin levels. The insulin receptors appear to be more concern in healthy than in OA chondrocytes, and certain responses are lessened whereas others seem completely triggered. It has been proposed that excess insulin may injury cartilage (Al-Jarallah *et al.*, 2016).

Insufficiency of vitamin D has concerned attention in the progress of numerous diseases. It is well-defined that vitamin D is complicated in bone mineralization (Lim *et al.*, 2017). Though, it has revealed that hypovitaminosis D is responsible for more pathologic disorders than formerly supposed. For example, MetS, IR, and DM. Beyond this, each risk factor is subjected to its own regulation through both genetic and developed factors. This regulation of risk factors can be seen with low serum 25(OH)D levels, which have been related to instabilities in glucose metabolism (Roomi *et al.*, 2015).

The aim of the current revision was to estimate vitamin D and some biochemical and hormonal factors among OA patients with and without MetS, also study the effect of gender.

Materials and Methods

This study was carried through February 2019 to August 2019. Eighty patients who attended to the National Diabetic Center Al-Mustansiryah University; their ages ranged between 48–60 years and equated with 30 healthy individuals as control group. The study was approved by an institutional ethics committee of Iraqi Ministry of Health and National Diabetic Center, Al-Mustansiryah University and the procedures followed were in accordance with the applied guidelines.

Waist circumference (WC) was estimated and BMI was deliberate as weight (Kg) divided by height (m^2). Blood samples were obtained from every person after 10-12 hours fasting. Laboratory assessments were down, which encompassed fasting serum glucose (FSG), glycated hemoglobin (HbA1c), lipid profile comprising: total cholesterol (TC), triacylglycerol (TAG), very low density lipoprotein cholesterol (VLDL), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C). They were measured using a chemical analyzer. Serum insulin, serum luteinizing hormone (LH), follicle stimulating hormone (FSH), and vitamin D3 were estimated using Enzyme Linked Immuno Sorbent Assay (ELISA) kits. Hypovitaminosis D was considered to be < 20 ng/ml (Holick, 2009).

Insulin resistance representing by homeostasis model assessment-2 for insulin resistance (HOMA2-IR) is calculated using Microsoft downloaded freely.

Metabolic Syndrome Criteria

Criteria of MetS is set if three and more of the recognized current features are present according to the (NCEP ATPIII, 2001).

1. Abdominal obesity; WC >102 cm for male; > 88 cm for female.
2. Indicators FSG $\geq$110 mg/dl.
3. Level of TAG $\geq$150 mg/dl.
4. Level of HDL-C < 40 mg/dl for male, < 50 mg/dl for female.
5. Blood pressure (BP) $\geq$130/85 mm Hg.

Statistical Analysis

The results were done using means±SD; t-test was used to estimate the variances between different sets. A p value < 0.05 is designate as significant.

Results

Anthropometric and clinical parameters of the study groups are shown in table 1. The measurement of adipose tissue distribution (WC and BMI) displayed that the OA patients with MetS had abdominal obesity. A substantial increase (p= 0.01) in systolic- and diastolic- BP (SBP and DBP) was detected in OA patients with MetS as paralleled to the controls.

A substantial increase (p < 0.05) in FSG and HbA1c

was found in OA patients with and without MetS as paralleled to the control. Also, there was a substantial rise (p= 0.01) in serum insulin and HOMA2-IR in OA patients with MetS as paralleled to the controls. Furthermore, a substantial rise (p= 0.01) was detected in serum lipid profile, except HDL-C which was considerably reduced in OA with MetS as paralleled to those without MetS and controls. A reduction in LH/FSH ratio was found in OA with MetS as paralleled with the two groups, but it was not substantial, (Table 2).

Table 3 shows serum vitamin D3 levels in OA patients and controls. There was a substantial reduction (p= 0.01) in vitamin D3 in OA with MetS as paralleled to controls. Distribution of serum vitamin D3 sufficiency in OA patients are shown in Fig. (1 and 2). Hypovitaminosis D is common in females patients with and without MetS as compared to males.

Table 1: Anthropometric and clinical parameters in patients and controls.

Parameters	Means ± SD			*p* value
	OA with MetS(n= 35)	OA without MetS (n= 45)	Control (n= 30)	
Sex (M/F)	(14/21)	(24/21)	(15/15)	-
Age (years)	56.16±2.91[a]	54.71±2.16[a]	49.4±2.13[a]	0.06
WC (cm)	111.11±6.96[a]	97.41±6.87[b]	87.33±7.28[b]	0.01
BMI (Kg/m^2)	34.70±3.71[a]	25.66±2.73[b]	21.2±2.78[b]	0.01
SBP (mmHg)	145.0±10.0[a]	135.0±5.01[b]	120.0±10.0[b]	0.01
DBP (mmHg)	90.0±5.01[a]	85.0±5.20[a]	68.0±9.0[b]	0.01

Similar letters designate that there are no substantial variances and different letters designate substantial variances, p < 0.05: significant.

Table 2: Metabolic and hormonal factors in patients and controls.

Parameters	Means ± SD			*p* value
	OA with MetS(n= 35)	OA without MetS (n= 45)	Control (n= 30)	
FSG (mg/dl)	138.05±15.45[a]	118.87±14.98[b]	82.76±8.92[c]	0.01
HbA1c (%)	11.28±2.72[a]	7.46±2.39[ab]	4.05±0.53[b]	0.01
Insulin (µU/ml)	26.24 ±5.73[a]	21.30±6.43[a]	10.96±5.9[b]	0.06
HOMA2-IR	8.28±2.73[a]	5.14±3.47[b]	3.41±1.41[b]	0.06
TC (mg/dl)	274.84±17.42[a]	218.93±13.21[b]	135.23±14.7[c]	0.01
TAG (mg/dl)	298.45±14.44[a]	222.25±16.91[b]	93.13±19.72[c]	0.01
HDL-C (mg/dl)	32.62±15.35[a]	45.12±6.16[b]	52.46±5.56[c]	0.01
LDL-C (mg/dl)	182.53±13.06[a]	129.36±16.29[b]	64.14±11.60c	0.01
LH/FSH ratio	0.94±0.28[a]	1.12±0.67[a]	2.43±0.88[a]	0.08

Similar letters designate that there are no substantial variances and different letters designate substantial variances, p < 0.05: significant.

Table 3: Serum vitamin D3 levels in patients and controls.

Parameters	Means ± SD			*p* value
	OA with MetS(n= 35)	OA without MetS (n= 45)	Control (n= 30)	
Vitamin D3 (ng/ml)	11.68±6.43[a]	19.11±8.42[a]	35.7±1.41[c]	0.01

Similar letters designate that there are no substantial variances and different letters designate substantial variances, p < 0.05: significant.

Discussion

Osteoarthritis, the most predominant form of arthritis, causes disability of the joints and pain. There are numerous factors, which are usually deliberated vital causative reasons to OA progress such as aging, mechanical stress, and metabolic mediators (Sellam and Berenbaum, 2013).

In this study, abdominal obesity representing by WC and BMI, also high BP were initiate to be connected with OA in the current study which can simply clarify the relations between those constituents and OA. These outcomes support formerly obtainable indication of a direct essential role between BMI and OA (Zengini *et al.*, 2018).

Lifestyle-associated metabolic disorders include disorders of glucose and lipid metabolism such as hyperglycemia, hypercholesterolemia, and dyslipidemia. It has been proposed that hyperglycemia or diabetes status is related with an increased risk of OA (Veronese *et al.*, 2019).

Metabolic syndrome has a pathogenic influence on OA through two principle pathways: 1) Hyperglycemia, which improves overproduction of pro-inflammatory cytokines, and advanced glycation end products in joint tissues; and 2) IR, which might has a vital role locally and through the systemic low-rate inflammatory state (Courties and Sellam, 2016). Under normal situations, insulin suppresses adipose tissue lipolysis; though, in the situation of IR, insulin is incapable to correctly suppress lipolysis, resulting in moderately more FFA being liberated into the plasma, which may modulate OA progression (Courties *et al.*, 2015).

In this study, there was a substantial rise in serum insulin in OA with MetS group as paralleled to those without MetS and controls.

The present results propose the existence of IR in OA patients with MetS, which is reflecting by high HOMA-IR value. This disorder is one of the leading pathogenetic mechanisms of MetS which progressively donate to the morbidity and mortality of the affluent individuals.

The main clinical appearance of accumulative IR is dysglycemia. Consequently, the assessment of IR via HOMA-IR is a main index for the main prevention of T2DM and is

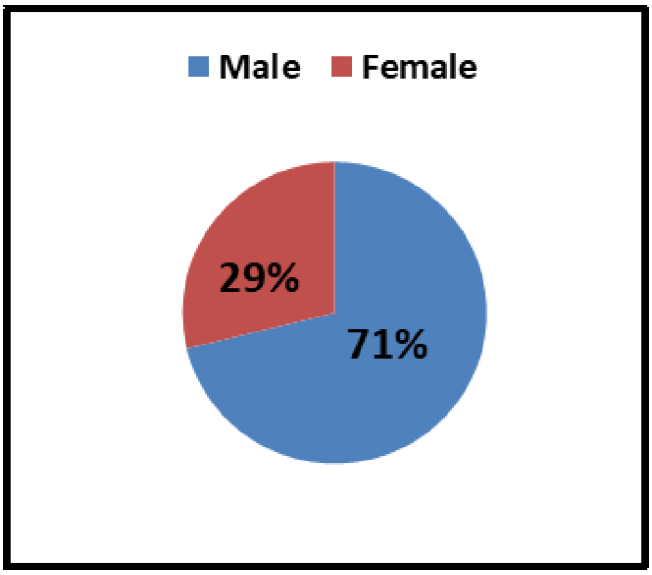

Fig. 1: Distribution of serum vitamin D3 sufficiency in OA patients with MetS.

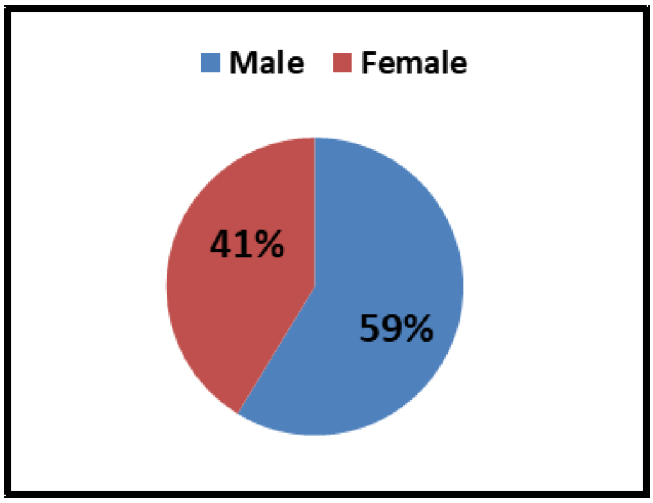

Fig. 2: Distribution of serum vitamin D3 sufficiency in OA patients without MetS.

establish in strategies for the screening of high-risk groups. These outcomes are parallel to those stated in previous study (Tang *et al.*, 2015).

Current lines of researches have demonstrated that high blood glucose foremost to reduced osteoblast-mediated bone formation, accelerated bone resorption, and reduced bone quality (Al-Daghri *et al.*, 2017).

Two studies reported the risk of fractures related with lipid levels (Tatsuno et al, 2013, Ahmed, 2017). It has shown that elevated LDL-C and low levels of HDL-C are related with low bone mineral density. In this study, all MetS subjects had dyslipidemia.

Dysregulation of LH and FSH secretion is connected to irregularities at the hormones axis, metabolic conflicts, and infertility. It was experimented that a lower ratio of LH/FSH is related with obesity, IR, and improved risk of T2DM. It has been suggested that FSH level is greatest strongly related with IR in association with LH levels and LH/FSH ratio (Stefanska *et al.*, 2019). The nongonadal function of FSH is probable due to the existence of extragonadal FSH receptors in adipose tissue, blood vessels, bones, and hepatocytes (Kumar, 2018).

Additionally, the consequences of this revision also found that serum levels of LH and FSH in MetS subjects were higher than those in the control group of same age, indicating that FSH could be related to the loss of chondrocytes, which was consistent with some previous study (Ahmed and Tahir, 2017).

Vitamin D3 employs an effect on numerous physiological functions, such as immune system response, reproduction, sex hormone synthesis, normalization of the menstrual cycle, and metabolic pathways (Guilherme *et al.*, 2017).

It has been suggested that vitamin D3 insufficiency involves a higher incidence of cardiovascular (CV), autoimmune, and cancer diseases (Dorsch *et al.*, 2014). Vitamin D3 synthesis in human is one influence that regulates the amount of cholecalciferol obtainable to healthy persons. Several influences, comprising air pollution, lifestyle, and the dose of ultraviolet (UV) radiation received affect this synthesis (Schlogl and Holick, 2014).

The present study supposed that MetS components, such as hyperglycemia, high levels of TAG, and hypertension, were contrariwise related with serum concentration of vitamin D3. In previous study, vitamin D3 deficiency was connected with a risk for MetS, hypertension, and ischemic heart disease (Al-Dabhani *et al.*, 2017).

Numerous mechanisms have been suggested to clarify the association between vitamin D3 and future risk of MetS. As vitamin D3 is fat soluble and might be kept in adipose tissue, vitamin D3 levels can be diminished in the blood of obese subjects (Naidu *et al.*, 2018). Vitamin D3 has moreover been revealed to inhibit the release of cytokines from the immune cell. Subsequently, the negative regulatory impact of vitamin D3 on renin activity (Li *et al.*, 2002). The relationship between vitamin D3 and CV risk includes the influence of vitamin D on improving insulin sensitivity by directly act-ing on cardiac tissue as a response to injury and vascular compliance (Sugden *et al.*, 2008).

Current revision inveterate the relationship between

age and serum vitamin D3. Means of age occur between 48 and 60 years. This stage of life especially in women is categorized by the decreased production of hormones in the ovaries. Lower levels of estrogen donate to lower vitamin D-binding protein, and accordingly lower 25(OH)D levels in blood. This deficit of 25(OH)D can negatively disturb biological functions, ensuing in several disorders particularly in women. As stated by previous study, women at this age more often undergo laboratory analysis to determine 25(OH)D levels. It has found that postmenopausal women identified with MetS had lower levels of this vitamin than their premenopausal counterparts. In the present investigation, hypovitaminosis D3 is common in females patients over half of OA patients with and without MetS as compared to males, which is in agreement with the study of Chon *et al.*, 2014.

Conclusions

The present revision shown elevated levels of FSG, insulin, and lipids accompanied with hypovitaminosis D. Hypovitaminosis D is common in OA patients with MetS which is revealing of irregular bone homeostasis and mineral metabolism among individuals with IR.

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