ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.pharmascope.org/ijrps

Relationship between Metabolic Syndrome and Diffuse Idiopathic Skeletal Hyperostosis in Sample of Iraqi Patients

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Article History:

Received on: 19 Apr 2020
Revised on: 10 Jun 2020
Accepted on: 15 Jun 2020

Keywords:

back pain,
diffuse idiopathic skeletal hyperostosis,
metabolic syndrome

ABSTRACT

Diffuse idiopathic skeletal hyperostosis is a non-inflammatory disease characterised by calcification of soft tissues, mainly ligaments and enthuses, as well as by ossification of the anterior longitudinal ligament. To assess the relationship between Metabolic Syndrome and Diffuse Idiopathic Skeletal Hyperostosis among a sample of middle and old age Iraqis.A cross-sectional study was conducted from October 2018 to May 2019 at the Rheumatology Unit of Baghdad Teaching Hospital, Iraq and Basra Teaching Hospital, Iraq. A total of 282 patients were included in the study. Data were gathered using a pre-constructed data collection sheet for patients that evaluate: age, gender, occupation, education, smoking, weight, height, waist circumference, and body mass index were calculated. Clinical data about back pain, limitation in movement or any neurological symptoms were identified, serum lipid profiles (serum triglycerides, serum high-density lipoprotein), fasting blood sugar, haemoglobin A1c and serum uric acid were obtained. Diffuse Idiopathic Skeletal Hyperostosis was reported in 18 (6.4%) patients. High waist circumference was reported in 175 patients, high triglycerides found in 208 patients, while low HDL found in 162 patients. We reported 147 patients who had elevated blood pressure and 106 patients with elevated blood glucose. Diffuse Idiopathic Skeletal Hyperostosis was significantly more frequent in patients with metabolic syndrome compared to those with no metabolic syndrome, (9.2%) vs (3.1%). There is a significant association between diffuse idiopathic skeletal hyperostosis and metabolic syndrome among a sample of middle and old age Iraqi people.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i3.2541

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INTRODUCTION

Diffuse idiopathic skeletal hyperostosis (DISH) is a non- inflammatory disease characterised by calcification and ossification of the spinal ligaments and regions where tendons and ligaments attach to bone (Hannallah *et al.*, 2007). This condition is characterised by flowing ossifications on the anterolateral side of at least four contiguous vertebrae. Mainly in the thoracic spine with relative preservation of the intervertebral disc (IVD), the new bone formation is most frequently observed on the right

side of the thoracic spine. Aortic pulsations have been suggested to prevent ossification on the left side (Kim *et al.*, 2018).

Diffuse Idiopathic Skeletal Hyperostosis (DISH) has been linked to metabolic and constitutional factors such as obesity, high waist circumference, hypertension, type 2 Diabetes mellitus, hyperinsulinemia, dyslipidemia, elevated growth-promoting peptides, hyperuricemia. The association of DISH with excess body weight has been well known since the early descriptions by Forestier and other investigators (Pariente-Rodrigo *et al.*, 2017).

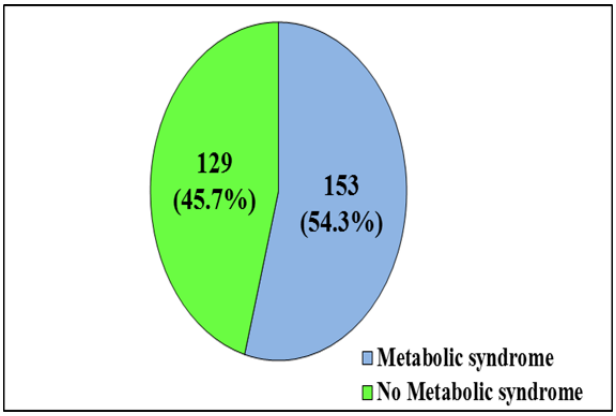

Figure 1: Distribution of the studied group according to presence of DISH (N = 282)

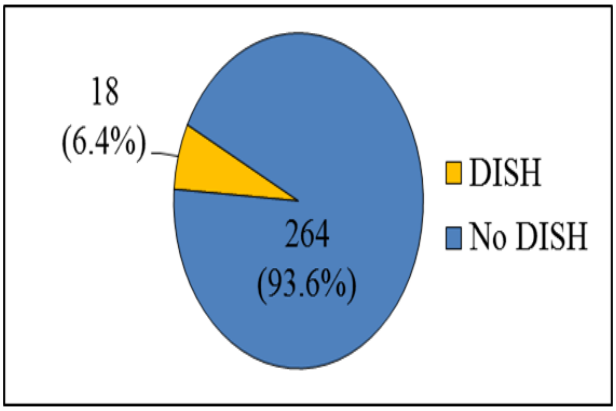

Figure 2: Distribution of metabolic syndrome among the studied group

It has been assumed that the high serum insulin levels in type 2 D.M. may contribute to the formation of DISH (Mader *et al.*, 2017).

Relationship between the metabolic syndrome and diffuse idiopathic skeletal hyperostosis: Both metabolic syndrome (M.S.) and DISH sharply increase with old age group. Previous research confirmed the association of metabolic factors as risk factors for DISH (Pillai and Littlejohn, 2014). Metabolic abnormalities have been reported to be associated with DISH, including obesity, high waist circumference, hypertension, diabetes mellitus, hyperinsulinemia, and dyslipidemia (Srikanthan *et al.*, 2016). The metabolic factors present in patients with DISH, such as insulin, likely interact with key candidate cellular targets linking to new bone formation, these include chondrocytes and periosteal mesenchymal cells within the enthesis (Han and Lean, 2016).

Patients And Methods

Study design and setting

A cross-sectional study was conducted at the Rheumatologic unit in Baghdad Teaching Hospital, and Al Sader Teaching Hospital, during the period from October 2018 to May 2019.

Study population

A total of 282 patients were involved in the study. Women were 208 (73.8%).

Inclusion criteria

All patients aged ≥50 years who had back pain and/ or limit the range of motion of the spine were included.

Exclusion criteria

Patients with one or more of the following criteria were excluded from the study

1. Congenital diseases of the lumbar spine.
2. Spondylolisthesis and spinal deformities.
3. Previous surgery of the lumbar spine.
4. Retinoid- Degenerative Related Changes.
5. Inflammatory diseases of the spine (seronegative spondyloarthropathy).
6. Malignancy.

Data collection

Data were collected using a data collection sheet containing questionnaires for the patients. The questionnaires included the first part for the general demographic data: name, age, gender, height, weight, body mass index (measured for all patients according to the equation BMI=weight/ height^2), waist circumference, residence (urban, rural), employment (employed, unemployed), marital status (unmarried, married, widow, and divorced) and smoking status (current smoker, ex-smoker, never). The second part for clinical and laboratory data about back pain (cervical, dorsal, lumbar), limitation of movement, dysphagia, neurological symptoms (numbness, paresthesia, loss of sphincter, saddle anaesthesia, paralysis), X-ray finding, Hb A1C, blood pressure, serum triglyceride, serum uric acid, serum high-density lipoprotein (HDL), serum fasting blood sugar were measured.

Table 1: Demographic andmedical characteristics of the studied group (N = 282)

Variable		No.	%
Mean age (SD*) = 52.7 (8.1) year			
Sex	Man	74	26.2
	Woman	208	73.8
Education	Illiterate	36	12.8
	Primary	84	29.8
	Secondary	111	39.4
	Collage	51	18.1
Occupation	Housewife	171	60.6
	Retired	34	12.1
	Private worker	44	15.6
	Employee	33	11.7
Smoking	Smoker	44	15.6
	Non-smoker	238	84.4
HT	Yes	46	16.3
	No	136	83.7
Received treatment for HT	Yes	41	89.1
	No	5	10.9
DM	Yes	36	12.8
	No	246	87.2
Received treatment for DM	OHD	29	80.6
	Insulin	7	19.4

DM, diabetes mellitus, HT; hypertension, OHD; oral hypoglycemic drug, SD: standard deviation

Table 2: Mean and standarddeviation values of Metabolic Syndrome components and HbA1C of the studied group (N = 282).

Parameter		Mean	SD
Blood glucose (mg /dL)		95.6	16.3
HbA1C (%)		5.0	1.3
Serum triglycerides (mg /dL)		180.2	33.2
HDL(mg /dL)	Male	43.6	14.6
	Female	48.7	15.9
Waist circumference (cm)	Male	98.4	13.8
	Female	93.8	12.7
SBP (mmHg)		133.6	6.1
DBP (mmHg)		84.7	5.6

DBP; diastolic blood pressure, HbA1C; glycosylated hemoglobin, HDL; high density lipoprotein.

Clinical methodology

Standing height was measured in centimetres using a stadiometer, and body weight was measured in kilograms (kg) with light clothes and without shoes using a weighing scale. Waist circumference was measured in centimetres at the end of the normal expiration with tap placed horizontally midway between the subcostal margin and the iliac crest in a standing position (to assess central obesity (which defined as >102 cm in men and >88 cm in women according to National Cholesterol Education Program ATP-Third criteria for M.S.). Bodyweight classified according to body mass index (BMI); normal (BMI 18.5-24.9 kg/m2), underweight (BMI <18.5 kg/m2), overweight (BMI 25-29.9 kg/m2), obese (BMI 30-40 kg/m2), and morbidly obese (BMI >40 kg/m2). Blood pressure measurement was done by using a mercury sphygmomanometer in either arm when the patient relaxed in sitting position and his feet on the ground, and the arm at the level of the

Table 3: Levels of Metabolic syndrome components of the studied group (N =282)

Component of Metabolic syndrome		No.	%
Increased waist circumference	Yes	175	62.1
	No	107	37.9
Elevated triglycerides	Yes	208	73.8
	No	74	26.2
Reduced HDL	Yes	162	57.4
	No	120	42.6
Elevated blood pressure	Yes	141	50.0
	No	141	50.0
Elevated blood glucose	Yes	39	13.8
	No	243	86.2

Table 4: The frequency of Metabolic Syndrome components in the DISH.

Parameter	Percentage of DISH	No. of patients	Men	Women
Increase waist circumference	83.3	15	6	9
Elevated triglycerides	66.7	12	5	7
Reduced HDL	44.4	8	3	5
Elevated blood pressure	61.1	11	6	5
Elevated blood glucose	27.8	5	2	3

Table 5: Cross-tabulation for the relationship between metabolic syndrome and DISH among the studied group

Metabolic syndrome	DISH				Total	
	Yes		No.			
	No.	%	No.	%	No.	%
Yes	14	9.2	139	90.8	153	54.3
No	4	3.1	125	96.9	129	45.7
Total	18	6.4	264	93.6	282	100.0

Odds' ratio (OR) = 3.15
95% CI of OR : [1.10 – 9.81]
P. value = 0.038 (significant)
CI: confidence interval

heart. A full history was taken about duration and type of back pain, and a medical examination was performed for all patients.

Laboratory methodology

Blood samples were collected from all individuals under aseptic venipuncture for measuring HbA1C, triglyceride, HDL, fasting blood sugar used an instrument SIEMENS-RXL-MAX-224514-AX made in the USA at Bagdad Teaching Hospital, and ADAVMS-A1C/HA-8160 made in Japan ARKRAY 2013 at Basra Teaching Hospital.

Radiological Methodology

Plain X-ray was performed to all patients in the form of lateral and anteroposterior views of dorso lumbar spine or cervicodorsal used Digital AGFA/ DX-D400 made in Belgium 2013 in Bagdad Teaching Hospital, and Digital KL/W-500 made in Japan 2014 in Basra Teaching Hospital.

Patients Consent and Ethical approval

Table 6: Results of Binary logistic regression analysis for the covariates of DISH

Variables in tl	B	SE	OR	95% C.I. for OR		P. value
				Lower	Upper	
Age	0.11	0.04	1.12	0.97	1.89	0.27
Sex	0.17	0.01	1.19	0.26	3.15	0.87
Education	0.32	0.37	1.38	0.20	2.33	0.37
Occupation	0.17	0.14	1.19	0.91	1.56	0.21
Smoking	0.72	0.67	2.05	0.55	7.63	0.29
Hypertension	0.28	1.91	1.32	0.27	3.18	0.88
DM	0.65	0.14	1.92	0.12	8.32	0.39
Metabolic syndrome	1.29	0.60	3.64	1.13	11.72	0.030

OR; Odds ratio, P; probability value, SE; Standard error.

Free verbal consent was taken from individuals for involvement in the study, and Ethical approval was received from the Department of Medicine, College of Medicine, University of Baghdad.

Study protocol

Diagnosis of DISH based on reliant on Resnick and Niwayama's (1976) highly specific criteria. Diagnostic criteria of M.S. was considered according to the NCEP ATP III criteria (Alberti, 2005).

After approval of the presence or absence of DISH and M.S., the study participants categorised into four subgroups according to their findings; DISH with M.S., DISH without M.S., no DISH with M.S., no DISH without M.S. and these are the only possible combinations.

Statistical analysis

Data of patients were checked for any errors or inconsistencies then transferred into a computerised statistical software; statistical package for social sciences (SPSS) version 25 was used in all statistical analyses and procedures. Descriptive statistics were presented as mean ± standard deviation (S.D.), frequencies (number of cases) and proportions (percentages). Chi-square (X 2) was used to find the significance of the relationship between metabolic syndrome and DISH. Odds' ratio was calculated, which is an estimator of the risk of occurrence of an event in a group compared to another group. Value of OR more than once indicated that the factor under study (M.S.) is a risk factor to the outcome (DISH), and the result is more likely to occur among the exposed group. Binary logistic regression was performed to control the possible confounding effect of other variables (age, gender, occupation, education, smoking, hypertension, and D.M.). On the correlation between M.S. and DISH. The level of significance (P. value) of < 0.05 considered as significant. Finally, the results were presented in tables and or figures with an explanation for each table.

RESULTS AND DISCUSSION

There were 282 patients enrolled in this study with a mean age of 52.7 ± 8.1 years. Women were dominant, represented 73.8% (Table 1).

The medical history of the studied group revealed that 46 (16.3%) patients were hypertensive; among them, 41 (89.1%) were receiving antihypertensive treatment. On the other hand, 36 (12.8%) patients had diabetes, and 29 (80.6%) of them were on oral hypoglycemic drugs (OHD) and 7 (19.4%) patients on other modes of treatment including insulin. Table 1.

DISH was reported in 18/282 patients (represented as 6.4%), and 14 of them were men (Figure 1)

Tables 2 and 3 summarise the mean values and standard deviations of the variables that considered as components of Metabolic Syndrome in addition to the HbA1c.

Patients with three or more criteria (i.e. with metabolic syndrome) were 153 represented (54.3%) of the studied group (Figure 2).

Table 4 below shows the frequency of component of M.S. among patients with DISH, and we found that percentage of patients with DISH and H.T. were 61.1% patients. From patients with DISH, 27.8% had elevated fasting blood sugar, 83.3 % had increased waist circumference, 66.7 % had increased serum triglycerides, and 44.4% had reduced HDL level.

To assess the relationship between Metabolic Syndrome and DISH among the studied group, cross-tabulation was performed for DISH as a disease

against M.S. as the risk factor, (Table 5), results of this analysis revealed that DISH was significantly more frequent in patients with metabolic syndrome compared to those with no metabolic syndrome, (9.2%) vs (3.1%), respectively, (P. value = 0.038). Moreover, odds' ratio was calculated, and it was 3.15, which indicated that patients with M.S. were about three folds more likely to have DISH compared to healthy population (without M.S.).

Further analysis was performed using the binary logistic regression to control the possible confounding effect of other variables that may interfere with the correlation between DISH and M.S. Results of this analysis is shown in (Table 6) where the relationship between metabolic syndrome and presence of DISH still significant (P. value = 0.030) after adjustment for other variables (age, gender, occupation, education, smoking, hypertension and D.M.).

There are few published data available concerning the association between Diffuse Idiopathic Skeletal Hyperostosis and MS. Up to the best of our knowledge there was no local or regional study discussed the relationship between the DISH and M.S. In this study the mean age was (52.7 $\pm$ 8.1) years, which agree with Sruti P.et al (Australia) (Pillai and Littlejohn, 2014) who reported [mean age $\pm$ standard deviation = 50 $\pm$ 33.8], that confirmed that DISH is more common at age >50 years. These results differed from the cohort study done by Mader I. et al. (Israel) (Mader and Lavi, 2009) who identified 18 (12.8%) patients were diagnosed before the age of 50 years. This discrepancy explains that they used long cohort study comparing group A (18 patients with DISH diagnosed before the age of 50 years), group B (20 patients of similar age with osteoarthritis), and group C (24 patients with DISH diagnosed after the age of 60 years). In the current study, 18/ 282 patients had DISH, which represented 6.4% of the studied group. This finding was similar to the results of Sruti P. et al. (Pillai and Littlejohn, 2014) who reported 19 (7%) cases of DISH in 265 patients. We reported 14 cases of DISH and have MS, 4 cases of DISH without M.S., which was statistically significant and was in agreement with Mader I. et al. (Israel) (Mader and Lavi, 2009) and Sruti P. et al. (Pillai and Littlejohn, 2014), and this suggests that DISH was more common in M.S. than the general population. In light of our findings, we found 11 men had DISH, and seven women also had DISH which means that DISH more common in men which agree with Hiromitsu T.et al (Toyoda *et al.*, 2017) in which the men were predominant and percentage of DISH in men and women above 50 years was 35% vs 15% respectively. Increased waist circumference (for man $\geq$ 40 inches, for woman $\geq$ 35 inches) was reported in 62.1% patients which similar to the finding of Mansour A. et al. (Iraq) (Mansour *et al.*, 2007). Elevated triglycerides were reported in 73.8% patients, while reduced HDL (< 40 mg/ dl in man and < 50 mg/dl in the women) was found in 57.4% and that agree with Sruti P. et al. (Pillai and Littlejohn, 2014). I n the current study we found elevated blood pressure in 52.1% patients and high fasting blood glucose was found in 37.6% of patients, and these results were closest to Sruti P.et al (Pillai and Littlejohn, 2014). In light of our findings, we found 54.3% of individuals of the studied group had M.S., which is closest to Al-Thani M. et al. study (Al-Thani *et al.*, 2016). But our results disagree with Ismael S.et al (Ismael *et al.*, 2016) in Iraq which showed the prevalence of metabolic syndrome was 30.6%. It was higher in women (45.5%) than men (16.3%). This discrepancy because of the difference in the mean age ($\pm$ S.D.) and also may be due to differences in the prevalence of obesity, sedentary lifestyle, family history of specific cardiovascular, D.M., hyperlipidemia, hypertension and physical inactivity which is used as risk factors for M.S. in this study. In this study we showed that 83.3% of patients with DISH had increase waist circumference, 66.7 % had increase serum triglycerides, 44.4 % had reduced serum HDL, 61.1% had elevated blood pressure, and 27.8% had elevated serum fasting blood sugar. These results were statistically significant and similar to Sruti P.et al (Pillai and Littlejohn, 2014) which showed a strong association between DISH and insulin intolerance and other components of M.S.

The Relationship between DISH and M.S. still significant after adjustment for other variables (age, gender, occupation, education, smoking, hypertension and D.M.) using the binary logistic regression to control the possible confounding effect and found no impact of these variable. There was disagreement with Abdul Rudha S. et al. (Iraq) (Abdulsada *et al.*, 2017) study which showed that epidemiological factors (age, sex, occupation, and family history of diabetes) were strongly related to M.S. These differences arose because Abdul-rudha S. et al. used two groups as control and used other variables like young age women with beta-thalassemia disorder. Also, our results disagree with Mader I. et al. (Mader and Lavi, 2009) in considering age, gender and occupation as essential risk factors affect the relationship between DISH and M.S. and that are because in our current study we used a cross-sectional survey while Mader I. et al. used a cohort study design and long length of follow up.

We found that DISH was significantly more frequent in patients with metabolic syndrome com-

pared to those with no metabolic syndrome, (9.2%) vs (3.1%), respectively. Patients with M.S. were about three folds more likely to have DISH compared to healthy population (without M.S.) this agreed with other studies as Mader I. et al. (Mader and Lavi, 2009) and Sruti P.et al. (Pillai and Littlejohn, 2014).

CONCLUSIONS

Diffuse Idiopathic Skeletal Hyperostosis was significantly more frequent in individuals with M.S. compared to those with no M.S. Patients with DISH have a high rate of central obesity, dyslipidemia and insulin intolerance. We also demonstrated the need for further studies to a better-defined background of M.S. factors that promote the new bone formation, which characterises DISH.

ACKNOWLEDGEMENT

Authors wish to thank all patients who kindly participated in the study. Besides, we appreciate the medical staff in Baghdad Medical city and Al Sader Teaching Hospital for their great deal of helps they provided.

Funding

This research received no grant from any funding agency in public, commercial or not-for-profit sectors.

Conflict of interest

The authors declare that there is no conflict of interest.

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