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Original Article

Effect of metabolic syndrome on union rate of fractures

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Abstract

Introduction: Increase of inflammatory markers is the most important problem in metabolic syndrome. C-reactive protein (CRP) is an undefined component of metabolic syndrome, and its increase is regarded as a dependent risk factor to cause complications. Considering the high prevalence of metabolic syndrome and relation of these diseases with different inflammatory factors, it is assumed this syndrome may affect fractured bone healing process. Therefore, the hypothesis is studied for the first time in analytical study.

Methods: This analytical and descriptive study was conducted on 48 patients with isolated fracture of tibia and femur shafts resulting from low-energy trauma. In this study, 24 patients with metabolic syndrome criteria matched considering age, gender, type of fracture, and treatment method were compared with 24 metabolically health persons. Level of high sensitivity hs-CRP (High-sensitivity CRP) inflammatory marker was also determined in these patients. Union rate and duration as well as a relation between inflammatory marker and union rate were studied.

Results: Prevalence of nonunion and delayed union were seen in 8 (33.3%) and 3 (12.5%) patients with metabolic syndrome, respectively. However, there was not any case of nonunion in the metabolically health group. There was a statistically significant difference between these groups. According to the regression model, hs-CRP level played a significant role with sensitivity of 95% considering nonunion prediction [P = 0.001, OR (Odds ratio) = 2.3 and CI (Confidence interval) 95% = 1.4-3.8] while other factors of metabolic syndrome did not play any important role in nonunion prediction.

Conclusion: Prevalence of nonunion in patients with metabolic syndrome suffering from a fracture and undergoing orthopedic surgery is higher than healthy people. It seems that the increase of inflammatory markers plays an important role in causing and predicting of nonunion in these patients.

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Introduction

Metabolic syndrome is a known risk factor of cardiovascular diseases. This syndrome includes increase of abdominal fat, hypertension, increase of glucose and triglycerides and decrease of high-density lipoprotein (HDL)-cholesterol level.[1] Metabolic syndrome is defined as a set of metabolic disorders, which their concurrent occurrence in every person is more possible than their single occurrence. In spite of medical advancements, prevalence of this syndrome is increased. It has a close relation with progression of cardiovascular diseases

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and diabetes type II.[2]

Prevalence rate of metabolic syndrome in asymptomatic persons has been reported 22.8 and 40.0% respectively for American adults[3] and older-than-60 years persons.[4] Prevalence of metabolic syndrome is 12-21% for Chinese older-than-20 years persons.[5] According to the study conducted by Azizi et al. in Tehran, Iran, older than 20 years persons demonstrated 33.7% of prevalence of metabolic syndrome. The older the persons of both genders, the higher the prevalence of metabolic syndrome.[6] According to similar results obtained by Zabetian et al. prevalence of metabolic syndrome was reported 32.1% in Iran.[7]

On the other hand, there is a close relation between metabolic syndrome and increase of inflammatory markers in the patients. According to the findings, high inflammatory markers and C-reactive protein (CRP) has a direct relation with high risk of fractures. Some studies referred to the relation found between CRP and decrease of bone mineral density.[8]

Nonunion is an important problem encountered by orthopedic surgeons. It is detected relying on the lack of union symptoms in two radiographic plans and clinical evidences during a specific period.[9] There is different healing time considering the involved bones. Nonunion may be attributed to injury velocity, intensity of soft tissue damage, type of fracture (open or closed), crushed bone, and bone loss. There are other factors involved in the union process including treatment method, infection and associated diseases.[10]

Metabolic and endocrine diseases, e.g. thyroid, parathyroid and osteomalacia diseases, estrogen deficiency, Cushing diseases, Paget's diseases, and Malabsorption syndrome, are regarded as important factors in delay of bone formation and fracture healing process.[11] The present study aims at evaluating effects of metabolic syndrome as an important and prevalent metabolic disease on fractures healing process and determining the relation between union rate and inflammatory markers, which are increasing in this syndrome. This is the first study in this regard, and there are only some studies about role of metabolic syndrome in increasing fractures risk, especially vertebra fractures.

Methods

This analytical and descriptive study was conducted on 48 patients with fracture of tibia and femur shafts referring to orthopedic trauma center of Tabriz University of Medical Sciences, Iran, from 2010-2013. The traumatic patients suffered from isolated and non-comminuted fractures in their tibia and femur shafts due to low energy trauma resulting from falling. The patients were matched considering type of fracture, surgical treatment, age, and gender. In this study, 24 patients with metabolic syndrome criteria were placed in one group and there were other 24 patients with factures, but without any other disease or problem in the control group. Metabolic syndrome is detected based on the latest criteria of National Cholesterol Education Program Adult Treatment Panel III or suffering from one of three cases of abdominal fat (> 102 cm for men and > 88 cm for women), HDL < 40 mg/dl for men and < 50 mg/dl for women, hypertriglyceridemia > 150 mg/dl, hypertension (blood pressure > 130/85 mmHg), or glucose disorder in the form of fast blood glucose > 100 mg/dl. The groups were compared considering the understudy variables.

Patients with open fractures, crushed fractures, soft tissue damage, any systemic diseases as well as patients with history of smoking, consumption of alcohol and mineral supplements during last 6 months and older-than-50 years patients were exclude from the study. To attend the study, informed letter of satisfaction was received from the patients and the study was confirmed by Ethics Committee of the Tabriz University of Medical Sciences. Considering similar method and their indications, the patients underwent orthopedic surgery including open reduction and internal fixation using intramedullary nails. Before

surgery, antibiotic prophylaxis was done for all patients through intravascular injection of cefazolin which continued at least for 24 h after surgery.

The patients were continuously followed up for 9 months (biweekly during the 1st month and every month for 8 months) considering union based on radiographic evidences and clinical examinations. The patients of both groups demonstrated the same rehabilitation during the 1st week, and relative weight tolerance was seen in lower limb fractures after 2 days. Radiographic evidences confirmed union if it is seen at least in two plans and clinical examinations. Nonunion cases were studied considering infection as the first step such that white blood cell, erythrocyte sedimentation rate, and CRP were checked and the patients were excluded from the study in case of observing any signs of infection.

A volume of 20 ml venous blood sample was taken from every participant after an overnight fast (> 8h) by a certified phlebotomist using standard laboratory techniques. Blood samples were collected into a Vacutainer® serum separator tube (SST) for analysis of lipids and glucose. After complete coagulation (30-45 min), the SST was centrifuged at 2500 RPM (Revolutions per minute) for 30 min. The serum was transferred from the spun SST into three labeled plastic tubes: the first tube was used for glucose analysis, the second for lipid panel, and the third one was stored at -70 °C to be used later for high sensitivity hs-CRP (High-sensitivity CRP). hs-CRP was measured using an immunoturbidimetric assay system while other laboratory metabolic components measured by Hitachi 911 instrument produced by Japan. The waist circumference was measured midway between the lowest lib and iliac crest with a flexible anthropometric tape.

The body mass index (BMI) was calculated as weight (kg) divided by height (m). Initial examinations of the patients included height measurement (cm) using a wall-mounted height testing instrument with the scale of 1 cm and weight measurement (kg) with a Sega scale. BMI was calculated in accordance with the formula of weight (kg)/height (m^2). The patients completed a food frequency questionnaire, which was designed and standardized by Iranian Nutrition Institute.

The data were statistically analyzed using the SPSS statistical package for Windows (version 16, SPSS Inc., Chicago, IL, USA) and was demonstrated as mean ± SD (Standard deviation) and 95% confidence interval (CI). Normality of the distribution was checked for each variable (one sample Kolmogorov-Smirnov test). Independent T-test was used to check the difference found between means of the groups. Sensitivity of the factors was estimated by area under the receiver operating characteristic curve. Logistic regression model was used to determine factors role in fractures union. Chi-square and Fisher's exact tests were used to determine statistical difference of qualitative variables. $P < 0.050$ was considered as statistically significant.

Results

The present study was conducted on 48 patients including 32 (66.7%) male and 16 (33.3%) female with age average of 39.5 ± 14.8 years. The groups were the same considering age, gender, and type of fracture. There were 8 women and 16 men in every group. Furthermore, there were 14 cases of tibia and 10 cases of femur isolated fractures all treated through open reduction and internal fixation methods using intramedullary nails. Table 1 refers to laboratory findings of both groups. According to this table, there was statistically significant difference between two groups considering metabolic syndrome criteria, hs-CRP level, and measured inflammatory markers.

In patients with metabolic syndrome criteria, there were 8 (33.3%) cases of nonunion and 3 (12.5%) cases of delayed union. However, there was not seen any case of nonunion in the control group, but one case of delayed union. There was statistically significant difference between two groups considering union rate ($P = 0.002$).

Table 1. Comparison of qualitative and laboratory findings measured in two groups

Variable	Metabolic syndrome (n = 24)	Normal patients (n = 24)	P
Age (year)	38.8 ± 8.0	40.1 ± 7.8	0.200
TG (mg/dl)	202.5 ± 58.5	96.5 ± 42.2	0.001
HDL (mg/dl)	38.7 ± 11.4	51.8 ± 12.6	0.004
SBP (mmHg)	142.8 ± 14.5	106.1 ± 9.2	0.001
DBP (mmHg)	88.2 ± 8.3	68.7 ± 7.2	0.010
Waist circumference (cm)	109.4 ± 12.8	70.0 ± 22.2	0.005
FBS	99.8 ± 13.6	87.7 ± 9.4	0.010
Weight (Kg)	100.8 ± 12.4	87.7 ± 9.2	0.020
Height (cm)	156.9 ± 4.3	165.5 ± 6.5	0.020
BMI	32.9 ± 4.2	22.7 ± 4.3	0.010
hs-CRP (mg/dl)	4.2 ± 1.7	0.9 ± 0.2	< 0.001

TG: Triglyceride; HDL: High-density lipoprotein; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; BMI: Body mass index; hs-CRP: Highly sensitive C-reactive protein

According to the regression model, hs-CRP level played a significant role in predicting of nonunion (P = 0.001, OR = 2.3 and CI 95% = 1.4-3.8) with sensitivity of 95% shown in figure 1 while other factors of metabolic syndrome did not play any important role in nonunion prediction.

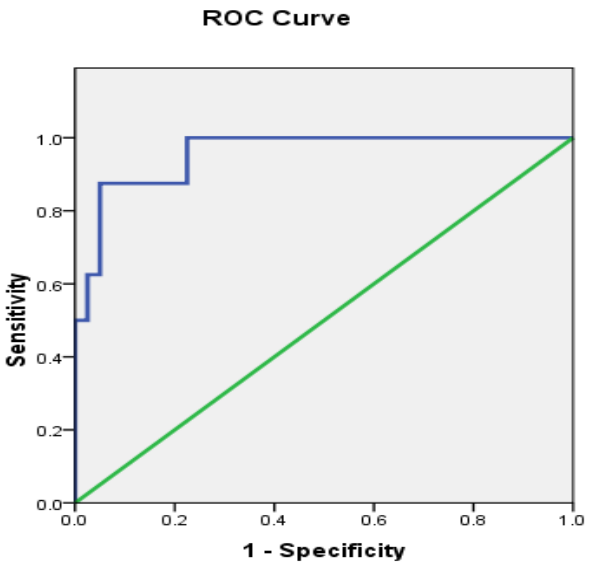

Figure 1. Sensitivity of highly sensitive C-reactive protein in prediction of metabolic syndrome

Discussion

In lower limbs, nonunion may occur in any bone, and it has been reported 3-8% for tibia and femur fractures. However, open and crushed fractures and fractures with more dislocation demonstrate a higher rate of nonunion.[9,12] There are different factors involved in nonunion such as mechanical factors involved in fixation method of fracture. Appropriate stabilization plays an important role in preventing from nonunion.[13]

Metabolic, endocrine, and even nutritional factors may affect healing of fractured bones.[13] According to the observational data, there were controversies about the relation found between metabolic syndrome and fractures within recent 10 years.[14] Findings of meta-analysis studies do not strongly support role of metabolic syndrome in increasing fracture risk.[14] According to Sun et al. metabolic syndrome does not play any role in increasing fracture risk.[14] In contrary, the study conducted by Everson-Rose et al. indicates to role of metabolic syndrome in physical and functional condition of patients, which may be involved in fractures process.[15]

Sedlár et al. evaluated role of inflammatory reactions in patients underwent orthopedic surgery. In this study, inflammatory reactions and inflammatory markers, especially CRP was increased significantly.[16] del Prete et al. studied 68 patients with hip fracture and indicated to post-treatment increase of interleukin-6 and tumor necrosis factor alpha inflammatory markers in some patients.[17] These inflammatory markers are increased due to infectious nonunion and have high sensitivity in detecting infectious nonunion.[18,19] Fracture and surgical treatment are involved in reactive response. Increase of CRP level seen in metabolic syndrome is associated with some complications.[20]

According to our findings, there is a significant difference between the control group and the patients with metabolic

syndrome criteria considering prevalence rate of nonunion of 33.0%, which is higher than the mentioned general prevalence rate of nonunion. In similar findings, Wright and Khan[21] suggested that inflammatory markers and CRP level was associated with an increase of complications of fractures treatment and nonunion rate. Our study also referred to the important role of CRP in predicting nonunion with sensitivity of 95%. According to Brinker et al., metabolic and endocrine abnormalities play a significant role in progressing and causing of nonunion in some patients.[11] Pourfeizi et al. suggest that metabolic and endocrine disorders should be considered in nonunion of low-energy and unjustifiable fractures.[13]

In this study, unjustifiable nonunion in patients with metabolic syndrome (in comparison with other patients suffering from similar fractures and taking benefit from the same treatment methods) may be attributed to metabolic disorders where increase of inflammatory markers level played a significant role.

Conclusion

Prevalence of nonunion in patients with metabolic syndrome suffering from a fracture and undergoing orthopedic surgery is higher than healthy persons. It seems that the increase of inflammatory markers plays a significant role in causing and predicting nonunion in these patients.

Limitations

The present study tried to completely match two groups to have results with high reliability. Considering that nonunion causes are multifactorial, however, it was not possible to exactly match the groups. Nutritional condition of people is an involved variable, which may affect the results. Using a food frequency questionnaire, which was designed and standardized by Iranian Nutrition Institute, it was tried to minimize differences in this regard.

Conflict of Interests

Authors have no conflict of interest.

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