

Association of serum osteocalcin levels with glucose metabolism in trauma patients

Yanping Yang, MS, Weixi Zhong, MS, Jianyin Huang, MS, Lei Geng, MS, Qiming Feng, MD*

Abstract

Osteocalcin (OC) is an endocrine hormone that regulates glucose metabolism.

The aim of this study was to investigate the relationship between serum OC levels and glucose metabolism after trauma.

This was a retrospective study of trauma patients admitted to the Department of Emergency Medicine between October 2017 and April 2019. Age, height, weight, injury severity score, and previous medical history were recorded. Serum N-terminal mid-fragment of OC (N-MID OC), hemoglobin Alc (HbA1c), fasting plasma glucose (FPG), fasting insulin (FINS), C-peptide, and other biochemical indicators were measured. Differences between the HbA1c-L (HbA1c <6.5%) and HbA1c-H (HbA1c ≥6.5%) groups were compared. The association of N-MID OC with indicators of glucose metabolism was analyzed.

Out of 394 trauma patients, leukocyte and FPG levels in the HbA1c-H group (n=93) were higher ($P < .05$), while N-MID OC levels were lower ($P = .011$) than the HbA1c-L group (n=301). N-MID OC was negatively correlated with HbA1c in the total population ($r = -0.273$, $P < .001$) as well as in the HbA1c-L ($r = -0.289$, $P < .001$) and HbA1c-H ($r = -0.390$, $P < 0.001$) groups, and was positively correlated with C-peptide in the HbA1c-H group ($r = 0.395$, $P < .001$). The different quartiles in the HbA1c-L showed that N-MID OC declined with increasing HbA1c, which was higher than N-MID OC levels in the HbA1c-H group. Multiple linear regression analysis revealed that serum HbA1c was independently associated with serum OC levels after trauma ($\beta = -1.608$, $P < .001$).

This study strongly suggests the importance of serum OC on glucose metabolism in trauma patients. HbA1c is independently associated with serum OC levels.

Abbreviations: ALT = Alanine aminotransferase, AST = aspartate aminotransferase, DM = diabetes mellitus, ECLIA = electrochemiluminescence, FINS = Fasting insulin, FPG = fasting plasma glucose, HbA1c = hemoglobin Alc, ISS = injury severity score, N-MID OC = N-terminal mid-fragment of osteocalcin, OC = Osteocalcin, TBI = traumatic brain injury.

Keywords: blood glucose, HbA1c, osteocalcin, trauma

1. Introduction

Trauma is often accompanied by abnormal glucose metabolism, including elevated blood glucose and increased insulin levels,

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Department of Emergency Medicine, Shanghai JiaoTong University Affiliated Sixth People's Hospital, Shanghai, China.

* Correspondence: Qiming Feng, Department of Emergency Medicine, Shanghai JiaoTong University Affiliated Sixth People's Hospital, No. 600 Yishan Rd, Xuhui District, Shanghai 200233, China (e-mail: fengqiming04@126.com).

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leading to adverse treatment outcomes. Those adverse treatment outcomes are not only associated with acute insulin resistance after trauma but also with previous glucose metabolism of the patients.^[1,2] Orthopedic trauma patients with hyperglycemia, but with no prior diabetes mellitus (DM), are often diagnosed with occult DM and have higher glycated hemoglobin (HbA1c) and glycated albumin levels.^[3] Diabetic trauma patients are prone to developing infectious complications.^[4] The mechanism of abnormal glucose metabolism induced by trauma is complex, and the pathophysiological mechanism is currently not well understood.

Osteocalcin (OC) is a noncollagen protein secreted by osteoblasts. OC is encoded by chromosome 1 (1q25-q31) and is regulated by 1,25-dihydroxycholecalciferol. There are 3 γ -carboxyglutamic acid residues in the 17, 21, and 24 loci of the OC peptide chain, which have a high affinity for calcium ions, and OC gets deposited in the bone matrix after binding to hydroxyapatite.^[5] Serum OC contains carboxylated OC as well as undercarboxylated OC.^[6] While the C-terminal of OC is unstable and lyses easily, the middle fragment at N-terminal is relatively stable. It is easily detected in the serum due to its long half-life.^[7] The physiological function of OC is primarily to maintain normal bone mineralization, inhibit the formation of abnormal hydroxyapatite, and alleviate the growth of cartilage mineralization.^[5]

OC is also an endocrine hormone that can regulate glucose metabolism.^[8–10] Mice with knockout OC gene have shrunken pancreatic islets, a fewer number of islets with decreased insulin content, elevated peripheral blood glucose, thickened subcutaneous fat, and increased insulin resistance of peripheral tissue,^[11]

but the injection of recombinant OC can reduce the detrimental effect on body mass and glucose metabolism in the knockout phenotypes.^[12] OC stimulates the proliferation of islet cells and increases insulin secretion by acting on the receptors of islet β -cells, thus increasing insulin sensitivity in peripheral tissues, promoting glucose uptake of cells, and reducing blood glucose levels.^[11,12] Abnormal signals of insulin receptors on osteoblast cell surface affect intracellular signal transduction, thus influencing the expression of OC gene and secretion of OC; this, in turn, has a cascading effect that can promote or impede glucose metabolism in a bone resorption-dependent manner in mice and humans.^[13]

Bone regulates glucose metabolism via OC.^[14,15] Numerous clinical studies have investigated the relationships between serum OC levels and glucose metabolism indicators in healthy as well as disease conditions,^[16–19] but the conclusions have been inconsistent regarding the association of OC with blood glucose, insulin, and C-peptide in different studies. Many studies focused on hyperglycemia after traumatic brain injury (TBI), leading to poor clinical outcomes and increased mortality,^[20–22] and serum OC levels decreased in TBI patients.^[23] To our knowledge, the relationship of serum OC levels with indicators of glucose metabolism in patients with trauma has not yet been reported.

Therefore, the present study aimed to evaluate the relationship of the levels of the stable N-terminal mid-fragment of OC (N-MID OC) in the serum with HbA1c, fasting plasma glucose (FPG), fasting insulin (FINS), and C-peptide in patients with closed injuries who did not undergo emergency surgery.

2. Materials and methods

2.1. Patients

This was a retrospective study of trauma patients admitted to the Department of Emergency Medicine of Shanghai Jiao Tong University Affiliated Sixth People's Hospital between October 2017 and April 2019. Inclusion criteria included patients aged ≥ 18 years suffering from trauma and closed injuries, and the time interval of blood drawn from the day of injury to the next day was < 24 hours. Exclusion criteria included patients who underwent emergency surgery; brain trauma; severe liver damage [alanine aminotransferase (ALT) > 3 times the upper limit of normal in the absence of a previous history of chronic liver disease]; previous history of chronic anemia, hypertension, diabetes, malignant tumors, hyperparathyroidism or thyroid dysfunction; fracture in the past 1 year; recent administration of medicines that were known to affect bone metabolism such as vitamin D and calcitonin, etc.^[16–19] This study was approved by the Ethics Committee of the Sixth People's Hospital of Shanghai, China. The patients were divided into the HbA1c-H group (HbA1c $\geq 6.5\%$) and HbA1c-L group (HbA1c $< 6.5\%$).

2.2. Biochemical measurements

Patient characteristics, such as age, height, weight, previous medical history, and use of medication, were extracted from the medical charts. Apart from routine checks such as blood pressure and heart rate, the injury severity score (ISS)^[24] was also recorded. Venous blood was collected routinely after a 12-hour fast, and the following parameters were checked: routine hematology tests, liver function, kidney function, electrolyte combination, thyroid functions, tumor indicators, HbA1c, FPG,

FINS, and C-peptide. HbA1c was determined by HPLC using Bio-Rad D-10 (Bio-Rad, Inc. USA). FPG was tested by the glucose oxidase method. FINS concentration was measured by radioimmunoassay (Linco Research, St Charles, MO). Fasting serum C-peptide levels were measured using an immunofluorescence assay (Cobas E601 analyzer; Japan Hitachi, Tokyo, Japan). Blood samples (4 mL) were collected separately for measuring OC; serum was extracted after centrifugation and stored at -20°C until further use. Electrochemiluminescence (ECLIA) was performed for N-MID OC using the Cobas-e-601 automated ECLIA immunoassay (Roche, Switzerland), and t-OC detection reagent (Roche Diagnostics Products, Shanghai, China). Body mass index (BMI) was defined as: $\text{BMI} = \text{weight (kg)} / \text{height (cm}^2\text{)}$.

2.3. Statistical analysis

Statistical analyses were carried out using SPSS 21.0 (IBM Corp, Armonk, NY). Categorical data were represented by percentages, and the Chi-square test was used. Continuous data that satisfied the normal distribution were expressed as means \pm standard deviations (SD). Differences between the 2 groups were analyzed by 2-tailed Student *t* test, and 1-way analysis of variance (ANOVA) was used to compare data among > 2 groups. Continuous data with a skewed distribution were presented with medians and quartiles, and the Wilcoxon rank-sum test was used. The relationships of N-MID OC with indicators of glucose metabolism were analyzed using the Pearson correlation analysis (continuous data met normal distribution) or Spearman correlation analysis (continuous data met skewed distribution) and multiple linear regression analysis. $P < .05$ was considered to be statistically significant.

3. Results

A total of 394 trauma patients (296 males, 98 females) met the inclusion criteria. Irrespective of the HbA1c status, the average age of the patients was 49.2 ± 16.1 years, the average BMI was $23.4 \pm 2.0 \text{ kg/m}^2$, the time interval from injury to blood collection was 12.1 ± 7.1 hours, the average ISS was 16.5 ± 9.2 , and the average N-MID OC concentration was $11.4 \pm 5.6 \mu\text{g/L}$. Patients were classified into the HbA1c-L group (HbA1c $< 6.5\%$, $n = 301$) and the HbA1c-H group (HbA1c $\geq 6.5\%$, $n = 93$). There were no significant differences in age, sex, BMI, ISS, the time interval from injury to blood collection, hemoglobin, ALT, aspartate aminotransferase (AST), calcium, creatinine, FINS, and C-peptide between the 2 groups ($P > .05$). Compared with the HbA1c-L group, the levels of leukocytes and FPG in the HbA1c-H group were higher ($P < .05$), while N-MID OC levels significantly lower ($P = .11$) in the HbA1c-L group (Table 1).

Correlation analyses showed that N-MID OC was related to biochemical parameters and indicators of glucose metabolism in trauma patients (Table 2). Among all traumatic populations, serum N-MID OC was negatively correlated with age ($r = -0.108$, $P = .047$) (Fig. 1A) and HbA1c ($r = -0.273$, $P < .001$) (Fig. 1B). In the HbA1c-L group, serum N-MID OC was associated with ISS ($r = -0.124$, $P = .029$) (Fig. 1C), leukocytes ($r = 0.115$, $P = .043$) (Fig. 1D), creatinine ($r = 0.142$, $P = .013$) (Fig. 1E), and HbA1c ($r = -0.289$, $P < .001$) (Fig. 1F). In the HbA1c-H group, serum N-MID OC was negatively correlated with HbA1c ($r = -0.390$, $P < .001$) (Fig. 1G), while it was positively correlated with C-peptide ($r = 0.395$, $P < .001$) (Fig. 1H). In order to further investigate the relationship between N-MID OC and HbA1c,

Table 1
Demographic and clinical characteristics of the study subjects.

	HbA1c-L group [HbA1c < 6.5% (n=301)]	HbA1c-H group [HbA1c ≥ 6.5% (n=93)]	P
Age, y	49.05 ± 15.63	52.15 ± 12.45	.165
Male, n (%)	224 (74.42%)	72 (77.42%)	.183
BMI, kg/m ²	23.27 ± 3.27	23.73 ± 1.73	.564
Injury severity score	16.61 ± 9.26	15.36 ± 8.70	.443
Injury time from trauma to blood collection, h	12.35 ± 6.35	11.85 ± 8.32	.633
Leukocytes, × 10 ⁹ /L	10.07 ± 5.28	12.03 ± 5.82	.037
Hemoglobin, × 10 ¹² /L	107.00 (91.00–123.00)	104.00 (92.00–128.00)	.719
ALT, U/L	53.89 ± 79.78	56.83 ± 67.50	.832
AST, U/L	71.92 ± 85.25	72.36 ± 143.53	.979
Calcium, mmol/L	2.06 ± 0.41	2.04 ± 0.17	.836
Creatinine, μmol/L	65.95 ± 29.91	76.53 ± 47.11	.063
Osteocalcin, μg/L	11.62 ± 5.76	9.11 ± 3.69	.011
HbA1c (%)	5.37 ± 0.37	7.46 ± 1.61	<.001
FPG, mmol/L	6.29 ± 1.74	10.37 ± 3.17	<.001
FINS, mIU/L	13.43 ± 11.75	13.28 ± 9.57	.946
C-peptide, pmol/L	3.34 ± 2.17	2.99 ± 1.61	.380

Data are represented as mean ± S.D. or median (interquartile range).

ALT=alanine aminotransferase, AST=aspartate aminotransferase, BMI=body mass index, FINS=fasting insulin, FPG=fasting plasma glucose, HbA1c=hemoglobin A1c.

patients were grouped based on quartiles (Q1-Q4) in the HbA1c-L group and then compared with HbA1c-H group. The results showed that N-MID OC in the Q1-Q4 groups was higher than the HbA1c-H group ($P < .001$, $P < .001$, $P = .001$, and $P = .037$, respectively). Moreover, serum N-MID OC showed a decreasing trend with increasing HbA1c (Fig. 2). Multiple linear regression analysis showed that HbA1c was independently associated with serum N-MID OC levels after adjusting age, ISS, leukocytes, calcium, and creatinine ($\beta = -1.608$, $P < .001$) (Table 3).

4. Discussion

In the present study, we investigated the relationship between serum N-MID OC with parameters of glucose metabolism in patients with trauma and closed injuries who did not undergo emergency surgery. Our results show that the levels of leukocytes

and FPG in the group with HbA1c ≥ 6.5% were significantly higher, while that of N-MID OC was significantly lower. There was a negative correlation between N-MID OC and HbA1c. ISS, creatinine, and C-peptide were also correlated to N-MID OC. HbA1c is independently associated with serum OC levels.

Studies suggest that OC is involved in chronic inflammation^[25,26] and that osteoblast precursors and inflammatory cells are released simultaneously at an injury site.^[27] Our study concurs with previous studies, as we show a positive correlation between N-MID OC and leukocytes, which are mediators of inflammation. Moreover, levels of leukocytes are higher in the HbA1c-H group. GPRC6A, the putative receptor of OC, is expressed in leukocytes,^[25] and thus, it is possible that OC might influence an inflammatory response associated with leukocytes, though direct mechanistic studies are required to determine this possibility.

Table 2
Correlation of serum osteocalcin with anthropometric parameters and glycometabolism parameters.

	Total (n=394)		HbA1c-L group [HbA1c < 6.5% (n=301)]		HbA1c-H group [HbA1c ≥ 6.5% (n=93)]	
	r	P	r	P	r	P
Age, y	-0.108	.047	-0.092	.108	-0.025	.895
BMI, kg/m ²	-0.105	.053	-0.101	.059	0.008	.546
Injury severity score	-0.033	.536	-0.124	.029	-0.091	.626
Leukocytes, × 10 ⁹ /L	0.098	.072	0.115	.043	-0.034	.856
Hemoglobin, × 10 ¹² /L	0.063	.249	0.072	.209	0.031	.868
Alanine aminotransferase, U/L	-0.040	.465	-0.047	.409	-0.039	.837
Aspartate aminotransferase, U/L	-0.062	.259	0.088	.122	-0.025	.893
Calcium, mmol/L	0.101	.063	0.026	0.644	0.196	.290
Creatinine, μmol/L	0.092	.090	0.142	0.013	-0.150	.419
HbA1c (%)	-0.273	<.001	-0.289	<0.001	-0.390	<.001
FPG, mmol/L	-0.048	.373	0.072	0.209	-0.239	.195
FINS, mIU/L	-0.047	.432	-0.053	0.385	0.248	.212
C-peptide, pmol/L	0.054	.356	0.031	0.610	0.395	<.001

BMI=body mass index, FINS=fasting insulin, FPG=fasting plasma glucose.

$P < .05$ was considered statistically significant.

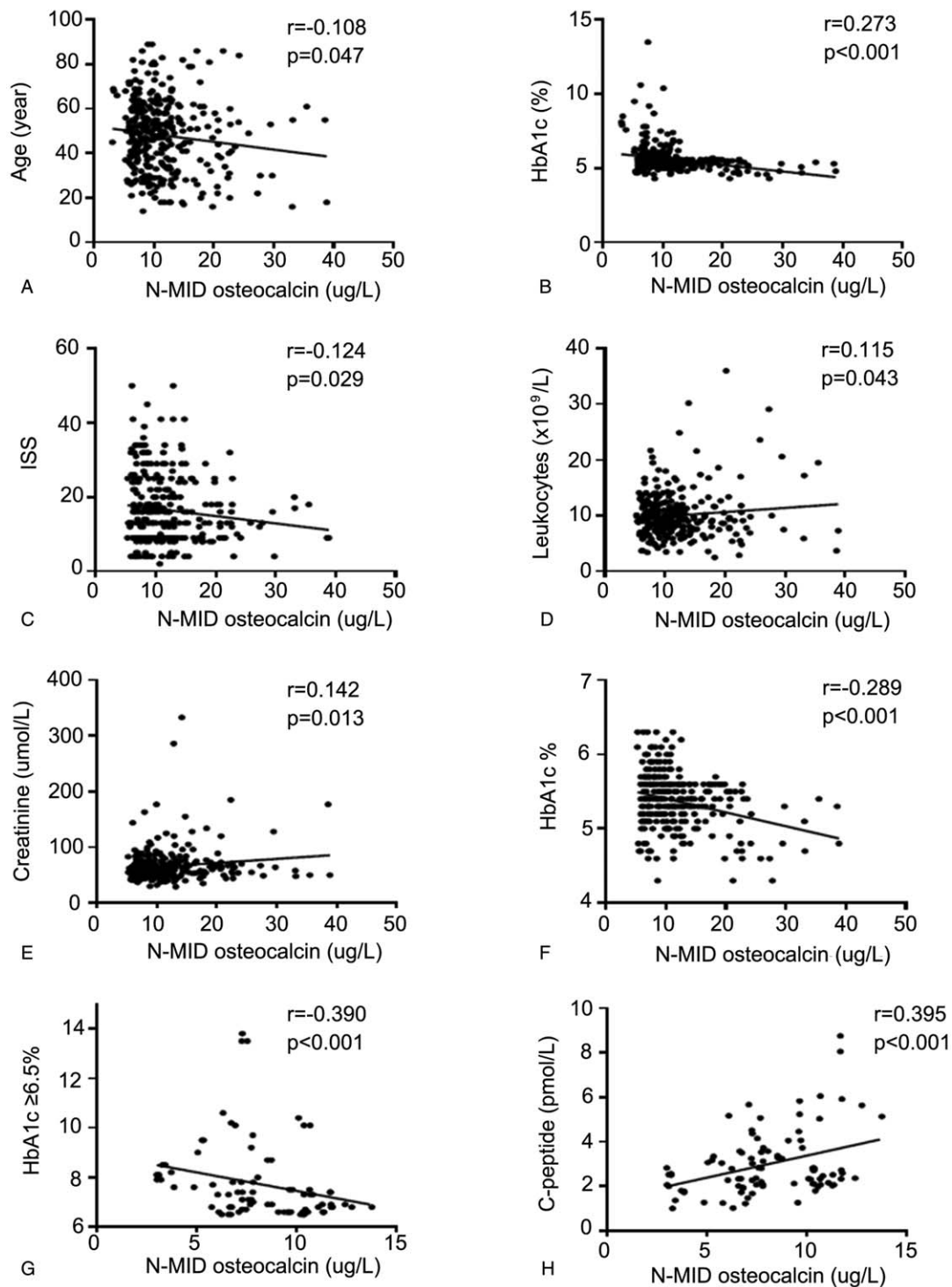


Figure 1. Correlation between N-MID osteocalcin (N-MID OC) and biochemical parameters, as well as indicators of glucose metabolism in trauma patients. Correlation of N-MID OC with (A) age, and (B) HbA1c in the total study population. Correlation of N-MID OC with (C) Injury Severity Score (ISS), (D) Leucocytes, (E) Creatinine, and (F) HbA1c in the HbA1c-L (HbA1c <6.5%) group. Correlation of N-MID OC with (G) HbA1c, and (H) C-peptide in the HbA1c-H (HbA1c ≥6.5%) group. $P < .05$ was considered to be statistically significant for all the analyses.

Serum N-MID OC levels were significantly lower in patients with HbA1c ≥6.5% than in those with HbA1c <6.5%. Previous studies revealed that serum OC levels were lower in individuals with abnormal metabolism, such as obese individuals,^[17] patients

with nonalcoholic fatty liver,^[28] and diabetics compared with normal individuals.^[19,29,30] In addition, correlation analyses in the present study showed that serum N-MID OC was significantly negatively correlated with HbA1c in both HbA1c-

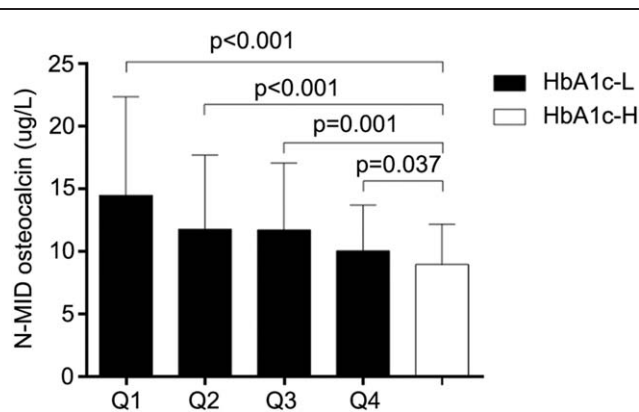


Figure 2. Relationship between N-MID OC and HbA1c in trauma patients. Trauma patients were grouped into quartiles (Q1-Q4) based on the HbA1c status. HbA1c-L and HbA1c-H groups were compared. $P < .05$ was considered to be statistically significant.

H and HbA1c-L group as well as in the total study population. Previous studies revealed that there are significant negative correlations between OC and HbA1c in patients with coronary heart disease and diabetes,^[18,19] which may be because there is insulin resistance in osteoblasts due to long-term glucose metabolism, leading to disturbance in the intracellular insulin signaling pathway, thus interfering with the expression and synthesis of the OC gene.^[31] Trauma is an acute condition, usually resulting in acute insulin resistance, which predominantly involves the liver and skeletal muscles. The liver mediates acute insulin resistance through TNF α and JNK activities as well as serine phosphorylation of IRS-1, while the skeletal muscle is mainly through elevated glucocorticoids after trauma.^[1,2] Nevertheless, there is currently little knowledge about whether acute insulin resistance in osteoblasts during acute events such as trauma, hemorrhagic shock, and severe infection causes genetic expression of OC and deficiency of OC synthesis. Glucocorticoid-induced insulin resistance corresponds to decreased under-carboxylated OC in circulation in healthy people.^[32] The relationship between OC and HbA1c in our study was consistent with previous studies, as mentioned above, and multiple linear regression analysis revealed that HbA1c was independently associated with serum OC levels. Patients who underwent emergency surgery were not included in our study, and hence, the effects of fluid resuscitation (including crystalloid, colloidal fluids and blood products, etc) during surgery on HbA1c could be excluded.

In our study, creatinine was shown to be correlated to N-MID OC in the HbA1c-L group. An earlier study has shown decreased OC and increased creatine kinase levels in trauma and bone injury.^[33] OC was directly correlated with urine albumin to

creatinine ratio patients with type 2 diabetes.^[34] Thus, potential changes in renal filtration caused by trauma, which can be assessed by changes in creatinine excretion, might be a plausible explanation.^[35]

In the present study, N-MID OC was positively correlated with C-peptide only in the HbA1c-H group, but the relationship of N-MID OC with FPG and FINS was not significant in the total trauma population. This may be because traumatic stress leads to rapid fluctuation in blood glucose and insulin concentration. In previous studies, conclusions regarding the relationship of OC with FPG, FINS, and C-peptide are inconsistent. In some studies, N-MID OC was negatively correlated with FPG in the healthy population,^[16] obese adolescents,^[17] and diabetic population,^[19,36] but the correlation of N-MID OC with FINS and C-peptide was not observed.^[16,19,29,30,36] In other studies, serum OC was positively correlated with FINS,^[37] but there is no correlation with FPG, FINS, and C-peptide.^[38] One study that recruited trauma patients did report that serum OC levels were negatively correlated with FPG ($P < .05$) and positively correlated with FINS ($P < .05$).^[39] Although our study did not show statistical significance, the trend of correlation of FPG and FINS with serum OC remained similar to the previous study.

Our study has limitations. The sample size was small with the ethnic Chinese population, and hence, results from a larger diverse population are warranted. Levels of sex hormones in female patients were not tested.

In summary, our study highlights that HbA1c is independently associated with serum N-MID OC levels, while other parameters had negligible or no association with serum OC levels. Our study sheds some light on the importance of serum OC for regulating glucose metabolism in trauma patients. Although mechanistic studies are required, determining the levels of serum OC and status of HbA1c in patients with trauma and closed injuries might be useful in knowing the predisposition of the patient to hyperglycemia, which can, in turn, cause other physiological complications.

Author contributions

In this study, Dr. Yanping Yang contributed to study design, data collection of subjects and writing the original manuscript. Dr. Weixi Zhong and Dr. Jianyin Huang contributed to data collection of subjects. Dr. Lei Geng is mainly responsible for examining the literature. MD. Qiming Feng contributed to the proofreading of design schemes and the delivered manuscripts.

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Table 3
Multiple linear regression analysis to assess the independent factors affecting N-MID osteocalcin.

	Standardized					
	β	S.E.M	β	t	P	95% CI
HbA1c	-1.608	0.333	-0.256	-4.824	<.001	-2.264 to 0.952

Adjusting age, injury severity score, leukocytes, calcium, and creatinine. $P < .05$ was considered statistically significant.

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