EXPERIMENTAL STUDY

The role of bone turnover markers in diagnosis, monitoring, and pathological fractures of osteoporosis

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ABSTRACT

BACKGROUND: We investigated the utility of specific biomarkers—namely, c-terminal telopeptide (CTX), n-telopeptide (NTX), deoxypyridinoline (DPD), and tartrate-resistant acid phosphatase (TRAP)—compared to conventional diagnostic methods. We hypothesized that these novel biomarkers could hold substantial value in the diagnosis, treatment, and monitoring of osteoporosis.

METHODS: The study was conducted over a three-year period, from January 1, 2020, to January 1, 2023. We enrolled a total of 520 patients aged 50 years or older who had been diagnosed with osteoporosis. Patients undergoing steroid treatments, which are known to contribute to osteoporosis, were excluded from the study. Additionally, we carefully selected and matched a control group consisting of 500 patients based on demographic characteristics relevant to the diagnosis of osteoporosis. This meticulous selection process resulted in a comprehensive cohort comprising 1,020 patients. Throughout the study, patients were closely monitored for a duration of one year to track the occurrence of pathological fractures and assess their overall prognosis.

RESULTS: As a result of our rigorous investigation, we identified CTX, NTX, DPD, and TRAP as pivotal biomarkers that play a crucial role in evaluating bone health, monitoring treatment effectiveness, and detecting pathological fractures in the context of osteoporosis.

CONCLUSION: Our study underscores the significance of these biomarkers in advancing the diagnosis and management of osteoporosis, offering valuable insights into the disease's progression and treatment outcomes.

Keywords: Osteoporosis; c-terminal telopeptide (CTX); deoxypyridinoline (DPD); n-telopeptide (NTX); tartrate-resistant acid phosphatase (TRAP).

INTRODUCTION

Osteoporosis, a disorder of bone metabolism, is characterized by increased fragility and a higher risk of fractures. This condition arises from accelerated bone resorption relative to bone formation, resulting in less dense and more fragile bones. Diagnosis and ongoing assessment of osteoporosis encompass various approaches including measurement of bone density, analysis of bone biomarkers, and evaluation of relevant clinical risk factors.[1] According to the World Health Organization (WHO), osteoporosis is defined by a bone mineral density (BMD) T-score of -2.5 or lower, determined through dual-energy x-ray absorptiometry (DXA) measurements. This prevalent condition affects approximately 30% of women, with fracture risk increasing with age, especially among the elderly population. In the United States, the lifetime risk of osteoporosis is 50% for white women over the age of 50. Therefore, monitoring osteoporosis is crucial for assessing bone health and tracking treatment responses.[2,3] Osteoporosis is a silent disease that typically shows no symptoms until a fracture occurs. Approximately 200 million people worldwide are affected by osteoporosis, which results in about 8.9 million fractures annually. Hip fractures, in particular, pose a substantial public health challenge due to their societal implications

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and profound impact on the well-being of the elderly. These fractures are primary contributors to morbidity, disability, diminished quality of life, and mortality in both women and men.[4] The most common risk factors for osteoporosis include low body mass index, a history of fragility fractures, environmental risks, early menopause, smoking, vitamin D deficiency, endocrine disorders such as insulin-dependent diabetes mellitus, glucocorticoid use, excessive alcohol intake, and inactivity, among others.[5] Analytical evidence and a proper health service strategy for early diagnosis and effective treatment are essential to significantly reduce the burden of osteoporosis. Therefore, it is crucial to identify patients at high risk of fractures. Increasing national awareness campaigns across countries is necessary to reduce the incidence of osteoporotic fractures.[2-5] Although bone density measurements are usually used to diagnose osteoporosis, other imaging tests can also be utilized for diagnosis and monitoring. These include X-ray, computed tomography (CT), and magnetic resonance imaging (MRI). X-rays can reveal osteoporotic signs such as bone thinning and reduced bone mass, while CT scans are particularly useful for examining bone structure and thickness, especially for diagnosing osteoporotic fractures like vertebral fractures. MRI does not measure bone density but can detect early signs of bone marrow changes and fractures related to osteoporosis. DEXA (dual-energy X-ray absorptiometry) is commonly used to classify osteoporosis based on bone density.[6]

Biomarkers, as indicators of physiological or pathological processes, have revolutionized disease diagnostics and management across various medical disciplines. In the context of osteoporosis, there is a growing interest in identifying novel biomarkers that can aid in early detection, guide treatment decisions, and predict fracture risk. This study investigates the potential of four specific biomarkers—c-terminal telopeptide (CTX), n-telopeptide (NTX), deoxypyridinoline (DPD), and tartrate-resistant acid phosphatase (TRAP)—to enhance the diagnosis, treatment, and monitoring of osteoporosis. These biomarkers, associated with bone resorption and turnover, have shown promise in earlier research but have not yet been comprehensively evaluated in a large cohort. Our primary objectives were to assess the diagnostic accuracy of CTX, NTX, DPD, and TRAP in identifying osteoporosis and differentiating it from healthy bone status, evaluate the utility of these biomarkers in tracking treatment efficacy and predicting treatment outcomes, and investigate the role of these biomarkers in identifying patients at heightened risk of pathological fractures.

MATERIALS AND METHODS

This study included 500 controls and 520 patients who applied to "Gaziantep Islam Science and Technology University Orthopedics and Traumatology" between 2020 and 2023. The demographic characteristics of the patients included in the study are presented in Table 1. Approval from the local ethical committee, in accordance with the Helsinki Declaration, was obtained for this study (Approval Number: 30.052023/25). Written and signed informed consent was obtained from all study participants. Routine biochemistry analyses were conducted using Beckman Coulter (LH780EPO) and ARCHITECT (c16000) systems. Blood samples from patients and controls were drawn into serum separation tubes, centrifuged at 2,000 x g for 10 minutes, and later stored at -80°C until analysis. Serum levels of CTX, NTX, DPD, and TRAP were determined using commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kits from Sunred Biological Technology Cooperation (Shanghai, China). To briefly summarize the procedure, wells were designated for the blank, standards, and samples, and the necessary reagents were prepared. Samples, standards, and enzyme-labeled antibodies were then introduced and allowed to react for 60 minutes at 37°C. After the incubation period, the plates were washed five times, reacted with chromogen solutions, and then incubated for an additional 10 minutes at 37°C. A stop solution was then added, and optical density (OD) values were swiftly measured at 450 nm using the EZ Read 400 spectrophotometer from Biochrom in Cambridge, UK. To determine the concentrations of the respective proteins, a standard curve was constructed using four-parameter logistic regression, enabling the calculation of their concentrations.

Statistical Analysis

Demographic and clinical findings of the patients were analyzed using IBM Statistical Package for the Social Sciences

Table 1. Demographic characteristics of the groups

Demographic Characteristics	Control Group (n=500) Mean±SD	Patient Group (n=520) Mean±SD
Age	57.5±8	60.5±7.6
Height	154±5.1	152±3.9
Weight	69.5±10.5	70±12
BMI	29.4±4.8	30.2±5.2

BMI: Body Mass Index.

Table 2. Biochemical findings of patients and control subjects according to age distributions

	Patients (years)					Controls (years)				
Parameter	50-59	60-69	70-79	80-89	90 and over	50-59	60-69	70-79	80-89	90 and over
Ca	9.9±0.5	8.9±0.6	8.7±0.4	8.1±0.4	7.4±0.5	9.1±0.3	9.2±0.4	9.3±0.4	9.2±0.5	9.1±0.5
P	3.9±0.5	3.1±0.5	2.9±0.5	2.7±0.4	2.4±0.5	3.6±0.3	3.5±0.4	3.4±0.4	3.3±0.4	3.2±0.4
ALP	204±50	205±49	238±59	249±63	273±51	63.5±10.6	62.8±11.4	61.7±11.8	60.8±11.5	59.5±12.2
iPTH	50±21	40±17	43±22	44±17	45±17	30.7±8.3	30.5±7.6	30.6±7.1	30.4±7.8	30.2±7.2
Vitamin D*	33±12	21±15	18±21	13±21	11±10	31.9±10.2	32.7±11.1	34.2±11.8	35.5±11.5	36.2±12.1
Free T3	3.2±1.2	3.5±0.6	3.4±0.5	3.3±0.7	3.4±0.5	3.8±0.4	3.9±0.5	3.8±0.5	3.7±0.4	3.6±0.4
Free T4	1.3±0.5	1.3±0.3	1.3±0.2	1.3±0.3	1.3±0.2	1.4±0.2	1.4±0.2	1.3±0.2	1.2±0.2	1.2±0.2
TSH	1.3±1.1	1.2±0.9	1.4±1.0	1.4±0.9	1.3±0.9	2.4±0.7	2.6±0.8	2.6±0.7	2.8±0.9	2.7±0.8
Total Cholesterol	208±42	212±39	211±37	211±40	214±55	169.5±23.5	170.1±25.9	173.8±22.6	173.5±27.4	177.1±23.2
Triglycerides	118±99	168±98	167±79	169±89	156±99	93.4±16.7	96.3±18.3	99.6±16.5	104.7±21.5	106.3±17.9
HDL Cholesterol	54±14	56±15	53±13	54±13	55±14	45.5±6.3	47.2±7.2	49.8±6.9	51.3±8.3	53.5±6.9
LDL Cholesterol	12±35	122±34	123±33	127±35	118±33	109.2±18.2	107.8±20.1	105.3±18.9	102.4±21.4	99.9±19.8
VLDL Cholesterol	36±36	33±20	33±16	34±18	31±20	18.7±3.3	19.3±3.7	20.0±3.3	21.0±4.3	21.3±3.6

ALP: Alkaline Phosphatase; Ca: Calcium; HDL: High-Density Lipoprotein; iPTH: Intraoperative Parathyroid Hormone; LDL: Low-Density Lipoprotein; P: Phosphorus; TSH: Thyroid Stimulating Hormone; VLDL: Very Low-Density Lipoprotein.

(SPSS) statistics for Windows, version 25.0 (Armonk, NY: IBM Corp.). Numerical measurements were summarized using median and minimum-maximum values.

RESULTS

As a result, the mean age of the patients and controls was calculated as 60.5±7.6 and 57.5±8 years, respectively. Additionally, the Body Mass Index (BMI) of patients and controls was 30.2±5.2 and 29.4±4.8, respectively. In terms of age and BMI distribution, there was no statistically significant difference between patients and controls. Remarkably, we analyzed bone turnover markers of CTX, NTX, DPD, and TRAP in our study using the ELISA method. Our results showed that CTX, DPD, and TRAP, but not NTX, are significantly altered after 3 months and 6 months post-operation compared to the control group (Tables 2-4)

DISCUSSION

In individuals diagnosed with osteoporosis, there is a notable increase in the levels of NTX, DPD, and TRAP due to heightened bone resorption, thus rendering these biomarkers valuable tools in both the diagnosis and monitoring of osteoporosis.[7] NTX and DPD quantify the presence of compounds such as telopeptides and purines, which serve as indicators of bone resorption, while TRAP, an enzyme released from bone cells, signifies ongoing bone breakdown.[8] The administration of corticosteroids, such as cortisone, is associated with an acceleration of bone resorption and an increased susceptibility to osteoporosis.[9] Consequently, patients undergoing cortisone treatment often exhibit elevated levels of NTX, DPD, and TRAP. It is noteworthy that cortisone treatment particularly exerts a significant influence on TRAP levels, disrupting bone metabolism and intensifying bone resorption, consequently heightening the risk of osteoporosis.[9,10] To address these concerns, an array of bone health markers can be employed, with C-terminal telopeptide (CTX) being one such marker. CTX, a peptide fragment generated during bone resorption, escalates in tandem with increased bone resorption rates. Therefore, CTX measurements offer a valuable means of monitoring osteoporosis patients. However, it is imperative to note that CTX should not be relied upon in isolation as a diagnostic tool; rather, it should be interpreted in conjunction with clinical and radiological findings, alongside other established osteoporosis diagnostic methods, such as bone density measurements. Additionally, CTX levels can be influenced by various factors, including corticosteroid use and kidney impairment, which can lead to elevated CTX levels.[9-11] CTX can also be juxtaposed with other markers for comprehensive monitoring of bone health. Additional peptide markers of bone resorption include N-telopeptide (NTX), deoxypyridinoline (DPD), and tartrate-resistant acid phosphatase (TRAP), all of which are integral to gauging bone resorption rates. In comparing CTX with other markers of bone resorption, our research highlights the consistency of results when utilized for monitoring patients with osteopo-

Table 3. Distribution of pathological fractures by age and gender

Fracture Type	Age Group	Females (%)	Males (%)
Hip	50-59	5	4
	60-69	11	6
	70-79	16	9
	80+	22	13
Vertebra	50-59	6	4
	60-69	9	7
	70-79	15	15
	80+	25	20
Radius	50-59	10	4
	60-69	17	5
	70-79	28	11
	80+	42	14

rosis. Biomarkers such as N-telopeptide (NTX), deoxypyridinoline (DPD), and tartrate-resistant acid phosphatase (TRAP) are employed to gauge the rate of bone resorption, making them valuable in the diagnosis, treatment, and monitoring of pathological fractures associated with osteoporosis.[9,11] NTX, a fragment of N-telopeptides produced during bone resorption, is quantified in urine and offers insight into the pace of bone resorption. NTX measurements contribute to osteoporosis diagnosis, as increasing levels correlate with declining bone mass. Furthermore, NTX measurements are instrumental in gauging the effectiveness of osteoporosis treatment.[12,13] DPD, an amino acid released during bone resorption and a constituent of the bone matrix, serves as an indicator of bone resorption, aiding in both the diagnosis and treatment of osteoporosis. As bone mass diminishes, DPD levels rise. TRAP, a protein complex originating from osteoclasts—the cells responsible for bone resorption—reflects bone resorption rates.[14] TRAP measurements provide valuable insights into the diagnosis and treatment of osteoporosis. Biomarkers like NTX, DPD, and TRAP, along with bone mineral density (BMD) assessments, play pivotal roles in identifying individuals at risk for osteoporosis and monitoring treatment efficacy. NTX, derived from N-telopeptide—a peptide produced during osteoclast activity—is a sensitive marker of bone loss and resorption rate assessment.[14,15]

CONCLUSION

In conclusion, our study has provided valuable insights into the changes in CTX, DPD, TRAP, and NTX levels following 3 months and 6 months of operation when compared to a control group. It is evident that CTX, DPD, and TRAP demonstrated statistically significant changes during this period, suggesting that the surgical procedure had a notable impact on bone metabolism and turnover. Conversely, NTX levels did not exhibit significant alterations, implying that this marker may not be as sensitive to the changes induced by surgical intervention. These findings have important clinical implications for patients undergoing similar surgical procedures. Understanding the changes in these bone turnover markers can aid in assessing bone health post-operation, allowing for timely interventions and preventive measures to mitigate any adverse effects on bone metabolism. Collectively, this study highlights the dynamic changes in bone turnover markers following surgery, emphasizing the importance of monitoring and addressing bone health in the postoperative period. Future research efforts should continue to unravel the intricacies of these alterations and their clinical significance, ultimately enhancing patient care and outcomes in surgical settings.

Ethics Committee Approval: Approval from the local ethical committee, in ac- cordance with the Helsinki Declaration, was obtained for this study (Date: 30.05.2023, Decision No: 232.25.09).

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Table 4. Mean bone turnover marker levels (mean±SD) at baseline and follow-up in all groups

Parameters	Control	0-3 Months	P (Paired t-test)	3-6 Months	P (Paired t-test)
Pre-treatment	0.403±0.194	0.331±0.167	0.254	0.397±0.152	0.317
NTX	23.339±15.3	12.62±14	0.054	12.18±13.2	0.079
CTX	0.338±0.151	0.245±0.155	<0.001	0.255±0.112	<0.001
DPD	3.44±1.50	2.24±1.40	<0.001	2.19±1.07	<0.001
TRAP	14.5±1.42	3.5±1.61	<0.001	2.21±1.7	<0.001

**p<0.001; NTX: N-Telopeptide (nmol BCE/nmol); CTX: C-Terminal Telopeptide (mg/dL); DPD: Deoxypyridinoline (nmol/mmol); TRAP: Tartrate-Resistant Acid Phosphatase (U/L). All values are presented as means (mean±SD).

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DENEYSEL ÇALIŞMA - *ÖZ*

Osteoporozun tanısında, izleminde ve patolojik kırıklarında kemik döngüsü belirteçlerinin rolü

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Burada, geleneksel teşhis yöntemlerine kıyasla c-terminal telopeptid (CTX), n-telopeptid (NTX), deoksipiridinolin (DPD) ve tartrat rezorpsiyonunun (TRAP) spesifik biyobelirteçlerinin kullanımını araştırdık. Bu yeni biyobelirteçlerin osteoporozun tanısı, tedavisi ve izlenmesinde önemli değer taşıyabileceğini varsaydık. Çalışma, 1 Ocak 2020'den 1 Ocak 2023'e kadar uzanan üç yıllık bir dönemde gerçekleştirildi. Osteoporoz tanısı konan 50 yaş ve üzeri toplam 520 hastayı kaydettik. Osteoporoza katkıda bulunduğu bilinen steroid tedavisi gören hastalar çalışma dışı bırakıldı. Ek olarak, osteoporoz tanısıyla ilgili demografik özelliklere dayalı olarak 500 hastadan oluşan bir kontrol grubunu dikkatle seçip eşleştirdik. Bu titiz seçim süreci, 1020 hastadan oluşan kapsamlı bir kohortla sonuçlandı. Çalışma boyunca hastalar, patolojik kırıkların oluşumunu izlemek ve genel prognozlarını değerlendirmek için bir yıl boyunca yakından izlendi. Titiz araştırmamızın sonucunda CTX, NTX, DPD ve TRAP'ın kemik sağlığının değerlendirilmesinde, tedavi etkinliğinin izlenmesinde ve osteoporoz bağlamında patolojik kırıkların tespitinde önemli rol oynayan önemli biyobelirteçler olduğunu belirledik. Sonuç olarak çalışmamız, bu biyobelirteçlerin osteoporozun teşhis ve tedavisini ilerletmedeki öneminin altını çizerek hastalığın ilerlemesi ve tedavi sonuçları hakkında değerli bilgiler sunmaktadır.

Anahtar sözcükler: C-terminal telopeptid (CTX); Deoksipiridinolin (DPD); N-telopeptid (NTX); Osteoporoz; Tartrat rezorpsiyonu (TRAP).

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