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The Influence of Serum Lactate Dehydrogenase and Lactic Acid Levels on the Occurrence and Progression of Osteoporosis

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Abstract: ***Objective:*** *By collecting and analyzing serum lactate dehydrogenase (LDH) and lactic acid levels in patients with osteoporosis, and comparing them with other common biochemical indicators used in osteoporosis diagnosis, this study aims to explore the impact of serum LDH and lactic acid levels on the occurrence and progression of osteoporosis, further clarify their relationship with osteoporosis, and provide new clinical evidence for the scientific prevention and treatment of osteoporosis.* ***Methods:*** *A retrospective analysis was conducted on 150 patients who underwent bone mineral density (BMD) measurement at the Bone Density Room of Tianjin Hospital from June 2024 to December 2024. Based on BMD T-scores, the patients were divided into three groups: normal bone mass, osteopenia, and osteoporosis, with 50 cases in each group. General data of the three groups, including name, gender, age, weight, height, BMI, serum LDH, lactic acid, and other related clinical biochemical indicators [alkaline phosphatase (ALP), serum calcium, serum phosphorus, uric acid, urine creatinine, cystatin C, P1NP, β-CTx were collected from the Clinical Laboratory of Tianjin Hospital. The correlation and degree of correlation between serum LDH, lactic acid and BMD T-scores were analyzed and compared with other clinical biochemical indicators. Differences within and between groups were also compared to comprehensively evaluate the impact of serum LDH, lactic acid levels, and other biochemical indicators on the occurrence and progression of osteoporosis. All clinical data collected in this study were approved by the Ethics Review Committee of Tianjin Hospital, complying with ethical requirements.* ***Results:*** *Comparative analysis showed that there was a significant negative correlation between serum LDH and BMD T-scores in 150 patients (correlation coefficient: -0.669), indicating that higher serum LDH levels were associated with lower BMD T-scores and more severe osteoporosis. In contrast, lactic acid levels showed a significant positive correlation with BMD T-scores (correlation coefficient: 0.732), meaning higher lactic acid levels were associated with higher BMD T-scores and milder osteoporosis. Comprehensive comparison of the correlation between other biochemical indicators and BMD T-scores revealed that serum calcium, serum phosphorus, and urine creatinine had a certain positive correlation with BMD T-scores, i.e., higher levels of these indicators were associated with higher BMD T-scores and milder osteoporosis.* ***Conclusion:*** *Serum LDH and lactic acid, as clinical biochemical markers, are significantly correlated with BMD T-scores. LDH is negatively correlated with BMD T-scores, while lactic acid is positively correlated with BMD T-scores. These two indicators have a significant impact on the occurrence and progression of osteoporosis. The conclusions of this study are expected to better guide the diagnosis and treatment of osteoporosis and provide more scientific basis for clinical decision-making.*

Keywords: Osteoporosis, Lactate Dehydrogenase, Lactic Acid, Clinical Indicator, Influence.

1. Overview and Epidemiological Characteristics of Osteoporosis

Osteoporosis is a systemic bone disease characterized by low bone mass, destruction of bone tissue microstructure, increased bone fragility, and susceptibility to fractures [1]. In 2001, the National Institutes of Health (NIH) defined it as a skeletal disease characterized by decreased bone strength and increased fracture risk [2]. Osteoporosis can occur at any age but is more common in postmenopausal women and elderly men. Etiologically, it is divided into primary and secondary osteoporosis. Primary osteoporosis includes postmenopausal osteoporosis (Type I), senile osteoporosis (Type II), and idiopathic osteoporosis (adolescent type). Postmenopausal osteoporosis generally occurs within 5-10 years after menopause in women; senile osteoporosis typically occurs in individuals over 70 years old; idiopathic osteoporosis mainly affects adolescents, with its etiology not yet fully clarified. Secondary osteoporosis is caused by diseases, drugs, or other clear etiologies that affect bone metabolism [3-4].

With the aging of China's population, the prevalence of osteoporosis has risen rapidly, becoming a major public health issue. According to the seventh national census in China, the population over 60 years old is 264 million (accounting for approximately 18.7% of the total population), and the population over 65 years old exceeds 190 million (accounting for approximately 13.5% of the total population) [5], making China the country with the largest elderly population in the world. National epidemiological surveys on osteoporosis show that the prevalence of osteoporosis in people over 50 years old is 19.2%, including 32.1% in women and 6.9% in men; the prevalence in people over 65 years old is 32.0%, including 51.6% in women and 10.7% in men [6-7]. Based on the above epidemiological data, it is estimated that the number of people with osteoporosis in China is approximately 90 million [6], including about 70 million women. Osteoporotic fractures are extremely harmful and are one of the main causes of disability and death in elderly patients. Within one year after a hip fracture, 20% of patients may die from various complications; approximately 50% of patients become disabled, with a significant decline in quality

of life [8-9]. Moreover, the medical and nursing care for osteoporosis and fractures impose a heavy burden on families and society. It is estimated that by 2035, China's medical expenses for major osteoporotic fractures (wrist, vertebral, and hip) will reach 132 billion yuan; by 2050, this expenditure will rise to 163 billion yuan.

2. Overview of Biochemical Indicators Related to Osteoporosis

Bone minerals, hormones, cytokines, bone resorption markers, bone formation markers, genes, receptors, trace elements, etc., determine the internal environment and metabolic regulation process of bone metabolism, and are also important factors determining bone quality and strength [10]. Laboratory diagnosis of osteoporosis involves experimental analysis of blood, tissue fluid, cells, proteins, and living tissues to scientifically evaluate and judge the dynamic changes of systemic bone metabolism and the activity of bone metabolism, which is of great significance for clinical diagnosis and differential diagnosis of osteoporosis, treatment observation, and research on the regulatory mechanism of bone metabolic diseases [11]. Referring to the commonly used clinical biochemical indicators and bone metabolism-related indicators listed in the *2022 Expert Consensus on Laboratory Diagnosis and Influencing Factors of Osteoporosis*, this study mainly selected the following indicators: lactate dehydrogenase (LDH), lactic acid, alkaline phosphatase (ALP), serum calcium, serum phosphorus, uric acid, urine creatinine, cystatin C (CysC), P1NP, β-CTx, and focused on analyzing the relationship between LDH, lactic acid and the occurrence and progression of osteoporosis.

There is currently no unified conclusion on the exact impact of LDH and lactic acid levels on the occurrence and progression of osteoporosis. Previous studies have mostly suggested that elevated lactic acid levels indicate that the body is in a state of injury. Chronic high lactic acid levels may reflect energy metabolism disorders (such as mitochondrial dysfunction) or chronic tissue hypoxia in the body, which may lead to impaired osteoblast function. Insufficient energy will weaken the proliferation, differentiation, and bone matrix synthesis ability of osteoblasts, resulting in reduced bone formation. Energy metabolism disorders may also affect osteoclasts, and the hypoxic environment itself may stimulate osteoclast activity, leading to increased bone resorption. In addition, the state of osteocytes deserves attention. Osteocytes are the main cells embedded in the bone matrix and are crucial for maintaining bone homeostasis. Hypoxia and insufficient energy supply may lead to increased apoptosis of osteocytes, damage the function and signal transduction of bone mechanoreceptors, and weaken bone structure.

Lactic acid is the end product of glycolysis, and its level usually increases under hypoxia (such as strenuous exercise, insufficient tissue perfusion) or mitochondrial dysfunction. Studies have shown that serum lactic acid levels can effectively indicate the cellular nutritional status and hypoxic state of patients [12]. Osteoblasts (responsible for bone formation) and osteoclasts (responsible for bone resorption) are highly active cells that require a large amount of energy (ATP) to perform their functions. When tissue damage or cell death occurs, LDH is released from damaged cells into the blood circulation, leading to an increase in serum LDH levels [13]. As a key enzyme in the glycolytic pathway, LDH plays a central role in cellular energy metabolism. Its five isozymes (LDH1-LDH5) are tetrameric structures composed of two subunits, myocardial type (H) and skeletal muscle type (M), in different proportions: LDH1 (H_4), LDH2 (H_3M), LDH3 (H_2M_2), LDH4 (HM_3), and LDH5 (M_4). Although these isozymes catalyze the same biochemical reaction (pyruvate ⇌ lactic acid), their affinity for substrates (Km value), maximum reaction rate (Vmax), and kinetic characteristics differ significantly due to differences in subunit composition. In terms of tissue distribution, LDH1 and LDH2 are mainly enriched in aerobic tissues such as the myocardium. The clinically commonly used α-hydroxybutyrate dehydrogenase (α-HBD) is actually the sum of the activities of LDH1 and LDH2; LDH3 is mainly derived from the lung and spleen; LDH4 and LDH5 (especially LDH5) are mainly derived from tissues with active glycolysis such as the liver and skeletal muscle [14]. In bone tissue biopsies of patients with osteoporosis (such as postmenopausal women, patients with chronic kidney disease, or those using glucocorticoids for a long time), LDH5 expression is significantly increased and is negatively correlated with bone mineral density (BMD). In the bone metabolic environment, LDH isozymes affect the dynamic balance between osteoblasts (bone formation) and osteoclasts (bone resorption) by regulating energy supply pathways and local microenvironmental acid-base balance. The core pathological feature of osteoporosis is the disruption of this balance, leading to reduced bone mass [15].

At present, there is a lack of sufficient and detailed clinical data analysis to further clarify the impact of serum LDH and lactic acid levels on the occurrence and progression of osteoporosis. This study is expected to better supplement the evidence in this regard by further comparing and analyzing the above indicators and other indicators that may affect bone metabolism, in order to provide a new reference path for the diagnosis and treatment of osteoporosis.

3. Sample Collection, Inclusion and Exclusion Criteria, and Diagnostic Criteria

This study is a retrospective study. The included biochemical indicators are all continuous variables, mainly comparing the mean differences of various indicators among the three groups. Therefore, the sample size calculation formula of F-test (based on analysis of variance) was used: $n = \frac{\psi \times (SD)^2}{(\mu_1 - \mu_{mean})^2}$, where: n is the minimum sample size required for each group; φ is the quantile of the non-central F distribution (needs to be checked by table or calculated by software); SD is the combined standard deviation (reflecting the degree of data variation); $\mu 1 - \mu mean$ is the minimum meaningful value of the difference between groups (such as the difference between the largest group and the total mean). After calculation, the minimum sample size required for each group in this study is 38 cases, and the minimum total sample size required for the three groups is 114 cases. To ensure the statistical significance of the inter-group comparison results, combined with the sample inclusion and exclusion criteria, and considering possible data missing, loss, and exclusion during sample collection, the final total sample size included in this study is 150 cases, with 50 cases in each group.

A total of 150 patients who underwent bone mineral density (BMD) measurement at the Bone Density Room of Tianjin Hospital from June 2024 to December 2024 were collected and analyzed, and all patients were enrolled consecutively. Inclusion criteria: 1. Patients with primary osteoporosis; 2. Age between 55 and 70 years old; 3. No anti-osteoporosis treatment before enrollment; 4. No strenuous aerobic or anaerobic exercise within two weeks before blood collection. Exclusion criteria: 1. Patients with secondary osteoporosis or other metabolic underlying diseases; 2. Patients under 55 years old or over 70 years old; 3. Patients diagnosed with osteoporosis and receiving relevant treatment; 4. Patients with strenuous exercise within two weeks before blood collection.

Currently, dual-energy X-ray absorptiometry (DXA) is commonly used in clinical practice to measure BMD, and the diagnosis of osteoporosis is mainly based on the patient's BMD T-score: T-score ≥ -1.0 indicates normal bone mass; -2.5 < T-score < -1.0 indicates osteopenia; T-score ≤ -2.5 indicates osteoporosis. The main sites for clinical BMD measurement are the lumbar spine, femoral neck, and total hip joint. To ensure the consistency of the results of this study, the T-scores included in this data statistics are all femoral neck T-scores. Based on the inclusion and exclusion criteria and T-scores, 150 patients were divided into three groups: normal bone mass, osteopenia, and osteoporosis, with 50 cases in each group. Meanwhile, the names, genders, ages, weights, heights, BMIs, serum LDH, lactic acid, and other related clinical biochemical indicators of the three groups were collected from the Clinical Laboratory of Tianjin Hospital. Based on the main purpose of this study, it is necessary to briefly explain the relevant steps for the determination of LDH and lactic acid levels: blood samples of all patients were collected from venous blood, and heparin anticoagulant tubes were used to collect blood. Fasting for 8-12 hours before blood collection, resting for ≥ 2 hours, ice bathing and centrifugation to separate serum within 15 minutes after blood collection, and automatic biochemical analyzers were used to determine lactic acid concentration and LDH value.

4. Statistical Analysis Methods

SPSS 26.0 was used for data analysis. Bone mineral density T-score, LDH, lactic acid, ALP, serum calcium, serum phosphorus, uric acid, urine creatinine, cystatin C, P1NP, and β-CTx conformed to normal distribution by Kolmogorov-Smirnov test; the above indicators were tested for homogeneity of variance before analysis of variance, and each continuous variable indicator conformed to homogeneity of variance; all indicators were continuous variables, and one-way analysis of variance (ANOVA) was used; multiple test correction (Bonferroni) was used for inter-group comparison and correlation analysis to avoid type I errors; Pearson and Spearman correlation coefficients were used to analyze the correlation between LDH, lactic acid, ALP, serum calcium, serum phosphorus, uric acid, urine creatinine, cystatin C, P1NP, β-CTx and bone mineral density T-score.

5. Comparison Results of Various Indicators in Total 150 Cases and Between Groups

Table 1: Comparison of mean differences of various indicators between groups ($\bar{x}\pm s$)

Group / index	normal bone mass ($\bar{x}\pm s$)	bone mass reduction ($\bar{x}\pm s$)	osteoporosis($\bar{x}\pm s$)
LDH（U/L）	201.12±43.98	214.96±57.42	241.14±53.34
Lactic acid（mmol/L）	7.52±2.62	8.30±2.58	6.08±2.09
ALP（U/L）	83.66±28.34	80.42±16.39	92.04±26.17
Blood calcium（mmol/L）	2.35±0.15	2.32±0.12	2.26±0.10
Blood phosphorus（mmol/L）	1.15±0.18	7.93±48.35	0.98±0.17
Uric acid（μmol/L）	291.80±95.37	287.34±83.91	267.30±70.73
Urinary creatinine（mmol/24h）	74.48±29.65	63.58±14.67	62.88±17.96
Cystatin C（mg/L）	1.02±0.30	2.16±8.78	1.05±0.31
P1NP（ng/mL）	52.71±17.23	43.35±19.45	48.08±22.14
β-CTx（ng/mL）	0.42±0.14	0.30±0.17	0.33±0.17

Table 2: Results of one-way analysis of variance (ANOVA) for various indicators

Results of one-way analysis of variance (ANOVA)

value / index	F	*P*
LDH（U/L）	7.67	<0.001
Lactic acid（mmol/L）	10.67	<0.001
ALP（U/L）	3.07	<0.05
Blood calcium（mmol/L）	5.19	<0.05
Blood phosphorus（mmol/L）	1.01	>0.05
Uric acid（μmol/L）	1.21	>0.05
Urinary creatinine（mmol/24h）	4.48	<0.05
Cystatin C（mg/L）	0.82	>0.05
P1NP（ng/mL）	2.82	>0.05
β-CTx（ng/mL）	7.99	<0.001

Table 3: Results of pairwise comparison of various indicators between groups

between-group comparison / index	normal bone mass VS bone mass reduction（*P*）	normal bone mass VS osteoporosis（*P*）	Bone mass reduction VS osteoporosis（*P*）
LDH（U/L）	0.379	0.001**	0.034*
Lactic acid（mmol/L）	0.250	0.010*	0.000**
ALP（U/L）	0.782	0.197	0.046*
Blood calcium（mmol/L）	0.576	0.006*	0.082
Blood phosphorus（mmol/L）	0.446	0.999	0.429
Uric acid（μmol/L）	0.962	0.314	0.459
Urinary creatinine（mmol/24h）	0.035*	0.023*	0.986
Cystatin C（mg/L）	0.504	1.000	0.521
P1NP（ng/mL）	0.049*	0.471	0.455
β-CTx（ng/mL）	0.000**	0.015*	0.558

explanation：**：P<0.001；*：P<0.05

Table 4: Comparison of Spearman correlation coefficients between various indicators and bone mineral density T-score in total and between groups

index \ Group	150 cases	normal bone mass	bone mass reduction	osteoporosis
LDH（U/L）	-0.669**	-0.540	-0.647	-0.686
Lactic acid（mmol/L）	0.732**	0.628	0.671	0.751
ALP（U/L）	-0.669*	0.148	-0.181	-0.119
Blood calcium（mmol/L）	0.597**	0.167	-0.045	0.076
Blood phosphorus（mmol/L）	0.448**	0.110	0.134	0.022
Uric acid（μmol/L）	0.175*	0.252	0.251	-0.166
Urinary creatinine（mmol/24h）	0.271**	0.315	0.117	-0.235
Cystatin C（mg/L）	-0.016	0.289	0.027	-0.284
P1NP（ng/mL）	0.753**	0.030	-0.143	0.064
β-CTx（ng/mL）	0.871**	0.106	-0.065	-0.099

explanation: *: At the 0.05 level(two-tailed), the correlation is significant;
**: At the 0.01 level(two-tailed), the correlation is significant.

6. Result Analysis

Combined with the analysis results of Table 1 and Table 2, it can be seen that among the indicators included in this study, LDH, lactic acid, and β-CTx have the most significant differences between groups (P<0.001), indicating that the above indicators have a significant impact on the occurrence and progression of osteoporosis. β-CTx is a bone metabolism-related indicator, which is used to evaluate the corresponding bone mass of patients in different age groups, and then evaluate the progression of osteoporosis. This study focuses on the impact of LDH and lactic acid levels on the occurrence and progression of osteoporosis. The significant differences of the above two indicators between groups indicate that serum LDH and lactic acid levels play different regulatory roles in different stages of the occurrence and development of osteoporosis. For LDH, the osteoporosis group was significantly higher than the normal bone mass group, and the LDH value gradually increased with the decrease of bone mass, indicating a significant linear negative correlation between them. The higher the LDH value, the smaller the bone mineral density T-score, and the more severe the osteoporosis; for lactic acid, the osteoporosis group was significantly lower than the normal bone mass group and the osteopenia group, indicating a significant positive correlation between them. The higher the lactic acid value, the larger the bone mineral density T-score, and the milder the osteoporosis.

It can be seen from the pairwise comparison results of various indicators in Table 3 that among the indicators included in this study, LDH, lactic acid, and β-CTx have the most significant differences after pairwise comparison between groups, which is consistent with the analysis results of Table 1 and Table 2, indicating that the above indicators have a significant impact on the progression of osteoporosis.

Before analyzing the data results in Table 4, it is necessary to briefly explain the Spearman correlation analysis method. Spearman correlation coefficient is used to measure the monotonic correlation degree between two variables (whether linear or not), with a value range of [-1, 1]. 1 indicates a perfect positive linear correlation; -1 indicates a perfect negative linear correlation; 0 indicates no linear correlation. The sign indicates the direction, and the absolute value indicates the strength; it can be used for data that meets or does not meet the normal distribution, and is more robust to outliers; it is suitable for ordered data (such as ranking, grade) or non-linear but monotonic relationships. It can be seen from the comparison of Spearman correlation coefficients between various indicators and bone mineral density T-score in total and between groups in Table 4 that in the analysis of the correlation coefficients between various indicators and bone mineral density T-score in 150 patients, LDH, lactic acid, serum calcium, serum phosphorus, urine creatinine, P1NP, and β-CTx have significant correlations at the 0.01 level. It can be inferred that the above indicators are significantly associated with the occurrence and progression of osteoporosis. Among them, lactic acid, serum calcium, serum phosphorus, uric acid, urine creatinine, P1NP, and β-CTx are positively correlated with bone mineral density T-score, indicating that the above indicators can regulate and delay the occurrence and development of osteoporosis.

7. Discussion and Conclusion

Osteoporosis is a systemic metabolic bone disease characterized by low bone mass and destruction of bone microstructure. Its continuous progression can lead to increased bone fragility and thus fractures. The global number of patients exceeds 200 million, and the risk in women is significantly higher than that in men (postmenopausal women have accelerated bone loss due to a sharp drop in estrogen). With the aging of the global population, the prevalence of people over 60 years old has exceeded 36% (women) and 23% (men). The 1-year mortality rate after hip fracture can reach 20%-30%, which is an important cause of disability and death in the elderly [16]. Its pathogenesis mainly involves the following aspects: imbalance of bone metabolism: the ability of osteoblasts to generate bone matrix decreases, and the bone resorption of osteoclasts increases, leading to bone resorption > bone formation; abnormal hormone regulation: estrogen deficiency (weakened inhibition of osteoclast activity), increased parathyroid hormone (promoting bone resorption), and vitamin D deficiency (affecting calcium absorption) are core factors; nutrition and metabolism: insufficient calcium intake, protein deficiency, abnormal levels of metabolites such as lactic acid, aggravating bone loss; genetics and environment: genetic factors account for 60%-80% of the risk of onset (such as vitamin D receptor gene polymorphism), and lifestyle factors such as sedentary behavior, smoking, and excessive drinking can also induce or aggravate the disease. In recent years, relevant studies have revealed the role of metabolites (such as lactic acid) and epigenetic modifications (such as histone lactylation) in bone metabolism, providing new ideas for the development of targeted drugs (such as preparations that regulate osteoblast metabolism). At the same time, moderate increase in lactic acid levels induced by exercise has been confirmed to improve bone mass by promoting osteogenic differentiation, providing theoretical support for non-pharmacological intervention [17].

Lactic acid is the end product of glycolysis, and its accumulation in the bone microenvironment may affect the function of osteoblasts and osteoclasts. Previous studies have shown that high concentrations of lactic acid may inhibit osteoblast differentiation, reduce the expression of alkaline

phosphatase (ALP) and osteocalcin (OCN), thereby reducing bone formation. In addition, lactic acid promotes osteoclast generation by activating the RANKL/NF-κB pathway and accelerates bone resorption, but this process may be regulated by intestinal flora metabolism, forming a complex network of interactions [18]. As the end product of glycolysis, the concentration of lactic acid is directly affected by LDH activity. A study by Shanghai Changzheng Hospital found that the serum lactic acid level of patients with osteoporosis was significantly reduced, and the histone lactylation level of bone marrow mesenchymal stem cells (BMSCs) was decreased, leading to reduced expression of osteogenic genes and ultimately bone loss [19]. This result indicates that lactic acid level is positively correlated with bone formation, and lactic acid regulates osteogenic-related genes (such as RUNX2, Osterix) through epigenetic modifications (such as histone lactylation) to promote bone formation. The results of this study show that there is a significant positive correlation between patients' lactic acid levels and bone mineral density T-scores, which is consistent with the above conclusions.

Studies have shown that lactic acid can participate in regulating the differentiation of bone marrow mesenchymal stem cells (BMSCs), and endothelial cells can produce lactic acid through aerobic glycolysis [20]. Specific knockout of pyruvate kinase M2 (PKM2) in bone vascular endothelial cells will reduce glycolysis level and lactic acid secretion, thereby inhibiting the differentiation of BMSCs into osteoblasts, leading to decreased bone mass and weakened osteogenic function. Exogenous supplementation of lactic acid can partially restore the osteogenic capacity of BMSCs, indicating that lactic acid is a core signaling molecule for crosstalk between blood vessels and bones. On the other hand, lactic acid can modify lysine 18 of histone H3, namely H3K18la lactylation modification, to activate osteogenic genes such as COL1A2, COMP, ENPP1, and TCF7L2. The levels of H3K18la and the expression of the above genes in BMSCs of osteoporotic patients are significantly reduced, affecting bone formation, thereby playing a role in the occurrence and development of osteoporosis.

Relevant studies have also shown that exercise can affect bone metabolism through lactic acid [21]. Exercise can increase blood lactic acid levels. Running training can significantly increase bone vascular density in ovariectomized (OVX) mice. Adenovirus overexpression of PKM2 can simulate the effect of exercise and rebuild the bone vascular network. Lactic acid can simultaneously activate the osteogenic differentiation of BMSCs and the proliferation of vascular endothelium, suggesting that exercise may indirectly activate the osteogenic differentiation of BMSCs by regulating lactic acid levels, and have a preventive and therapeutic effect on osteoporosis. A study on metabolomics detection of serum from the general population and patients with osteoporosis showed that the lactic acid level of patients with osteoporosis was relatively low, and the histone lactylation and related osteogenic gene expression of BMSCs were reduced [22], which further indicated that lactic acid level was associated with osteoporosis and could be used as a potential indicator to evaluate osteoporosis. This conclusion is also consistent with the results of this study.

In addition, relevant research conclusions also indicate that there is a clear dose-dependent relationship between lactic acid level and bone mass [23], and its core mechanism focuses on bone marrow microenvironment metabolism, stem cell differentiation regulation, and epigenetic modification. In vitro experiments show that lactic acid has a two-way dose-dependent effect on the osteogenic differentiation of BMSCs. Physiological concentrations (0.5-5 mM) of lactic acid can up-regulate osteogenic-related genes (such as COL1A2, RUNX2) by activating histone H3K18la modification, promote the differentiation of BMSCs into osteoblasts, and increase bone matrix synthesis; while high concentrations (>10 mM) of lactic acid inhibit osteogenic differentiation and promote adipocyte differentiation by inhibiting the Wnt/β-catenin pathway or inducing oxidative stress, leading to reduced bone mass. This phenomenon has been verified in ovariectomized (OVX) osteoporotic model mice [24]. Exogenous supplementation of low-dose lactic acid (2 mM) can restore the number and thickness of trabecular bone, while high-dose (20 mM) has no improvement or even aggravates bone loss. Relevant studies have shown that lactic acid produced by bone vascular endothelial cells through glycolysis has a positive dose-dependent relationship with bone vascular density and bone mass [25]. Specific overexpression of PKM2 (a key glycolytic enzyme) in endothelial cells can increase lactic acid secretion by 2-3 times, accompanied by the expansion of bone vascular network and the increase of bone formation rate (bone mineralization rate increased by 40%). After knockout of PKM2, lactic acid secretion decreased by more than 50%, bone vascular density decreased, and bone mass significantly decreased, while supplementation of medium-dose lactic acid (5 mM) can reverse this effect, but high-dose cannot further improve, suggesting that there is a lactic acid saturation threshold. Studies have shown that there is a certain linear correlation between exercise-induced lactic acid levels and bone mass [26]. Moderate exercise (such as jogging, resistance training) maintains serum lactic acid at 2-4 mM, and the bone mineral density of the lumbar spine and femoral neck increases by 3%-5% compared with resting state; while high-intensity exercise leads to a sudden increase in lactic acid (>8 mM), bone mineral density does not improve or even inhibits osteoblast activity due to excessive acidification. The above relevant conclusions provide an important reference for the next in-depth study of the dose relationship between serum lactic acid level and bone mass in this study.

Bone tissue is highly dependent on efficient energy supply to maintain the bone remodeling process. LDH is a key enzyme in the glycolytic pathway, catalyzing the interconversion between pyruvate and lactic acid. In bone tissue, the activity of LDH is closely related to the energy metabolism of osteoblasts and osteoclasts. Osteoblast differentiation requires a lot of energy support. LDH affects intracellular lactic acid levels by regulating glycolysis rate. High concentrations of lactic acid may inhibit osteoblast differentiation, reduce the expression of alkaline phosphatase (ALP) and osteocalcin (OCN), thereby reducing bone formation [27]; osteoclasts rely on glycolysis for energy during bone resorption. Increased LDH activity may promote lactic acid production, activate the RANKL/NF-κB signaling pathway, enhance osteoclast activity, and accelerate bone resorption. Abnormal LDH activity may disrupt bone metabolism balance. Decreased LDH activity may lead to insufficient lactic acid

production and inhibit osteogenic differentiation; while abnormally increased activity may lead to enhanced bone resorption by excessively promoting osteoclast function. Bone tissue is highly dependent on efficient energy supply to maintain the bone remodeling process.

LDH isozymes affect the activity and function of bone cells by regulating the balance between glycolysis and oxidative phosphorylation. LDH1/LDH2 are highly expressed in cells rich in mitochondria and play a protective role in normal bone metabolism as potential protective factors [28]: they tend to catalyze the oxidation of lactic acid to pyruvate, promote the tricarboxylic acid cycle and oxidative phosphorylation, provide continuous energy for osteoblast differentiation and bone matrix mineralization, support the mitochondrial respiratory chain function of osteoblasts, and ensure efficient energy supply; reduce microenvironment acidification, reduce lactic acid accumulation, and maintain a neutral pH environment. However, during the progression of osteoporosis, the LDH1/LDH2 ratio often decreases, and its protective effect is offset by LDH5. LDH4 (HM_3), although weaker than LDH5, still has the characteristic of promoting lactic acid production. In patients with CKD-MBD (chronic kidney disease-mineral and bone disorder), LDH4/LDH5 often increase simultaneously, jointly promoting high-turnover bone disease.

LDH5 has high pyruvate affinity and anti-substrate inhibition characteristics, driving the reduction of pyruvate to lactic acid and accelerating glycolysis under hypoxia or metabolic stress. Although this characteristic is beneficial in acute energy demand, long-term activation can lead to energy metabolism disorders of bone cells. Continuous activation of LDH5 causes a large accumulation of lactic acid, directly causing acidification of the bone microenvironment (decreased pH). The acidic environment ($pH < 7.0$) directly stimulates the differentiation of osteoclast precursors and the bone resorption activity of mature osteoclasts. H^+ ions can dissolve bone minerals (hydroxyapatite) and provide suitable degradation conditions for collagenase [29]. In addition, collagen synthesis and alkaline phosphatase (ALP) activity of osteoblasts are significantly reduced under acidic conditions, leading to blocked bone formation. Studies have shown that for every 0.1 decrease in pH, the mineralization ability of osteoblasts decreases by about 15%. It should be noted that LDH5 exacerbates bone remodeling imbalance through metabolic reprogramming. Osteoclasts are inherently dependent on glycolysis during bone resorption. High expression of LDH5 further strengthens their glycolytic phenotype and enhances their survival and bone erosion ability; high lactic acid levels inhibit TGF-β signaling pathway and HIF-1α stability, repress the expression of osteogenic-related genes (such as Runx2, Osterix), and weaken bone formation ability.

Relevant studies have also found that specific knockout of the key glycolytic enzyme PKM2 in bone vascular endothelial cells reduces lactic acid secretion and significantly decreases bone mass [30], suggesting that LDH-mediated lactic acid production is crucial for maintaining normal bone mass. Patients with chronic obstructive pulmonary disease (COPD) are often accompanied by bone metabolism disorders, and its mechanism may be related to enhanced glycolysis and changes in LDH activity caused by hypoxia. Long-term inflammatory response and glucocorticoid use further aggravate bone resorption. Some clinical studies have shown that serum LDH isozyme determination is not directly related to bone mineral density, but may be indirectly related to secondary factors such as muscle atrophy [31]. LDH is involved in bone metabolism balance by regulating lactic acid production, and its abnormal activity may lead to osteoblast-osteoclast imbalance, thereby inducing or aggravating osteoporosis. Through data analysis, this study found that LDH has a significant negative correlation with bone mineral density T-score, that is, continuous abnormal LDH metabolism will significantly disrupt bone balance and bone integration ability, thereby aggravating the progression of osteoporosis. Future studies need to further clarify the specific role of LDH in different cell types (such as osteoblasts, osteoclasts, endothelial cells) and explore precise treatment strategies based on metabolic regulation.

It is necessary to discuss the bone metabolism-related indicators P1NP and β-CTx. Type I procollagen is hydrolyzed to remove the additional peptide segments at its carboxyl and amino ends to generate procollagen. The carboxyl-terminal additional peptide segment removed from procollagen is called type I procollagen C-terminal propeptide (P1CP), and the amino-terminal additional peptide segment is called type I procollagen N-terminal propeptide (P1NP). The content of P1CP or P1NP in serum reflects the ability of osteoblasts to synthesize bone collagen and is a specific and sensitive indicator of new bone formation [32]. Serum P1CP is increased in patients with bone metabolic diseases, renal insufficiency, children in the developmental stage, bone tumors, bone metastases, osteoporosis, Paget's disease, osteomalacia, and postmenopausal women [33]. Type I collagen C-terminal cross-linked peptide (CTx) is the most widely used collagen degradation marker. α-CTx and β-CTx are isomers. The level of CTx reflects the bone resorption activity of osteoclasts. Serum CTx levels are increased in patients with osteoporosis, Paget's disease, multiple myeloma, and tumor bone metastases [34].

P1NP and β-CTx are the most commonly used and recognized markers reflecting the two opposite directions (resorption vs. formation) in the bone remodeling cycle. They are the "two sides of the same coin" for understanding bone metabolic status. In terms of anti-resorptive therapy, β-CTx is the preferred indicator for monitoring efficacy and compliance. Its significant decrease (usually ≥50% decrease within 3-6 months) is a sign of effective treatment. P1NP will also decrease, but the response may be slower or smaller [35]. In terms of bone-forming therapy, P1NP is the preferred indicator for monitoring efficacy. Its significant increase (usually within 1-3 months) indicates that osteoblast activity is effectively stimulated. They are often used in combination to evaluate bone turnover status. Simultaneous detection can distinguish high-turnover (both high), low-turnover (both low), or uncoupled status (such as high resorption and low formation). This is of great significance for understanding the pathophysiology of osteoporosis and individualized treatment [36]. In addition, their combined application can predict fracture risk. Both increases are independent predictors of fracture risk independent of BMD, and their combined use can provide more comprehensive risk information. Their

combined application can also be used for drug holiday monitoring. Changes in their levels after drug withdrawal (especially rebound) help determine whether to restart treatment. β-CTx and P1NP are indispensable biomarkers in modern bone metabolism assessment. They are not competitive but powerful complementary tools. Understanding their core differences in biological nature, detection requirements, and response patterns to treatment is the key to accurately applying them to guide clinical decisions (especially individualized treatment monitoring and risk assessment of osteoporosis). The choice of which marker as the main monitoring indicator depends primarily on the type of treatment the patient is receiving (anti-resorptive vs. bone-forming). Strict adherence to standardized sampling procedures (especially early morning fasting for β-CTx) is the cornerstone of ensuring result reliability. Finally, the results of the markers need to be integrated into the patient's complete clinical treatment plan for comprehensive judgment.

In conclusion, serum LDH and lactic acid levels, as commonly used clinical biochemical markers, are significantly correlated with bone mineral density T-score. LDH level is significantly negatively correlated with bone mineral density T-score, and lactic acid level is significantly positively correlated with bone mineral density T-score. The above two indicators have a significant impact on the occurrence and progression of osteoporosis. The conclusions drawn from this study are expected to better guide the diagnosis and treatment of osteoporosis and provide a more scientific basis for clinical doctors' decisions.

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Declarations

Ethics Approval and Consent to Participate.

This study has been submitted to the Medical Ethics Review Committee of Tianjin Hospital and obtained an ethical approval statement (Ethics approval number: 2024 Medical Ethics Review 029).

This study is in line with the Declaration of Helsinki.

Informed consent has been obtained from all participants for this study.

Consent for Publication

Not Applicable.

Author Contributions

LB planned the study and wrote this manuscript; JK J, ZK M, HJ Z and ZW P performed the data extraction and statistical analysis; HW Y, JX M and XL M reviewed the manuscript. All the authors have read the manuscript and approved it for publication.

ADM Statement Request

The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

Competing Interests

The authors declare no competing interests.

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