Zeng. *Metab Target Organ Damage* 2024;4:1
DOI: 10.20517/mtod.2023.39

Metabolism and Target Organ Damage

Editorial

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Metabolic bone disease: from basic science to clinical frontier

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How to cite this article: Zeng LF. Metabolic bone disease: from basic science to clinical frontier. *Metab Target Organ Damage* 2024;4:1. https://dx.doi.org/10.20517/mtod.2023.39

Received: 23 Oct 2023 **Accepted:** 27 Nov 2023 **Published:** 30 Nov 2023

Academic Editor: Juan Pablo Arab **Copy Editor:** Dan Zhang **Production Editor:** Dan Zhang

INTRODUCTION

Metabolic bone disease is defined as a diverse group of disorders that result in abnormalities of (i) bone mass; (ii) structure mineral homeostasis; (iii) bone turnover; (iv) growth. The most prevalent form is osteoporosis, characterized by microstructural deterioration of bone tissue and decreased bone mineral density. 55% of the subjects aged ≥ 50 years worldwide suffer from osteopenia or osteoporosis[1]. The link between the lifetime risk of fracture of the hip, wrist, or vertebral regions and osteoporosis has already been identified. Beyond compromising athletic ability, osteoporotic fractures severely impact daily functionality and mobility, resulting in personal and societal burdens[1,2].

Metabolomics is a new kind of omics developed after genomics, transcriptomics, and proteomics. Its basic definition is "in the dynamic process of metabolism of organisms, through the systematic analysis of the changes in the spectrum of endogenous metabolites in the body fluids and tissues of organisms, to systematically study the biological status and regulatory function of organisms as a whole after external stimulation"[3]. Metabolomics emphasizes the study of the body as a complete system, which coincides with the overall regulatory effect of traditional Chinese medicine (TCM). It can amplify the subtle changes in

gene expression and protein expression on metabolite, which aids in uncovering the pathogenesis of osteoporosis and biomarkers after TCM treatment, and further analyzing the metabolic pathways related to these biomarkers, thereby clarifying the mechanisms through which TCM treats osteoporosis. In recent decades, significant progress has been made in pharmaceuticals and treatments for osteoporosis, particularly in bone homeostasis and bone remodeling[2].

METABOLIC DISORDERS AND OSTEOPOROSIS

It mainly focuses on lipid metabolism and osteoporosis, fatty acid metabolism and osteoporosis, amino acid metabolism and osteoporosis, sugar metabolism and osteoporosis. Relevant studies suggest that the above factors play an important role in the pathogenesis of osteoporosis[3].

STUDY ON METABOLOMICS OF SINGLE HERBAL MEDICINE FOR OSTEOPOROSIS

Xia's research found that Morindae Officinalis Radix exerts its anti-osteoporosis effect mainly by regulating arachidonic acid metabolism in rats with glucocorticoid-induced osteoporosis, while Prepared rhizome of Adhesive Rehmannia exerts its anti-osteoporosis effect mainly related to steroid biosynthesis in osteoporosis[4]. Pan *et al*. studied the effects of Shortorned Epimedium Herb on serum and urine metabolites in glucocorticoid-induced osteoporosis model mice by NMR, and found that Shortorned Epimedium Herb could treat osteoporosis by regulating glycolysis, aerobic oxidation, lipid metabolism, phospholipid metabolism, energy metabolism, amino acid metabolism, and intestinal flora disorder[5]. Based on GC-MS technology, Wang *et al*. found that Eucommia Ulmoides Oliv could induce downregulated glycine, lysine, docosahexaenoic acid, glucose and upregulated tryptophan rollback in the serum of ovariectomized osteoporosis rat model, and its mechanism may be related to regulating amino acid metabolism and oxidative stress[6]. Huang *et al*. have found that for the treatment of glucocorticoid-induced osteoporosis, rhizoma drynariae mainly plays a role by interfering with sphingolipid metabolism, anti-oxidation-oxidation balance and phenylalanine metabolism in the body, while for the osteoporosis model of rats induced by retinoic acid, rhizoma drynariae plays a role by regulating linoleic acid metabolism, glycerophospholipid metabolism, and arachidonic acid metabolism[7,8]. The above studies show that a single Chinese medicine can achieve the purpose of treating osteoporosis by regulating multiple metabolic pathways, and for osteoporosis caused by different reasons, the metabolic pathways regulated by the same Chinese medicine are not exactly the same.

METABONOMICS STUDY ON THE TREATMENT OF OSTEOPOROSIS BY CHINESE HERBAL COMPOUND

Under the guidance of the theory of traditional Chinese medicine, TCM compounds play the role of multi-way intervention in diseases through drug compatibility. Li conducted a study on the treatment of retinoic acid-induced osteoporosis in rats with self-made Shen-Ling Jian-Gu Capsule (Shortorned Epimedium Herb, Dipsaci Radix, Salviae Miltiorrhizae, Polygonum Multiflorum Thunb, Prepared rhizome of Adhesive Rehmannia, Rhizoma Corydalis, *etc*.), and found that Shen-Ling Jian-Gu Capsule could inhibit osteoporosis by regulating amino acid metabolism, energy metabolism, sugar metabolism, fat metabolism and hormone levels[9]. Luo *et al*. analyzed the plasma of primary osteoporosis mice treated with Zhen-Zhu Tiao-Zhi Prescription (Finger Citron Fruit, Fructus Ligustri Lucidi, Salviae Miltiorrhizae, Radix Notoginseng, Rhizoma Coptidis, Largehead Atractylodes Rhizome, Ligusticum wallichii, Eucommia Ulmoides Oliv), and found 12 potential biomarkers for anti-primary osteoporosis, the mechanism of which may be related to the regulation of phospholipid, arachidonic acid and energy metabolism[10]. Shu-Gan Bu-Shen Formula is composed of Shortorned Epimedium Herb, Bupleurum falcatum L., Achyranthes bidentata Blume, Fructus Psoraleae, Eucommia Ulmoides Oliv, Dipsaci Radix, Curcumae Radix. Wu's research found that it can reverse the plasma levels of four biomarkers: acetone, lactic acid, n-acetylglycoprotein, and fatty acid in

ovary-removed osteoporosis rats[11]. Liu *et al*. found that the serum metabolic spectrum of ovariectomized rats was close to that of normal rats after treatment with Jian-Gu Granule (composed of Shortorned Epimedium Herb, Common Macrocarpium Fruit, Common Yam Rhizome, Pilose Asiabell Root, *etc*)[12]. The analysis of differential metabolite-related pathways showed that Jian-Gu Granule may improve postmenopausal osteoporosis by regulating various metabolic pathways such as lipid metabolism, nucleic acid metabolism, and amino acid metabolism. Based on the metabolomics of GC-MS, Yuan *et al*. dug out the potential biomarkers of anti-osteoporosis of Gu-Shu Dan (Shortorned Epimedium Herb, Common Cnidium Fruit, rhizoma drynariae, Salviae Miltiorrhizae), including 11 biomarkers such as malic acid, malonic acid, adipic acid, glutaric acid and L-threonic acid, which were mainly related to amino acid metabolism, energy metabolism, fatty acid metabolism, and oxidative stress[13]. The above literature analysis found that in the treatment of osteoporosis, traditional Chinese medicine compounds primarily employ herbal remedies that nourish the liver and kidney. These compounds work through the compatibility of various drugs, utilizing multiple pathways to regulate the level of metabolism and achieve a therapeutic effect.

METABOLOMICS STUDY ON THE TREATMENT OF OSTEOPOROSIS BY CHINESE HERBAL EXTRACTS

Xu's study found that 9 biomarkers such as carnitine, 2-methylmalonic acid, and 5-hydroxy-n-formylguanine in the serum of ovariectomized rats with osteoporosis were significantly upregulated, while 20 biomarkers such as leukotriene F4 and PC (22:6/18:1) were significantly downregulated[14]. After the intervention of Cistanche phenylethanoid glycosides (CPhGs), 23 biomarkers were significantly reversed, and the metabolic pathway analysis showed that they were mainly related to fatty acid metabolism, amino acid metabolism, phospholipid metabolism, *etc*. Zhang *et al*. studied the intervention of Acanthopanax lignin in ovarian osteoporosis removal based on LC-MS technology and found that the main metabolic pathways regulated by acanthopanax lignin include unsaturated fatty acid biosynthesis, linoleic acid metabolism, arachidonic acid metabolism, primary bile acid synthesis, and tyrosine metabolism[15]. Acanthopanthoside exerts its effects mainly by interfering with steroid hormone biosynthesis, primary bile acid biosynthesis, glutathione metabolism, and tyrosine metabolism[16]. Si *et al*. showed that the treatment of ovariectomized osteoporosis by Osthole is mainly related to 13 metabolic pathways such as linoleic acid metabolism, starch and sucrose metabolism, arachidonic acid metabolism, alanine, aspartate and glutamate metabolism[17]. The above studies confirmed that in addition to single herb medicine and Chinese herbal compounds, Chinese herbal extracts can also play an anti-osteoporosis role by regulating different metabolic pathways.

SUMMARY AND CONCLUSION

No matter it is a single herbal medicine, Chinese medicine compound, or Chinese medicine extract, it can effectively realize the anti-osteoporosis effect by regulating the metabolic level of the body. With the continuous development of metabolomics detection technology, more and more studies have been conducted on the treatment of osteoporosis by Chinese medicine based on metabolomics. Through the study of metabolomics, people can accurately find the potential targets of Chinese medicine in the treatment of osteoporosis, and further reveal the mechanism of action of Chinese medicine in the treatment of osteoporosis. Through the study of metabolomics, the main metabolic pathways involved in TCM treatment of osteoporosis were found to be lipid metabolism, fatty acid metabolism, amino acid metabolism, energy metabolism, *etc*. At present, the methods used for differential metabolite detection mainly include LC-MS, GC-MS, and NMR. Different detection methods have their own advantages and disadvantages. Due to the complex composition of biological samples, different detection techniques can be used for detection according to the properties and characteristics of different samples. At present, the samples used for

differential metabolite detection are mainly serum and urine, and there is a lack of specific detection samples. Osteoporosis is a disease of bone metabolism. Synovial fluid in the joint cavity is in direct contact with bone tissue and receives substances from surrounding tissue, articular cartilage, synovial membrane, and bone. Therefore, synovial fluid may contain important biological information and be a choice for specific test samples. In addition, the studies on the treatment of osteoporosis with Chinese medicine based on metabolomics are mostly at the animal level, including the animal model of ovariectomized osteoporosis, the animal model of glucocorticoid-induced osteoporosis, the animal model of retinoic acid-induced osteoporosis and the animal model of primary osteoporosis. However, clinical studies are lacking and further studies are needed.

DECLARATIONS

Acknowledgments

I would like to thank all the authors and reviewers who contributed to the success of this Research Topic with their high-quality research and crucial comments. Thanks are due to other editors of this collection. This collection would not be realized without their input and dedication.

Author contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

Financial support and sponsorship

This research was funded by grants from the Research Fund for Bajian Talents of Guangdong Provincial Hospital of Chinese Medicine (No.BJ2022KY01); Project of Philosophy and Social Science Planning of Guangzhou (No.2022GZQN42); National Natural Science Foundation of China (No. 82004383); Guangdong Basic and Applied Basic Research Foundation (No. 2022A1515220131).

Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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