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Analysis on the correlation between the occurrence of vertebral artery ostium stenosis and the severity of osteoporosis in elderly patients with atherosclerosis

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To analyze the correlation between the occurrence of vertebral artery ostium stenosis (VAOS) and the severity of osteoporosis in elderly patients with atherosclerosis (AS), and disclose the physiopathologic mechanism of the correlation between VAOS and osteoporosis. 120 patients were divided into two groups. The baseline data of both groups were collected. The biochemical indicators of patients in both groups were collected. The EpiData database was established to enter all the data into the database for statistical analysis. There were significant differences in the incidence of dyslipidemia among risk factors of cardia-cerebrovascular disease (*P<0.05*). LDL-C, Apoa and Apob were significantly lower than the control group (*P<0.05*). BMD, T-value and Ca in the observation group were significantly lower than the control group, while BALP and serum phosphorus in the observation group were significantly higher than the control group (*P<0.05*). The more severe the VAOS stenosis, the higher the incidence of osteoporosis, and there was a statistical difference in the risk of osteoporosis among different VAOS stenosis degrees (*P<0.05*). Apolipoprotein A, B and LDL-C in blood lipids are important factors affecting the development of bone and artery diseases. There is a significant correlation between VAOS and the severity of osteoporosis. The pathological calcification process of VAOS has many similarities with the process of bone metabolism and osteogenesis, and shows preventable and reversible physiological characteristics.

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Keyword: atherosclerosis; vertebral artery ostium stenosis; osteoporosis; bone mineral density; alkaline phosphatase; phosphate.

INTRODUCTION

Some relevant studies show that posterior-circulation ischemic stroke accounts for about 25%-40% of the total strokes, and nearly 70% of posterior-circulation ischemic stroke is caused by artery and arterial embolism *(1-2)*. VAOS easily causes ischemic stroke in the posterior-circulation, because the initial part of vertebral artery ostium stenosis (VAOS) is prone to disturbance of hemodynamics and also prone to atherosclerosis (AS). The incidence of this disease is high, but no enough clinical attention has been paid to its diagnosis and treatment. At

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present, antiplatelet drugs and stent implantation are mainly used in clinical treatment, both of which have certain application limitations. In order to find a more effective and safe therapy, improve the clinical cognition of AS and VAOS and standardize the clinical diagnosis and treatment, it is necessary to conduct further studies on its pathogenesis *(3,4)*. The studies *(5)* have shown that osteoporosis is closely related to cardiovascular disease and AS disease, and the probability of VAOS in AS disease patients is as high as 40%. At the same time, from the anatomical and physiological perspective, the anatomical composition of vertebral artery is closely related to the bone of the cervical vertebral body, so we speculated a certain correlation between VAOS and osteoporosis *(6,7)*. Based on this, this study will compare AS patients with and without VAOS. Bone mineral density (BMD), T-value of bone mineral density, bone alkaline phosphatase (BALP), blood phosphorus (P) and other important indexes of bone metabolism were used as parameters to observe the severity of osteoporosis, to verify the correlation between VAOS and osteoporosis, so as to provide pathological mechanism and theoretical reference for the clinical study of VAOS treatment. The report is as follows.

Figure 1. — Overview system components.

MATERIALS AND METHODS

A prospective study was conducted to collect the data of elderly inpatients with AS in Department of Neurology, XXX Hospital from January 2018 to December 2019. A total of 60 patients with VAOS were included in the observation group, and 60 patients without VAOS who received DSA examination during the same period and had baseline data matching were listed in the control group.

Diagnostic criteria: referred to *Prevention of Atherosclerotic Cardiovascular Disease* (2017) *(8)* published by Japanese Atherosclerosis Society (JAS) and referred to the *Chinese Expert Consensus on Intravascular Treatment of Symptomatic Atherosclerotic Vertebral Artery Initial Stenosis (2017) (9)* published by the Cerebrovascular Disease Intervention Group of Stroke Prevention and Control Committee of the Chinese Preventive Medical Association.

Inclusion criteria: (1) Conformed to the above guideline diagnostic criteria and confirmed by digital subtraction angiography (DSA); (2) No other serious cardiovascular diseases; (3) The patient signed the informed consent.

Exclusion criteria: (1) Patients with intracranial or carotid bulb atherosclerosis or other types of artery stenosis ; (2) Patients with primary osteoporosis or other diseases affecting bone metabolism were excluded – Because many patients with very low bone mineral density or osteoporosis have been treated – ; (3) Long-term taking of calcium and other drugs that affect the study results.

The baseline data of both groups were collected, including age, gender, other arterial stenosis, and cardia-cerebrovascular disease risk factors (including hypertension, diabetes, dyslipidemia, smoking, alcohol drinking, body mass index, et al.).

The biochemical indicators of patients in both groups were collected, including triglyceride (TG), total cholesterol (TC), high density lipoprotein (HDL-C), low density lipoprotein cholesterin (LDL-C), apolipoprotein A (Apoa), apolipoprotein B (Apob), bone mineral density (BMD), BMD T-value, bone alkaline phosphatase (BALP), Blood Calcium (Ca) and Blood phosphorus (P).

The orthotopic (L2-L4) BMD of the lumbar spine was detected by dual-energy X-ray absorptiometry (source: Norland XR-600), and the BMD T value (T<-2SD for osteoporosis) was calculated. Fastening venous blood 3ml was collected, and the contents of Ca, P (complexometric titration), BALP (double-antibody sandwich ELISA), TG, TC,

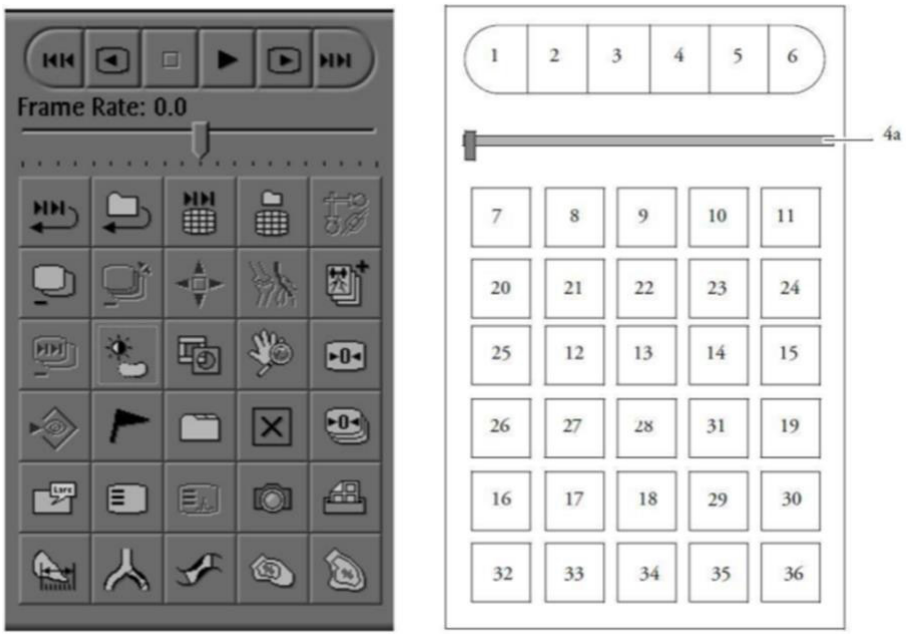

Figure 2. — Control room.

HDL-C, LDL-C, ApoA and ApoB were detected by automatic biochemical analyzer (source: Olympus AU600, Japan).

The indexes of blood lipid, blood glucose and bone metabolism were compared between the two groups, and the correlation between the degree of VAOS stenosis and the severity of osteoporosis was analyzed. Classification of VAOS stenosis degree *(10)*: Mild: Grade-1 DSA stenosis <25%; Moderate (grade 2-3) stenosis 26%-50%, 51%-75%; Severe (grade 4-5) stenosis was 76%-90% and ≥91%. Osteoporosis was diagnosed as T-value < -2SD.

The data were included in SPSS23.0 software for analysis, and the measurement data were compared using "t" test, and the indexes of lipid, apolipoprotein and bone metabolism were represented by $\bar{x} \pm s$. The count data was tested by Chi-square test, and the incidence of osteoporosis was represented by the rate (%), indicating a statistically significant difference ($P<0.05$).

RESULTS

Comparison of Baseline Data of Elderly Patients with AS between both Groups

Table I. — Overview system components

1. Live Monitor	6. Xper Imaging module	11. Xper module (option)
2. Reference Monitor	7. Data Monitor	12. Tube
2. 3D-RA Monitor	8. View Monitor	13. Flat Detector
4. Xper Module + viewpad	9. 3D-RA workstationr	14. C-arc
5. Xper Geometry module	10. Xper Review module	15. L-arm

There were no significant differences in baseline data (gender, age, BMI, hypertension, diabetes, smoking and alcohol consumption) between the two groups ($P>0.05$), while there were significant differences in the incidence of dyslipidemia among risk factors of cardia-cerebrovascular disease ($P<0.05$), as shown in Table I.

Comparison of Blood Lipid and Apolipoprotein Indexes of AS Patients between both Groups

There were no significant differences in TG, TC and HDL-C between the observation group and

Table II. — Control room review

22. Pixel displacement	23 Bony markers	24 Tracing	25 Sequence subtraction	33 Vascular analysis	34 Coronary analysis

Table III. — Comparison of bone metabolism indexes of AS patients between both groups ($\bar{x} \pm s$)

Group	Cases	BMD (g/cm2)	BMD T-value	BALP (IU/L)	Ca (mmol/L)	P (mmol/L)	PTH(ng/ml)	25(OH)D (μg/mL)
Observation group	60	0.68±0.15	-1.42±0.25	146.70±18.63	1.54±0.32	2.23±0.48	125.93±68.16	18.72±2.48
Control group	60	0.91±0.18	-1.13±0.22	121.45±14.37	1.96±0.37	1.46±0.35	156.15±93.49	26.54±2.52
t	-	7.604	6.745	8.313	6.651	10.040	2.023	17.132
P	-	0.001	0.001	0.001	0.001	0.001	0.045	0.000

the control group (*P>0.05*), while LDL-C, Apoa and Apob were significantly lower than the control group (*P<0.05*), as shown in Table II.

Comparison of Bone Metabolism Indexes of AS Patients between both Groups

BMD, T-value and Ca in the observation group were significantly lower than the control group, while BALP and serum phosphorus in the observation group were significantly higher than the control group (*P<0.05*), as shown in Table III.

Analysis on the Correlation between VAOS Degree and the Severity of Osteoporosis

The more severe the VAOS stenosis, the higher the incidence of osteoporosis, and there was a statistical difference in the risk of osteoporosis among different VAOS stenosis degrees (*P<0.05*), as shown in Table IV.

Table IV. — Analysis on the Correlation between VAOS Degree and the Severity of Osteoporosis (n, (%))

Group	Cases	Osteoporosis Rate
Severe	15	14 (93.33)
Moderate	27	12 (44.44)
Mild	18	5 (27.78)
χ^2	-	15.106
P	-	0.001

DISCUSSION

Atherosclerotic vertebral artery ostium stenosis (VAOS) is a common clinical senile ischemic cerebrovascular disease (ICVD). According to relevant studies, 9%-33% of posterior-circulation ischemic patients have VAOS or occlusion, but the diagnosis and treatment of this disease has not attracted enough clinical attention *(11)*. It has been clinically believed that VAOS is involved in the occurrence of posterior-circulation ischemia through thromboembolism and low perfusion mechanism. However, some studies *(12,13)* have shown that the plaque morphology and pathological characteristics of VAOS are significantly different from those of carotid artery.Previously, it was clinically believed that osteoporosis, VAOS as two independent of age-related diseases, but in recent years, many studies *(14,15)* show that osteoporosis and atherosclerotic cardiovascular disease of comorbid conditions, share common risk factors and physiological mechanism of osteoporosis in the pathologic process of calcium by the dissolution increases bone calcium deposition in the systemic circulation in the arterial wall lining, further increase the degree of atherosclerotic lesions, reduce vascular compliance; meanwhile, arteriosclerosis will also cause systemic pathological changes, reduce bone mineral content and increase the risk of osteoporosis. Therefore, by analyzing the correlation between VAOS and osteoporosis, this study aims to explore the possible mechanism of VAOS from the pathophysiology of

osteoporosis, and explore new ideas and methods for the treatment of VAOS on the theoretical basis.

VAOS is caused by arterial lesions, local accumulation of lipids and complex sugars, and the gradual formation of thrombosis, fibrous tissue hyperplasia and calcosis, followed by degeneration and calcification of the middle artery, artery closure, thickening and hardening, and narrowing of the lumen. The findings showed that there were significant differences in the incidence of dyslipidemia among risk factors of cardia-cerebrovascular disease ($P<0.05$). LDL-C, Apoa and Apob were significantly lower in the observation group ($P<0.05$). It lies in that apolipoprotein A and B are involved in extracellular cholesterol transport and play a role in maintaining internal environment balance in the metabolic pathway of the body. Those can regulate the influence of cardiovascular risk factors on the occurrence of arterial calcification. The LDL-C result may be attributed to the fact that oxidized LDL-C promotes the differentiation of osteoblasts in vascular smooth muscle cells, which leads to the mineralization of arterial wall. At the same time, oxidized LDL-C also stimulated bone marrow stromal cells to undergo gradual fat formation and significantly reduced bone mass. BMD, T-value and Ca in the observation group were significantly lower than the control group, while BALP and serum phosphorus were significantly higher in the observation group ($P<0.05$). The more severe the VAOS stenosis, the higher the incidence of osteoporosis, and there was a statistical difference in the risk of osteoporosis among different VAOS stenosis degrees ($P<0.05$), which indicates that various bone metabolism indexes are closely related to the formation of VAOS. It lies in that elevated blood phosphorus will promote vascular calcification signaling pathway, increase extracellular matrix degradation, and release osteoblasts, so this level is negatively correlated with VAOS. The reduced calcium absorption in VAOS patients decreases the free calcium level in blood, increases parathyroid hormone secretion, damages the functional balance of osteoblasts and osteoclasts, further changes bone structure and mechanics, decreases bone density, and increases BALP. The severity of stenosis is closely related to the degree of arterial calcification. The more severe the stenosis is, the greater the influence on the body and bone metabolites will be.

The results showed that there was a significant correlation between VAOS and the severity of osteoporosis, and the factor of blood lipid was an important factor affecting the development of bone and artery diseases. Some research proposed *(16,17)* that atherosclerotic - lipid - skeletal model could well explain the association between VAOS and osteoporosis. Oxidized LDL-C promotes osteoblastic differentiation in vascular smooth muscle cells, which leads to mineralization of arterial walls; meanwhile, oxidized LDL-C also stimulates bone marrow stromal cells to undergo gradual fat formation and significantly reduce bone mass. In addition, VAOS plaques are rich in lipids, a large number of macrophages and pro-inflammatory response factors. Inflammatory factors enhance the stimulation of osteoclast precursors and mature cells and aggravate the process of arterial calcification. Therefore, the association between VAOS and osteoporosis may also be explained by endothelial function, and the application of vasodilators plays an important role in the prevention of AS-induced cardiovascular disease and osteoporosis. The pathological calcification process of VAOS has many similarities with the process of bone metabolism and osteogenesis, and shows preventable and reversible physiological characteristics.

CONCLUSION

In conclusion, apolipoprotein A, B and LDL-C in blood lipids are important factors affecting the development of bone and artery diseases, and there is a significant correlation between VAOS and the severity of osteoporosis. The degree of stenosis and obstruction can be reflected according to the geometric characteristics of blood vessels and changes in blood density, and the bone metabolism indexes can be measured to prevent osteoporosis in patients, which will provide theoretical support to select more beneficial therapy for clinical VAOS .

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