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The correlation between vitamin D and inflammatory indicators in middle-aged and elderly patients with idiopathic membranous nephropathy

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ABSTRACT

This study investigates the relationship between vitamin D and inflammatory indicators in middle-aged and elderly patients with idiopathic membranous nephropathy (IMN). In this study, 100 middle-aged and elderly patients with IMN were enrolled in the nephropathy group and 100 healthy people were enrolled as a control group. The clinical data and test specimens were collected. The patients were categorized into deficiency group and lack group based on vitamin D level. The levels of serum vitamin 25 (OH) D, inflammatory indicators and clinical indicators were compared between the nephrotic group and the control group. The levels of inflammatory indicators and clinical indicators were compared. Pearson correlation analysis was applied to detect the correlation degree between serum vitamin 25 (OH) D, inflammatory indicators and clinical indicators in IMN patients. The outcomes compared with the control group, the levels of vitamin 25 (OH) D, IL-10, IFN-γ and ALB in the nephrotic group were significantly lower and CRP, IL-6, TNF-α, Cr, CysC, β2-MG were significantly higher (all $p<0.05$). Compared with the vitamin D deficiency group, the levels of IL-10, IFN-γ and ALB were significantly lower and NLR, CRP, IL-4, IL-6, TNF-α, 24 urinary protein, Cr, CysC, β2-MG were significantly higher in the vitamin D lack group ($p<0.05$). Vitamin 25 (OH) D level was negatively correlated with CysC, β2-MG, 24hUP, CR ($r=-0.412, -0.387, -0.382, -0.429$, all $p<0.05$) and was positively correlated with ALB ($r=0.463$, $p<0.001$). the conclusion Low vitamin D level in middle-aged and elderly patients with IMN is common and vitamin D supplementation can improve the clinical symptoms and delay the development of IMN.

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Introduction

Membranous nephropathy (MN) is not a rare glomerular disease characterized by immune complex deposition, second only to IgA nephropathy in incidence. Idiopathic membranous nephropathy (IMN) is a form of MN (1). IMN is regarded as a single-organ autoimmune disease, which is attributed to many cases of nephrotic syndrome (NS), accounting for 70%-80% of membranous nephropathy (2). Its incidence has been increasing and becoming the most common primary glomerular disease. Although there is a trend of younger age in recent years, it is still dominated by middle-aged and elderly people (3). Current studies have found that deficiency and lack of vitamin D are common in IMN patients. Vitamin D has a variety of immunomodulatory properties that support anti-inflammatory effects in disease. This regulation mainly focuses on promoting the production of anti-inflammatory cytokines and inhibiting the production of proinflammatory cytokines (4). Studies have shown that in addition to immunological and complement factors, which are widely concerned at present, inflammatory factors, is very crucial in the pathogenesis and progression for IMN. However, rare studies investigated the vitamin D level and senile patients with IMN. The present study investigates vitamin D levels and inflammation indicators in middle-aged and elderly IMN patients.

Materials and Methods

General information

100 middle-aged and elderly IMN patients from the Department of Nephrology, Minzu Hospital of Guangxi Zhuang Autonomous Region from 2021 to 2022 were collected. 100 healthy adults were enrolled as control. The current study has been agreed and received authorization from the Ethics Committee of Minzu Hospital of Guangxi Zhuang Autonomous Region.

Inclusion and exclusion criteria

All enrolled IMN patients were diagnosed by several examinations including light microscopy, renal biopsy, immunopathology electron microscopy and other routine examinations. Some patients suffered from diseases should be excluded including secondary membranous nephropathy, autoimmune diseases, infectious diseases,

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malignant tumors and metabolic diseases.

Detection methods

Serum, EDTA-anticoagulated whole blood and 24-hour urine were collected from IMN patients and healthy controls. SYSMEX automatic hematology analyzer was used to detect whole blood cell analysis and calculate NLR. Flow cytometry of BD Company was used to detect inflammatory factors (IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ). Hitachi 7600 automatic biochemical analyzer was used to detect C-reactive protein, 24-hour urinary protein, serum albumin, serum urea, and creatinine. Roche electrochemiluminescence immunoanalyzer Cobase6000 was used to detect vitamin 25 (OH) D. All the samples were tested with the original matching reagent. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines: 25 (OH)D< 20ng/mL is vitamin D lack, 20ng/mL≤25(OH)D< 30 ng/mL is vitamin D deficiency, and ≥30 ng/mL is vitamin D sufficiency(5). According to the results of vitamin D, the patients were divided into the vitamin D lack group, vitamin D deficiency group and vitamin D sufficient group to analyze the levels of inflammatory indicators and clinical indicators.

Statistical analysis

The whole data were calculated by SPSS21.0. (X±S) was the manifestation of all measurement data. T-test and one-way ANOVA were applied to compare two groups and multiple groups.

Results

The comparison of indicators between the IMN group and the control group

Compared with the control group, the levels of vitamin 25 (OH) D, IL-10, IFN-γ and ALB in the nephrotic group were significantly lower and NLR, CRP, IL-6, TNF-α, Cr, CysC, β2-MG were significantly higher (p<0.05). The comparison for indicators were shown in Table 1.

The comparison for indicators between the vitamin D lack group and vitamin D deficiency group

Compared with the vitamin D deficiency group, the levels of IL-10, IFN-γ and ALB in the vitamin D lack group were significantly lower and CRP, IL-4, IL-6, TNF-α, 24 urinary protein, Cr, CysC, β2-MG in the vitamin D lack group were significantly higher (p<0.05). The comparison

Table 1. The comparison of indicators between the IMN group and the control group. Where, IMN, Idiopathic membranous nephropathy.

indicators	IMN group (n=100)	Control group (n=100)	P
vitamin 25 (OH) D (ng/mL)	12.81±5.45	24.67±8.89	p<0.05
NLR	2.57±1.44	1.69±0.77	p>0.05
CRP	5.11±2.78	3.97±2.01	p<0.05
IL-2	0.11±0.93	0.08±0.05	p>0.05
IL-4	0.53±0.16	0.46±0.19	p>0.05
IL-6	14.83±6.78	2.82±1.09	p<0.05
IL-10	0.83±0.38	1.84±0.82	p<0.05
TNF-α	0.57±0.17	0.27±0.06	p<0.05
IFN-γ	2.31±0.78	3.16±0.79	p<0.05
24 urinary protein (g/24 h)	3.69±1.62	\	\
ALB(g/L)	25.78±6.24	47.78±6.65	p<0.05
BUN (mmol/L)	5.96±1.25	4.89±1.45	p>0.05
CR (μmol/L)	91.98±30.47	72.89±19.78	p<0.05
CYSC(mg/L)	1.15±0.48	0.74±0.27	p<0.05
β2-MG(mg/L)	3.39±1.73	2.16±1.09	p<0.05

Table 2. The comparison for indicators between the vitamin D lack group and vitamin D deficiency group.

indicators	Vitamin D lack group	Vitamin D deficiency group	P
vitamin 25 (OH) D (ng/mL)	7.62±4.31	23.32±4.16	p<0.05
NLR	2.59±1.53	2.33±1.01	p>0.05
CRP	6.91±3.61	3.12±1.89	p<0.05
IL-2	0.12±0.07	0.10±0.03	p>0.05
IL-4	0.51±0.318	0.37±0.356	p<0.05
IL-6	14.50±5.45	7.25±3.12	p<0.05
IL-10	0.58±0.55	1.06±0.76	p<0.05
TNF-α	0.61±0.08	0.13±0.63	p<0.05
IFN-γ	0.43±0.13	2.34±1.78	p<0.05
24 urinary protein (g/24 h)	3.37±1.78	1.32±1.08	p<0.05
ALB(g/L)	22.51±6.31	31.67±7.52	p<0.05
BUN(mmol/L)	6.54±1.74	5.07±0.97	p>0.05
CR (μmol/L)	92.26±38.22	64.28±15.32	p<0.05
CYSC(mg/L)	1.17±0.48	0.72±0.29	p<0.05
β2-MG(mg/L)	3.48±1.74	1.87±0.63	p<0.05

Table 3. The association between vitamin 25 (OH) D and clinical indicators, inflammatory indicators.

indicators	r	P
NLR	-0.118	p>0.05
CRP	-0.115	p>0.05
IL-2	-0.036	p>0.05
IL-4	-0.065	p>0.05
IL-6	0.043	p>0.05
IL-10	-0.043	p>0.05
TNF-α	0.134	p>0.05
IFN-γ	-0.012	p>0.05
24 urinary protein (g/24 h)	-0.386	p<0.05
ALB(g/L)	0.454	p<0.05
BUN (mmol/L)	-0.082	p>0.05
CR (μmol/L)	-0.429	p<0.05
CYSC (mg/L)	-0.412	p<0.05
β2-MG(mg/L)	-0.386	p<0.05

for indicators between the vitamin D lack group and the vitamin D deficiency group were shown in Table 2.

The association between vitamin 25 (OH) D and clinical indicators, inflammatory indicators

Vitamin 25 (OH) D level was negatively correlated with CysC, β2-MG, 24hUP, CR (r=-0.412, -0.387, -0.382, -0.429, all p<0.05) and was positively correlated with ALB (r=0.463, p<0.001). The association between vitamin 25 (OH) D and clinical indicators and inflammatory indicators was shown in Table 3.

Discussion

IMN is a pathological mode of glomerular injury caused by an autoimmune reaction, which is the main cause of NS and one of the main causes of end-stage renal disease (ESRD) (6). The clinical course of IMN is variable, and the prognosis of patients varies greatly. 1/3 patients have spontaneous remission, long-term persistent proteinuria, and slowly progress to ESRD after 5-15 years (7). At present, it is believed that the pathogenic mechanism of IMN is: the glomerular in situ antigen and antibody combine to form an immune complex to activate complement, and form a membrane attack complex to cause podocyte damage. As inflammatory mediators, cytokines such as interleukin (IL), tumor necrosis factor-α (TNF-α) and vascular endothelial growth factor (VEGF) are involved in the immune injury process of membranous nephropathy. Inflammatory factors are one of the important pathogenic factors in the occurrence and development of IMN, and chronic inflammation is one of the main pathological characteristics of IMN.

Vitamin D is a hormone with a broad spectrum of effects, which can regulate the body's calcium, phosphorus, PTH levels and regulate the homeostasis of multiple organs and regions, especially the immune system. Studies have shown that vitamin D can reduce the levels of serum pro-inflammatory cytokines and C-reactive protein in the acute phase, and play an important role in the proliferation and differentiation of renal cells, immune inflammatory response, other inflammatory chronic and acute diseases and cardiovascular and cerebrovascular diseases. This study found that the vitamin D level of middle-aged and elderly IMN patients was significantly lower than that of the control group, and all of them were lower than the normal value. Therefore, low vitamin 25 (OH) D levels are common in middle-aged and elderly IMN patients.

Interleukin (IL) is a cytokine involved in a variety of inflammatory pathways (8). IL-2 is a major autocrine and paracrine T cell growth factor, which can induce and enhance cytotoxic activity. IL-4 is a typical chemokine that can mediate T-cell activation and is of great value in the study of some inflammatory and autoimmune diseases (9). Vitamin D can promote the transformation of Th cells from Th1 to Th2, increasing the number of Th2 cells responsible for anti-inflammatory cytokines, while decreasing the number of Th1 cells responsible for secreting proinflammatory cytokines (10). This indicates that the immune status of middle-aged and elderly patients with idiopathic membranous nephropathy is disordered, with inflammation, increased secretion of proinflammatory factors and decreased secretion of anti-inflammatory factors. The lower the vitamin D level, the lower the anti-inflammatory factors and the higher the proinflammatory factors. C-reactive protein (CRP) is a product of acute inflammation, mainly induced by hepatocytes to produce inflammatory cytokines, especially IL-6.

Vitamin D has a kidney protective effect and is closely related to the kidney. In chronic kidney disease, vitamin D plays a certain role in the repair of non-specific immune disorders and inflammatory-mediated renal injury. The autoimmune reaction of antibodies in IMN and the circulation of target antigens on cells combine to form in situ immune complexes deposited in the space between cells and the basement membrane, leading to podocyte destruction, basement membrane thickening and glomerular filtration barrier damage, and then a series of abnormal indicators such as proteinuria, low plasma protein concentration and metabolic disorders. This may be related to the limitations of this study: the number of patients is not large enough, and the cross-sectional design lacks the changes of indicators before and after vitamin D treatment. Therefore, whether vitamin D can participate in the regulation of inflammatory indicators in middle-aged and elderly patients with IMN needs further large-scale studies to explore. In addition, Bioinformatics has been promoting the progress of medicine and plays a key role in the diagnosis, treatment and prognosis of diseases (11-16). Therefore, we should focus our attention on bioinformatics analysis in IMN.

In conclusion, low vitamin D level is common in middle-aged and elderly patients with idiopathic membranous nephropathy. The lower the vitamin D level, the more disturbed the inflammatory indicators such as CRP, IL-2, IL-4, IL-6, IL-10, TNF-α and IFN-γ, and the more serious the clinical indicators are. Therefore, vitamin D supplementation can improve clinical symptoms and delay the development of the disease.

Data sharing statement

All data generated or analyzed during this study are included in this published article.

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Author contributions

Zhihu Huang conceived the study design and content concept; Zuojie Lu, Shimin Dai, Lingyan Qin, Bo Nong and Cuibo Huang performed the data collection, extraction and analyzed the data. Zhihu Huang interpreted and reviewed the data and drafts.

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Disclosure

The authors declare that they have no competing interests.

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