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*Original Article*

# Efficacy of methotrexate on rheumatoid arthritis patients with coronary heart disease and its effects on carotid intima-media thickness and patch stability

Shuyun Wen[1*], Na Yang[1*], Fangying Zhu[1], Jing Lv[1], Qin Geng[2]

*[1]Department of Traditional Chinese Medicine Rheumatology, Dezhou People's Hospital, Dezhou, Shandong Province, China; [2]Department of Rheumatology, Central Hospital of Zibo, Zibo, Shandong Province, China. [*]Equal contributors.*

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**Abstract:** Objective: This study aims to investigate the efficacy of methotrexate on rheumatoid arthritis patients complicated with coronary heart disease, and its effects on carotid intima-media thickness and patch stability. Methods: A total of 130 patients with rheumatoid arthritis and coronary heart disease were selected from Dezhou People's Hospital from June 2016 to June 2017. The patients were treated with methotrexate for 6 months, and the treatment efficacy was observed. Results: After 6 months of treatment, the total effective rate was 84.62%. Moreover, the numbers of tender joint count and swollen joint count were significantly smaller, and morning stiff time after treatment were significantlyshorter than that before treatment (all P = 0.000). The carotid intima-media thickness and patch area after treatment were significantly lower than that before treatment (both P = 0.000). After treatment, the levels of total cholesterol, triglyceride, low density lipoprotein cholesterol, and high-sensitivity C-reactive protein, homocysteine, tumor necrosis factor were significantly lower than those before treatment (all P = 0.000). There was no significant difference in high-density lipoprotein cholesterol before and after treatment (P = 0.896). The incidence of adverse reactions was 9.23%. Conclusion: Methotrexate treatment on patients with rheumatoid arthritis and coronary heart disease has obvious efficacy, and can effectively reduce the progression of patch, improve the carotid intima-media thickness, relieve the inflammatory response of the body. It has a high promotional value in the future.

**Keywords:** Methotrexate, rheumatoid arthritis with coronary heart disease, carotid intima, patch stability

## Introduction

Rheumatoid arthritis (RA) is a systemic chronic autoimmune disease. With the continuous improvement of treatment strategies, joint disease in patients with RA has been greatly improved. However, there are still some patients, especially with cardiovascular and cerebrovascular diseases which induced by atherosclerosis (AS), whose prognosis is still not ideal [1]. Studies have shown that the incidence of cardiovascular adverse events (CAD) in patients with RA is approximately 13%, which was much higher than that in the normal population (5%), also, the mortality rate was approximately 50% higher than that in the normal population [2]. Therefore, RA is considered as an independent risk factor for CAD [3]. This may be due to the persistent inflammatory response during the course of RA in patients with endothelial cell damage, disorders of lipid metabolism, and acceleration with progression of atherosclerotic lesions [4]. Therefore, it is a great clinical significance to pay attention to the treatment of RA patients complicated with coronary heart disease. Studies have shown that early use of methotrexate could not only improve arthritis in patients with RA, but also reduce progression of AS, and reduce the risk of cardiovascular disease [5, 6]. However, there are only few studies on specific mechanisms.

This study selected 130 RA patients complicated with coronary heart disease in Dezhou People's Hospital from June 2016 to June 2017 to investigate the therapeutic value of methotrexate.

**Table 1.** Improvement of clinical symptoms ($\bar{x}$ ± sd)

| | Tender joint count | Swollen joint count | Morning stiff time (min) |
|---|---|---|---|
| Before treatment | 14.91 ± 6.13 | 13.97 ± 7.55 | 93.21 ± 46.74 |
| After treatment | 9.07 ± 6.92 | 8.76 ± 6.35 | 54.26 ± 24.66 |
| *t* | 7.203 | 6.021 | 8.404 |
| P | 0.000 | 0.000 | 0.000 |

**Table 2.** Comparison of carotid intima-media thickness and patch area ($\bar{x}$ ± sd)

| | Carotid intima-media thickness (mm) | Patch area ($mm^2$) |
|---|---|---|
| Before treatment | 1.88 ± 0.37 | 7.12 ± 1.73 |
| After treatment | 1.49 ± 0.32 | 5.98 ± 1.26 |
| *t* | 9.090 | 6.073 |
| P | 0.000 | 0.000 |

## Materials and methods

### *Patient information*

One hundred and thirty RA patients complicated with coronary heart disease were recruited in Dezhou People's Hospital from June 2016 to June 2017. Inclusion criteria were consisted of (A) confirmed based on the diagnostic criteria of non-acute RA which developed by Chinese Rheumatism Association in 2007, and the medical history was less than 1 year; (B) no medical treatment (including lipid-lowering, anti-rheumatic drugs) were taken before entering this study; (C) coronary heart disease was diagnosed by coronary angiography, but the degree of stenosis was less than 50% in the stable period of the disease, and heart function class ≥ 3 based on New York Heart Association [7]. Exclusion criteria consisted of (A) patients with severe arrhythmia; (B) patients with diabetes, heart failure, and malignancy; (C) patients with organic hepatorenal disorders, hypothyroidism, and Cushing syndrome; (D) the drugs that affect lipid metabolism were applied in the past one month; (E) unable to cooperate with the treatment and had poor compliance. Among the 130 patients, 48 cases were males and 82 cases were females. The age ranged from 53 to 78 years old, and mean age was 65.5 ± 7.3 years old. The disease duration ranged from 5 months to 6 years with an average of 3.6 ± 1.3 years. This study has got approval from Ethical Committee of Dezhou People's Hospital. The patients understood and signed the informed consent.

### *Methods*

Methotrexate tablets (Tonghua Maoxiang Pharmaceutical, China) were given to all patients. The starting dose was 10 mg once a week. After 2 weeks, the dosage gradually increased to 15 mg (once a week, per os) based on the treatment effect and tolerability. At the same time, on the 2nd day of methotrexate treatment, oral administration of folic acid (10 mg, once a day) was used to antagonize the toxic side effects of methotrexate [8]. The curative effect was evaluated after 6 months of continuous treatment. During the treatment period, followup was performed every 3 months to check the changes in the routine biochemical parameters, such as blood routine and liver function of the patient. Blood samples of the patients were collected before and after the treatment for 12 months to detect the relevant indicators.

### *Outcome measures*

Main outcome measures were as follows. Tender joint, swollen joint, and morning stiff time were recorded and compared before and after 6 months of treatment. Clinical efficacy was analyzed as follows [9]. If the score of inflammatory symptoms and physical signs decreased more than 75%, normal or tended to be normal erythrocyte sedimentation rate was considered to be recovered; if the scores of inflammatory symptoms and signs were reduced by 31% to 74%, and a significant decrease in erythrocyte sedimentation rate was regarded as effective; if the score of inflammatory symptoms and signs decreased by less than 30%, and no significant decrease or increase in ESR was considered as invalid. The total effective rate is calculated by dividing the number of recovered and effective cases by the total number of cases. Carotid intima-media thickness (IMT) was measured as follows [10]. Using Philips ie33 color Doppler ultrasound instrument, the thickest parts of proximal arterial, as well as proximal and distal carotid intima of the common carotid artery were detected before and 6 months after treatment. Then the IMT was recorded and averaged. The patch was determined as follows. The number and size of patches in patients were measured by color Doppler imaging. The patch area was cal-

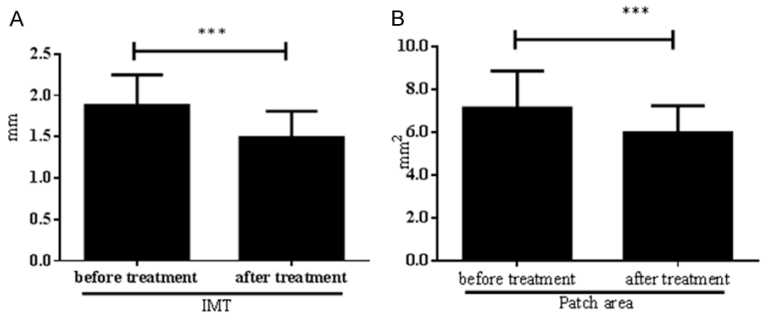


**Figure 1.** Comparison of carotid intima-media thickness and patch area Note: ***P < 0.001; IMT, intima-media thickness.

culated, and the intima media thickness ≥ 1.5 mm was considered as patch formation [11].

Secondary outcome measures were as follows. Venous blood was collected before treatment and after 6 months of treatment. Total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were determined by high performance liquid chromatography. High-sensitivity C-reactive protein (Hs-CRP) and tumor necrosis factor (TNF-α) were measured by enzyme-linked immunosorbent assay. Homocysteine (Hcy) was determined by liquid chromatography with fluorescence detection. The occurrence of adverse reactions was also recorded.

*Statistical analysis*

SPSS19.0 software was used for statistical analysis. Measurement data is expressed as mean ± standard deviation ($\bar{x}$ ± sd). The measurement data (before and after the treatment) was compared with t test. P < 0.05 indicated statistically significant difference.

## Results

*Clinical efficacy*

Compared with the data before treatment, tender joint, the swollen joint, and morning stiff time significantly reduced in 130 patients after 6 months of treatment (all P = 0.000, **Table 1**). Among the 130 patients, 38 cases were markedly effective, 72 cases were effective, while 20 cases were ineffective. The total effective rate reached 84.62%.

*Changes in carotid intima-media thickness*

Six months after treatment, the patient's carotid intima-media thickness and patch area were significantly lower than that before treatment (both P = 0.000, **Table 2**, **Figure 1**).

*Changes in blood lipid levels*

The TC, TG, and LDL-C levels after treatment were significantly lower than that before treatment (all P = 0.000, **Table 3**). However, there was no significant difference in HDL-C between before and after treatment (P = 0.896).

*Changes in levels of inflammatory factors*

The levels of Hs-CRP, Hcy, and TNF-α in patients after treatment were significantly lower than that before treatment (all P = 0.000, **Table 4**).

*Occurrence of adverse reactions*

During the treatment period, a total of 12 patients experienced adverse reactions, including 5 cases of gastrointestinal reactions (nausea, vomiting, etc.), 4 cases of elevated transaminases, and 3 cases of oral ulcers. The incidence of adverse reactions was 9.23%.

## Discussion

RA is a progressive form of synovitis. The lifespan of patients with RA is about 5-10 years shorter than that of ordinary people. Among them, death caused by coronary heart disease is 50%-72% higher than that of ordinary people. Both RA and coronary heart disease are immune-mediated inflammatory diseases. Inflammatory response in RA joints is similar to that of coronary heart disease patches. Both of them have been found TNF-α (the product of inflammation) in patients [12]. At the same time, the pathogenesis of RA and coronary heart disease are characterized by elevated CRP levels [13]. Research showed that RA complicated with coronary heart disease was about 3.5%, which is significantly higher than the incidence of the general population. Clinical treatment of RA complicated with coronary heart disease should be promptly intervened to improve the patient's prognosis [14].

Methotrexate is a commonly used drug for the treatment of RA [15]. This drug can inhibit the phosphoramidyl transferase which required for purine synthesis, thereby regulating the transi-

**Table 3.** Changes in blood lipid levels ($\bar{x}$ ± sd)

| | TC (mmol/L) | TG (mmol/L) | LDL-C (mmol/L) | HDL-C (mmol/L) |
|---|---|---|---|---|
| Before treatment | 6.08 ± 0.66 | 3.08 ± 0.42 | 3.77 ± 0.65 | 1.28 ± 0.69 |
| After treatment | 4.79 ± 0.21 | 2.15 ± 0.31 | 2.81 ± 0.34 | 1.29 ± 0.54 |
| *t* | 15.016 | 14.363 | 10.551 | 0.131 |
| P | 0.000 | 0.000 | 0.000 | 0.896 |

Note: TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein.

**Table 4.** Changes in levels of inflammatory factors ($\bar{x}$ ± sd)

| | Hs-CRP (g/L) | Hcy (μmol/L) | TNF-α (mg/ml) |
|---|---|---|---|
| Before treatment | 0.45 ± 0.08 | 21.88 ± 3.62 | 265.37 ± 60.36 |
| After treatment | 0.30 ± 0.07 | 15.38 ± 2.65 | 147.45 ± 30.21 |
| *t* | 16.089 | 16.519 | 19.919 |
| P | 0.000 | 0.000 | 0.000 |

Note: Hs-CRP, high-sensitivity C-reactive protein; Hcy, homocysteine; TNF-α, tumor necrosis factor alpha.

tion from the interstitial phase to the synthetic phase as well as the cell cycle of T lymphocytes. It can also improve immunity, and relieve the effect of RA [16]. In addition, methotrexate can also inactivate methylol glutarate CoA reductase and acetyl CoA carboxylase in the AMPK pathway, then inhibit the formation of LDL, LC, and TG in RA patients. It will eliminate patch, reduce the cholesterol load of atherosclerosis, and exert an ideal anti-atherogenic effect [17]. A previous study has shown that the use of methotrexate in patients with RA was significantly lower than that of carotid intima-media thickness, and effectively reduced the risk of RA-related cardiovascular and cerebrovascular events [18].

In this study, methotrexate was used to treat RA patients complicated with coronary heart disease. The results showed that after 6 months of treatment, 130 patients had significantly lower tender joint, swollen joint, and shorter morning stiff time than that before treatment. The total effective rate was achieved to 84.62%. These results suggest that methotrexate can effectively control the symptoms of joint inflammation in patients with RA.

At the same time, the carotid intima-media thickness and patch area of the treated patients were significantly lower than before treatment. These results suggest that methotrexate could stabilize patch and eliminate patch. In addition, the TC, TG, and LDL-C levels after treatment were significantly lower than before treatment. These results suggested methotrexate also had the purpose of improving lipid metabolism in RA patients, which is consistent with the previous report [19]. Therefore, the early use of methotrexate in RA patients complicated with coronary heart disease can not only control the condition of RA, but also improve lipid metabolism of RA patients. It also stabilizes atherosclerotic patch, reduces progression of atherosclerosis in RA patients, and reduces the risk of cardiovascular adverse events.

The development of RA is closely related to the body's chronic inflammatory response. In patients with RA, a large number of inflammatory cytokines such as IL-1, IL-6 and TNF-α are synthesized, which not only promotes the development of joint inflammation, but also promotes the development of atherosclerosis [20]. The previous study has reported that the level of inflammation in patients with RA was significantly associated with the occurrence of atherosclerosis and mortality from cardiovascular events [21]. The results of this study showed that the levels of Hs-CRP, Hcy, and TNF-α in patients after treatment were significantly lower than before treatment. These results suggested that methotrexate can effectively control the inflammatory response of the body, which may be its main mechanism of action to control RA condition and improve lipid metabolism, and slow the progression of early atherosclerosis.

In addition, during the treatment period, a total of 12 patients had adverse reactions, including 5 cases of gastrointestinal reactions (nausea, vomiting, etc.), 4 cases of elevated transaminases, and 3 cases of oral ulcers. The incidence of adverse reactions was 9.23%. All patients were tolerant and did not stop treatment. These results suggested that small doses of methotrexate were safe and feasible.

Due to the small sample size and short observation time, only the short-term efficacy of methotrexate was observed, and the exact correlation between the improvement of the inflammation level and the progression of atherosclerosis could not be determined. The above conclusions are only speculations. In the next study, we will increase the sample size and observation time to explore this issue. At the same time, only the effect of methotrexate on the stability of atherosclerotic patches in patients with non-acute RA was observed, and the efficacy of RA in different conditions was not explored. Moreover, the efficacy of combination therapy with methotrexate and other drugs was not compared. Thus, the effect of methotrexate on stability of atherosclerotic patches in patients with RA and the efficacy of combination therapy will be analyzed in the further study.

In conclusion, methotrexate had a definite curative effect on rheumatoid arthritis patients complicated with coronary heart disease. It could stabilize and eliminate patches, improve carotid intima-media thickness, relieve inflammatory reactions in the body, as well as has generalizable value in the future.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Shuyun Wen, Department of Traditional Chinese Medicine Rheumatology, Dezhou People's Hospital, No. 1751 Xinhu Street, Decheng District, Dezhou 253014, Shandong Province, China. Tel: +86-0534-2637794; E-mail: wenshuyun9df7@163.com

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