Short term effects of Technetium-99 conjugated with methylene diphosphonate (99Tc-MDP) & oral glucocorticoids on lipid profiles in Chinese patients with active rheumatoid arthritis

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Abstract

Objective Consideration of 99Tc-MDP and glucocorticoids are widely treated the patients with active RA in China, we wondered whether 99Tc-MDP or and oral glucocorticoids had an effect on lipid profiles in short term. Patients & Methods Patients with active RA were divided into two groups, who were treated with 99Tc-MDP or and GCs for 10 days. ESR, CRP and DAS28, lipid profiles were detected at baseline and the 10th day of treatment. Comparison of inflammatory markers and lipid profiles between treatment before and after was run by t test. The correlation coefficient between inflammatory markers and lipid levels was computed by nonparametric Spearman correlation analysis and line regression analysis. Results ESR, CRP and DAS28CRP or ESR were decreased significantly after treatment in the two groups. The levels of TG and ApoA1 were increased significantly in the group of 99Tc, while the ratio of ApoB/ApoA1 was decreased. In the group of 99Tc & GC, CHO, TG, and HDL-C, ApoA1 were increased after treatment, atherogenic index and the ratio of ApoB/ApoA1 both got down. Correlation analysis showed that CHO, LDL-C and ApoB inversely related to DAS28CRP or ESR in the group of 99Tc. HDL-C, TG and ApoA1, and ratio of ApoB/ApoA1 or atherogenic index were correlated with CRP, ESR or DAS28 ESR or CRP in the group of 99Tc & GC. Conclusions RA patients treated with 99Tc-MDP or and oral glucocorticoids occurred inflammatory attenuation, disease activity reduction as well as lipid profile changes.

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Statement of Conflict of interest

The authors have no conflicts of interest to declare.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval statement

The study has been performed according to the declaration of Helsinki, and that the procedures have been approved by the Medical Ethics Committee at the First affiliated Hospital of Xiamen University (KY202015-034).

Abstract

Objective Consideration of ^{99}Tc-MDP and glucocorticoids are widely treated the patients with active RA in China, we wondered whether ^{99}Tc-MDP or and oral glucocorticoids had an effect on lipid profiles in short term.

Patients & Methods Patients with active RA were divided into two groups, who were treated with ^{99}Tc-MDP or and GCs for 10 days. ESR, CRP and DAS28, lipid profiles were detected at baseline and the 10th day of treatment. Comparison of inflammatory markers and lipid profiles between treatment before and after was run by$t$ test. The correlation coefficient between inflammatory markers and lipid levels was computed by nonparametric Spearman correlation analysis and line regression analysis.

Results ESR, CRP and DAS28$_{\text{CRP or ESR}}$ were decreased significantly after treatment in the two groups. The levels of TG and ApoA1 were increased significantly in the group of^{99}Tc, while the ratio of ApoB/ApoA1 was decreased. In the group of ^{99}Tc & GC, CHO, TG, and HDL-C, ApoA1 were increased after treatment, atherogenic index and the ratio of ApoB/ApoA1 both got down. Correlation analysis showed that CHO, LDL-C and ApoB inversely related to DAS28$_{\text{CRP or ESR}}$ in the group of ^{99}Tc. HDL-C, TG and ApoA1, and ratio of ApoB/ApoA1 or atherogenic index were correlated with CRP, ESR or DAS28$_{\text{ESR or CRP}}$ in the group of ^{99}Tc & GC.

Conclusions RA patients treated with ^{99}Tc-MDP or and oral glucocorticoids occurred inflammatory attenuation, disease activity reduction as well as lipid profile changes.

Keywords

^{99}Tc-MDP & GC, Rheumatoid arthritis, Anti-inflammation, Lipid profile, Dyslipidemia

1 Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease involving joint pain, joint erosion, and eventually joint destruction [1]. Dyslipidemia is associated with active RA increasing the risk of cardiovascular events, which are the most common cause for mortality. Cardiovascular morbidity is increased more than twofold in RA patients compared to the general population. A wide range of cardiovascular diseases occur in RA patients, including atherosclerosis, thrombosis, and myocardial infarction, heart failure, valvular heart disease, arrhythmia, aortic aneurysms, myo-, peri and endocarditis, vasculitis, rheumatoid cardiac nodules, and cardiac amyloidosis [2-6]. The risk of cardiovascular disease in RA remains high even after adjustment for known cardiovascular risk factors including use of particular medications. Inflammation likely plays a prominent role. Proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, which are found in the synovial tissue, are also found in the circulation [7-9]. These circulating cytokines alter various aspects of metabolism in distant organs, including adipose tissue, skeletal muscle, liver, and vascular endothelium [10, 11]. A spectrum of proatherogenic changes result that include endothelial dysfunction, insulin resistance, and dyslipidemia, prothrombotic effects, and pro-oxidative stress [12-15].

Various studies have been found inconsistent results regarding correlations between inflammation and alterations in particular plasma lipids in the patients with RA who have been given different regimens. A study indicated that HDL-C (high density lipoprotein-cholesterol) were elevated in the patients with RA after treatment of adalimumab for 2 weeks, but LDL-C (low density lipoprotein-cholesterol) and TG (triglycerides) levels were not changed significantly [16]. Another study, in which infliximab was given for 2 years to patients with early RA showed that the levels of TC (total cholesterol), LDL-C and the atherogenic index increased during 24 months, while HDL-C initially increased concomitant with the three lipid parameters, and then decreased significantly after 3 months until the end of the study [17]. The literatures reported that atherogenic index remained constant, while other lipids such as TC, or HDL-C, or LDL-C, or TG increased significantly using infliximab in the patients with active RA for 3 weeks to 6 months [18-20]. In long-term study, the notable findings were that HDL-C, ApoA1 decreased and atherogenic index increased after treatment with DMARDs (disease-modifying anti-rheumatic drugs) and prednisolone in the patients with RA follow-up over 12-year period [21]. Overall, Dyslipidemia is a common complication in rheumatoid arthritis. The lipid profiles varied when disease activity was modified with intervention of drugs. Thereby, dyslipidemia may be attenuated or induced in RA.

Technetium-99 conjugated with methylene diphosphonate (^{99}Tc-MDP, Yunke Pharmaceutical Industry, China), is an anti-inflammatory drug patented in China (patent no. ZL94113006.1). Previous studies demonstrated that ^{99}Tc-MDP inhibits MAPK (mitogen-activated protein kinase) signaling thus reducing the production of proinflammatory cytokines such as IL-1β and IL-6 [22]. Additional studies suggested that ^{99}Tc-MDP reduced joint swelling by regulating the levels of BAP, TRAP and DKK-1[23]. Bone destruction was reduced and the rebuilding new bone enhanced by^{99}Tc-MDP in animal models of arthritis [24]. Thus,^{99}Tc-MDP had not only an effect on against inflammation and also on disease modifying in the patients with active RA. To date, ^{99}Tc-MDP was widely used to treat the patients with active RA in China for its efficacy and inexpensive. Same thing, glucocorticoids are also benefit to active RA, such as reducing disease activity and pain, as well as protective effects on joint destruction [25]. Glucocorticoids are also known, reversible cause of dyslipidemia [26]. ^{99}Tc-MDP combined with oral glucocorticoids were often used to the patients with active RA in China. No studies have evaluated whether ^{99}Tc-MDP and or glucocorticoids improves the dyslipidemia seen in patients with active RA. This study was designed to evaluate this issue.

2 Patients and methods

2.1 Patients with RA and evaluation of disease activity

Sixty-nine patients with RA who fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) for RA were given a 10-day treatment with ^{99}Tc-MDP or and oral glucocorticoids at the First Affiliated Hospital of Xiamen University in period of Feb. 2019 ˜ Dec. 2020 [27]. According with different therapy regimens, they were divided into two groups including ^{99}Tc-MDP (n = 27, as^{99}Tc) and combined with oral glucocorticoids (n = 42, as ^{99}Tc & GC) (Table1). Exclusion criteria included the combination of other autoimmune diseases (including secondary Sjögren's syndrome), hematological system, liver or kidney dysfunction ([?] 1.5 times of the upper limit of the cutoff value), pregnant women, oral hypolipidemic drugs and receiving intra-articular injection of corticosteroids in the last four weeks. None of the patients had diabetes mellitus, impaired glucose tolerance, and cerebrovascular diseases, cardiovascular disease, thyroid dysfunction, nephrotic syndrome, alcoholism, chronic liver disease, Cushing syndrome or obesity (body mass index $>$ 30 kg/m^2). Based on retrospective observation, the study was approved by the Medical Ethics Committee at the First affiliated Hospital of Xiamen University (KY202015-034).

The disease activities of the patients with RA were evaluated by erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and disease activity score 28 for rheumatoid arthritis with ESR or CRP ($DAS28_{ESR}$, $DAS28_{CRP}$). $DAS28_{ESR}$ was calculated following the equations: $DAS28_{ESR}$ = [0.56 x SQRT (T28) +0.28 x SQRT (SW28) + 0.70 x LN (ESR)] x1.08 +0.16, $DAS28_{CRP}$ = [0.56 x SQRT (T28) +0.28 x SQRT (SW28) + 0.36 x LN (CRP + 1)] x1.10 + 1.15, where SQRT is the square root, LN is logarithm, T28 is the number of total tender joints out of 28 joints and SW28 is the number of total swollen joints out of 28 joints. Twenty-eight joints including bilateral proximal interphalangeal joints, bilateral metacarpophalangeal joints, and bilateral wrist joints, bilateral elbow joints, bilateral shoulder joints and bilateral knee joints.

2.2 Therapy regimens and sampling

All patients receiving disease-modifying anti-rheumatic drugs (DMARDs) had to be on stable doses for at least 12 weeks before being included in the study (Supplementary Table1). The patients with RA in the group of^{99}Tc were treated with ^{99}Tc-MDP without oral glucocorticoids for 10 days as a course, whereas the patients in another group of ^{99}Tc & GC were given^{99}Tc-MDP and oral glucocorticoids. The dose of Oral glucocorticoids (prednisone or methylprednisolone) has been limited at [?] 10mg/day and has been stable for at least 4 weeks.^{99}Tc-MDP is composed of agent A (0.05ug^{99}Tc solution in a vial, 5ml) and B (5mg Methylenediphosphonic acid and 0.5mg stannous chloride, lyophilized). Agent A and B were mixed together for 5 minutes before ready to use.^{99}Tc-MDP was given as daily intravenous drips of 16.5 mg diluted with 250 ml normal saline for 10 days. Fasting blood samples from RA patients were collected at the beginning of treatment of^{99}Tc-MDP and on day 10 complied with procedure of hospital policies. These samples were transferred immediately to clinical lab for test.

Detection of inflammatory markers and Lipid profile

The laboratory parameters of patients were determined by the hospital clinical laboratory. ESR was measured by Monitor 20 (Electa lab, Italy) and CRP was detected using nephelometry on BN II (Siemens, Germany). The lipid profiles were performed by an automatic biochemistry analyzer 7600-20 (HITACHI, Japan) including TC, TG, and HDL-C, LDL-C, ApoA1, and ApoB. Atherogenic index was calculated by the equation (Atherogenic index = TC / HDL-C, TC is total cholesterol) and combined with the ratio of ApoB /ApoA1 to evaluate the risk of cardiovascular events.

Statistical analysis

The data was presented by mean +- SD including inflammatory markers and lipid profiles. The data of inflammatory markers and lipid profiles after treatment compared to baseline was analyzed by t test. difference is significant with $P < 0.05$. The correlation of between inflammatory markers and lipid profiles were computed using residuals by non-parameter Spearman correlation analysis and line regression analysis. The residual is equal to the value of post-treatment minus the value of baseline. The forementioned statistical

analysis was run by software Graphic Pad Prism8.0.

3 Results

The patients with active RA were given ^{99}Tc-MDP or and oral glucocorticoids for a course, the disease activities were apparently attenuated in the two groups of ^{99}Tc and^{99}Tc & GC. The inflammatory markers (ESR and CRP) went down, tender joint counts and swollen joint counts were reduced, in turn, $DAS28_{ESR}$ and $DAS28_{CRP}$ were decreased (Figure1 and Supplementary Table2). Comparison of treatment between before and after, the differences are significant in both groups ($P < 0.05$). These results demonstrated that^{99}Tc-MDP or and oral glucocorticoids are efficacious against inflammation in RA in short run. Thus, we investigated changes of lipid profiles in the two groups between post-treatment and before.

In the two groups of the patients with active RA, the lipid profiles were detected before treatment and after 10-day treatment enclosed TC, TG, and HDL-C, LDL-C, and ApoA1, ApoB. According to the above lipids, the ratio of ApoB/ApoA1 and atherogenic index have been calculated. It is significant with $P < 0.05$ comparing of lipid profiles after treatment (as treated) and before (as baseline) in the patients with active RA (Figure2 & Table2). TG and ApoA1 were increased after treatment of ^{99}Tc-MDP in the group of^{99}Tc ($P < 0.05$). The ratio of ApoB/ApoA1was decreased significantly after therapy ($P = 0.0036$). However, atherogenic index was also decreased, but the difference did not reach statistical significance ($P = 0.0856$). In the group of ^{99}Tc & GC, most of lipids were changed after the combined therapy except LDL-C and ApoB. The levels of TC, TG, and HDL-C, ApoA1 were elevated significantly, while the ratio of ApoB/ApoA1 and atherogenic index were both reduced, their P values < 0.05.

The correlation of between inflammation markers and lipid profile were computed by non-parameter Spearman correlation analysis and line regression analysis when the changes of lipid profiles were detected after treatment of ^{99}Tc-MDP or and glucocorticoids (Figure3 & Supplementary Table3). The data showed that disease activity scores ($DAS28_{CRP\ or\ ESR}$) were inversely correlated with CHO, LDL-C and ApoB ($P < 0.05$) in the group of^{99}Tc. In a word, there is a correlation between DAS28 decrease and partial lipids of TC, LDL-C and ApoB increases. The results were concordance in forementioned both of analysis methods. However, the results of between ESR and LDL-C were different in two analysis methods. That is, ESR was inversely related to LDL-C in non-parameter Spearman correlation analysis ($r = -0.4237$, $P = 0.0276$) (Supplementary Table3), while not in line regression analysis ($r = -0.3460$, $P = 0.0771$). It possibly caused by methodological difference. There was no correlation of between CRP and lipid profiles. The possible reason is that sample size is too small. These results needed a large scale of samples to be addressed.

In the group of ^{99}Tc & GC, CRP was negatively correlated with ApoA1, while positively correlated with the ratio of ApoB/ApoA1 and atherogenic index ($P < 0.05$). Also, there were correlation between ESR and partial lipids including HDL-C, ApoA1, and ratio of ApoB/ApoA1($P < 0.05$). ESR were inversely related to HDL-C, ApoA1, while positively related to ratio of ApoB/ApoA1. $DAS28_{CRP\ or\ ESR}$ were inversely correlated with TG, whereas positively correlated with atherogenic index. Moreover, $DAS28_{CRP}$ was also positively related to LDL-C (Figure4). These results are similar using two statistical analysis methods (Figure4 and Supplementary Table4). However, there were three exceptions which were significantly correlation using non parameter Spearman analysis ($P < 0.05$) while not using line regression between $DAS28_{CRP\ or\ ESR}$and the ratio of ApoB/ApoA1, $DAS28_{ESR}$ and LDL-C (Supplementary Table4).

4 Discussions

^{99}Tc-MDP, one of common anti-inflammation drug in China, which is widely used to active RA because of its efficacy and low price. Glucocorticoids are the common agents including prednisone, methylprednisone, and betamethasone, beclomethasone dipropionate, prednisolone, hydrocortisone, dexamethasone and so on, which are being widely used to different diseases for its anti-inflammation and immunosuppressive function [28, 29]. Especially, glucocorticoids are often the first-aid drug in emergency or critical situations. In this study, single ^{99}Tc-MDP or combined with oral glucocorticoids are effective to anti-inflammation treatment in the two groups, tender joint counts and swollen joint counts were reduced, sequentially disease activities got down. The inflammatory markers (ESR & CRP) and disease activities were decreased more in the group

of^{99}Tc & GC than in the group of^{99}Tc. The results also indicated that combination regimen was superior to single medication when disease activities got worse. So that depending upon the different disease activities, customized therapeutical regimens could be provided for the individual patients.

We found that the inflammatory markers (ESR, CRP) and DAS28 were not only decreased significantly in the patients with RA after a therapeutic course of ^{99}Tc-MDP and or oral glucocorticoids, but the partial lipids were also changed significantly. Therefore, nonfasting lipids including the atherogenic index and ApoB/ApoA1 ratio were reduced significantly. Reduced HDL-C and ApoA1 represent an important factor in the etiology of dyslipidemia in RA [30]. In present study, the level of ApoA1 was increased after treatment of^{99}Tc-MDP and or oral glucocorticoids in both groups. The levels of TC and HDL-C were elevated after treatment in^{99}Tc & GC. The increase of TC might cause by the increased level of HDL-C. Consequently, atherogenic index was decreased. Atherogenic index is regarded as a useful predictor of atherosclerosis by some practitioners [31, 32]. It predicts that the risk of cardiovascular events gets down when atherogenic index is reduced. A largest case-control study from 52 countries investigated which were the strongest risk factors for MI (myocardial infarction) among the ratio of ApoB/ApoA1**,** smoking, diabetes, hypertension, abdominal obesity, psychosocial, fruits and vegetables, exercise, and alcohol. This study found that all risk factors were statistically related to MI risk. The strongest and also the most prevalent risk factor, was the ratio of ApoB/ApoA1 both in men and women [33, 34]. In a subsequent paper, it also showed that the ratio of ApoB/ApoA1 had the strongest relation to MI-risk compared to all other measured lipids [35]. Although the ratio of ApoB/ApoA1 was decreased significantly after treatment with^{99}Tc-MDP and or glucocorticoids, ApoB/ApoA1has been seen the only significant correlation with ESR in the group of^{99}Tc & GC using line regression analysis, nonsenses of with CRP and DAS28$_{\mathrm{CRP/ESR}}$ in the two groups. However, using non parameter Spearman correlation analysis, the ratio of ApoB/ApoA1 was related to CRP, ESR and DAS28$_{\mathrm{CRP/ESR}}$ in the group of ^{99}Tc & GC. The possible reason is small size of samples, methodological difference might be a co-factor.

Notably, the levels of TG were increased after the treatment with^{99}Tc-MDP and or oral glucocorticoids. It has been reported that the levels of TG were elevated with oral glucocorticoids in the patients with RA [26, 36-38]. Whether this would influence cardiovascular risk is unclear. The interplay of between lipid profile and inflammation is complicated. The final cardiovascular risk and deleterious outcome depend upon multifactor and variable diseases. Further long-term studies with larger numbers of the patients are needed to address this issue. Furthermore, there are 6 out of 8 lipids changed significantly in the group of ^{99}Tc & GC, while only 3 lipids in the group of ^{99}Tc.The results of two groups showed that the lipids had been changed more using the regimen of^{99}Tc combined with oral glucocorticoids than using 99Tc-MDP alone.

The partial lipids were changed when the inflammation is attenuated using ^{99}Tc-MDP and or Oral glucocorticoids in our observation. There is an intriguing phenomenon that reduced DAS28$_{\mathrm{CRP\ or\ ESR}}$ was related with the increased CHO, LDL-C and ApoB in the group of ^{99}Tc, whereas reduced CRP, ESR and DAS28$_{\mathrm{CRP/ESR}}$ were related with increased ApoA1, HDL-C, and reduced atherogenic index in the group of^{99}Tc & GC. These results indicated that lipid profiles possibly got worse by increased CHO, LDL-C and ApoB though disease activity was decreased in the group of ^{99}Tc. Vice versa, dyslipidemia might be improved by increased ApoA1, HDL-C and reduced atherogenic index when the inflammatory condition got well in the group of ^{99}Tc & GC. The results of two groups presented different correlations of between inflammation and the partial lipids. It indicated that the risk of dyslipidemia should be considered when ^{99}Tc-MDP was used alone. While, Combination therapy of ^{99}Tc-MDP and glucocorticoids would be better for its effects of anti-inflammation and lipid metabolism regulation. Glucocorticoids have a differential effect on lipid profiles in the patients with underlying various diseases. Observational studies showed that the patients treated glucocorticoids exhibited variable changes of HDL-C in asthma, cardiac or renal transplants, and rheumatoid arthritis [39, 40]. The reasons behind the observed difference are factorial. The variable results in HDL-C levels among patients are dose-related and disease dependent [41, 42]. Moreover, glucocorticoid administration may have different short-term and long-term effects on lipids. The previous studies have suggested glucocorticoid-induced hepatic insulin resistance leads to increased production of VLDL and subsequent increased TG levels [43]. The mechanisms through which glucocorticoids and or^{99}Tc-MDP induce dyslipidemia are not yet well elucidated

so far.

In conclusion, despite treatment of ^{99}Tc-MDP and or oral glucocorticoids have the limited effects on lipid profiles upon short-term observation and small size of samples, the risk of dyslipidemia should be weighed when administration of^{99}Tc-MDP alone is formulated for the patients with active RA. Combined with oral glucocorticoids may be a good therapeutic regimen but the increasing level of TG should be monitored. Prolonged duration of ^{99}Tc-MDP and or oral glucocorticoid treatment and larger scale of patients will be desired to further address this issue.

Author contribution

Dr. Heqing Huang, Dr. Ying Wang and Dr. Qingyan Lin work equally to design the research study; Dr. Yan He, Xiaoli Zeng and Dr. Mengqin Zhang performed this research; Dr. Rongjuan Chen contributed data analysis; Dr. Yan Li provided constructive comments for critical revision; Dr. Jingxiu Xuan drafted the paper and approved the submitted and the final version.

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Table 1 Demographic of Patients with RA

Number
Sex (Female)
Age (Mean ± SD)
BMI
Hypertension
Alcohol
Smoking
Female Menopause (N, %)
Age of Menopause
Duration of Disease (Y)
Drugs*
Anti-CCP*
RF*

DMARDs include Methotrexate, Leflunomide, and Sulfasalazine, Hydroxy chloroquine, Thalidomide, and Iguratimod, whi

Table 2 Lipid profile of the patients with RA between before and after treatment in the two groups of ^{99}Tc and ^{99}Tc & GC

Lipid profile / Group	^{99}Tc Baseline	^{99}Tc Treated	^{99}Tc P values	^{99}Tc & GC Baseline	^{99}Tc & GC Treated	^{99}Tc & GC P values
CHO	3.85 ± 0.84	3.90 ± 0.88	0.7465	4.33 ± 0.99	4.65 ± 1.18	**0.0024**
TG	1.05 ± 0.57	1.22 ± 0.54	**0.0441**	0.89 ± 0.28	1.19 ± 0.39	**< 0.0001**
HDL-C	1.05 ± 0.27	1.11 ± 0.23	0.1083	1.06 ± 0.21	1.32 ± 0.32	**< 0.0001**
LDL-C	1.93 ± 0.56	1.96 ± 0.61	0.9782	2.66 ± 0.93	2.68 ± 0.98	0.7414
Apo A1	1.22 ± 0.24	1.30 ± 0.24	**0.0179**	1.08 ± 0.26	1.30 ± 0.32	**< 0.0001**
Apo B	0.74 ± 0.18	0.73 ± 0.19	0.1993	0.87 ± 0.25	0.89 ± 0.22	0.8376
Atherogenic Index	4.11 ± 2.36	3.57 ± 0.64	0.0856	4.13 ± 0.87	3.56 ± 0.64	**< 0.0001**
Ratio of Apo B/Apo A1	0.65 ± 0.21	0.58 ± 0.18	**0.0036**	0.84 ± 0.31	0.69 ± 0.20	**0.0001**

Note: The bold number is meant that it is significant with P value < 0.05.

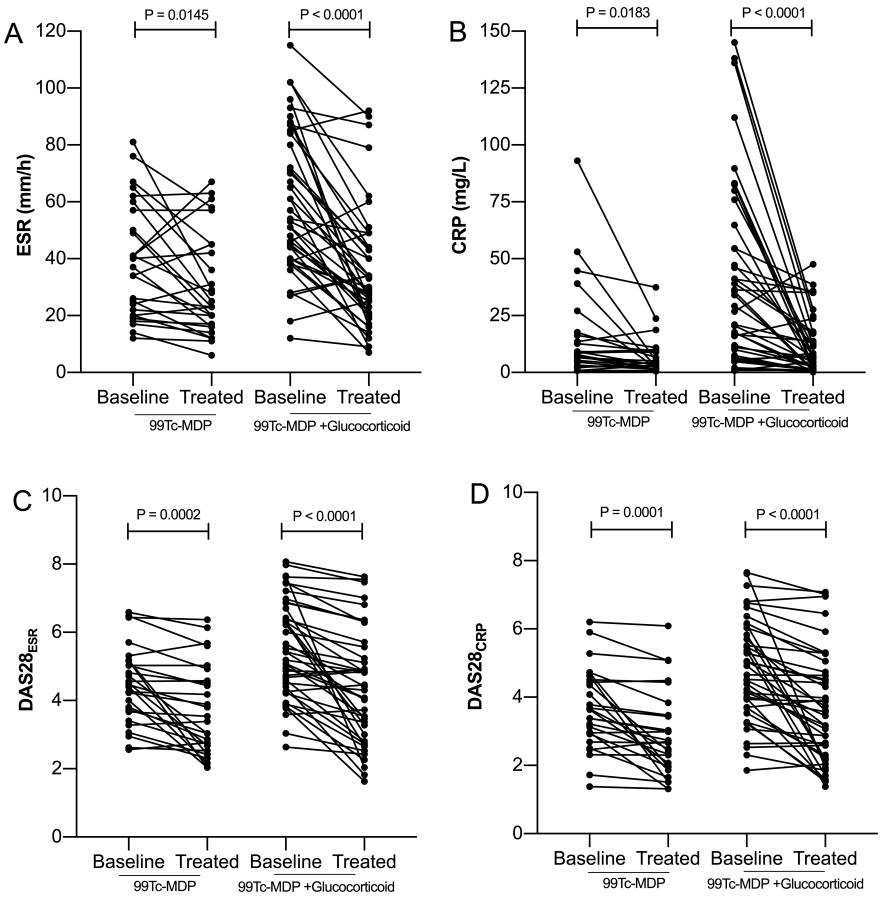

Figure 1 Inflammation improvement of the patients with RA via treatment with ^{99}Tc-MDP or and glucocorticoids Inflammatory markers of ESR and CRP were detected after treatment of^{99}Tc-MDP and or oral glucocorticoids and before in the two groups (A & B). Disease activity of DAS28$_{\text{ESR or CPR}}$changed before and treated with ^{99}Tc-MDP and or oral glucocorticoids in the two groups (C & D). The inflammatory markers and DAS28 $_{\text{ESR or CRP}}$ were decreased significantly after treatment, all P values < 0.05 in the two groups. In Figure1, before and after the treatment of ^{99}Tc-MDP or and oral glucocorticoids were also called as Baseline and treated.

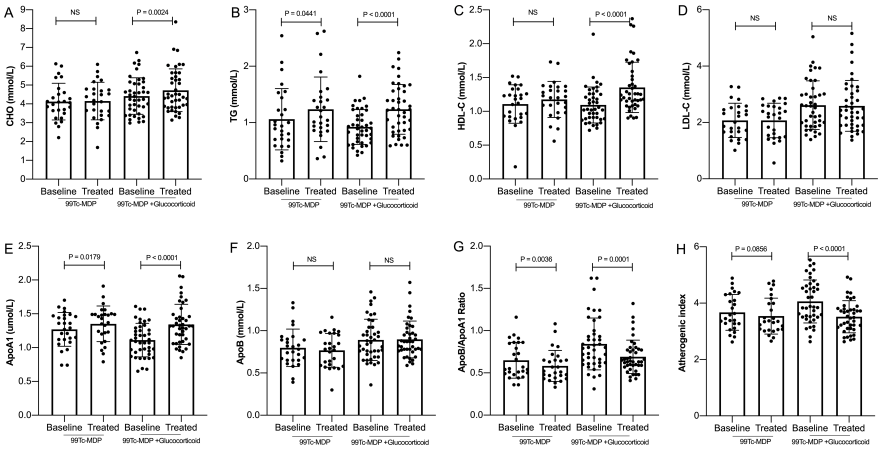

Figure2 Comparison of lipid profiles of the patients with RA between treated and baseline in the two groups of ^{99}Tc and ^{99}Tc & GC Lipid profiles were measured after treatment of ^{99}Tc-MDP and or glucocorticoids (as Treated) and before (as baseline) including CHO, TG, and HDL-C, LDL-C, and ApoA1, ApoB from Figure 2 A-F. non fasting lipids including the ratio of ApoB/ApoA1 and atherogenic index presented in figure of G and H. The levels of TG and ApoA1 were significantly increased in the group of ^{99}Tc, the P values were separately 0.0441 and 0.0179 (B, E). The ratio of ApoB/ApoA1 was decreased in Figure 2G. In the group of ^{99}Tc & GC, the levels of CHO, TG and HDL-C, ApoA1 were elevated after treatment (All P values < 0.05) (A, B, C, E). In Figure 2G and 2H, the ratio of ApoB/Apo A1 and atherogenic index were decreased with P <0.05.

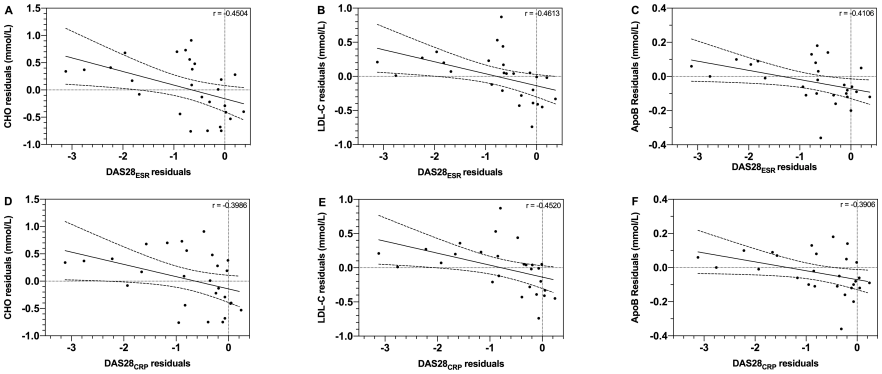

Figure 3 The correlation of between disease activity DAS28$_{\text{ESR or CRP}}$ and lipid profiles in the group of^{99}Tc by line regression analysis The correlation of between DAS28$_{\text{ESR}}$ and TC, LDL-C, the ratio of ApoB/ApoA1 presented negatively correlation in the upper of figure (A-C). The correlation of between DAS28$_{\text{CRP}}$ and TC, LDL-C, the ratio of ApoB/ApoA1 were also negatively correlation in the lower of figure (D-F). r is correlation coefficient which was exhibited at the top right corner in every figure in this panel.

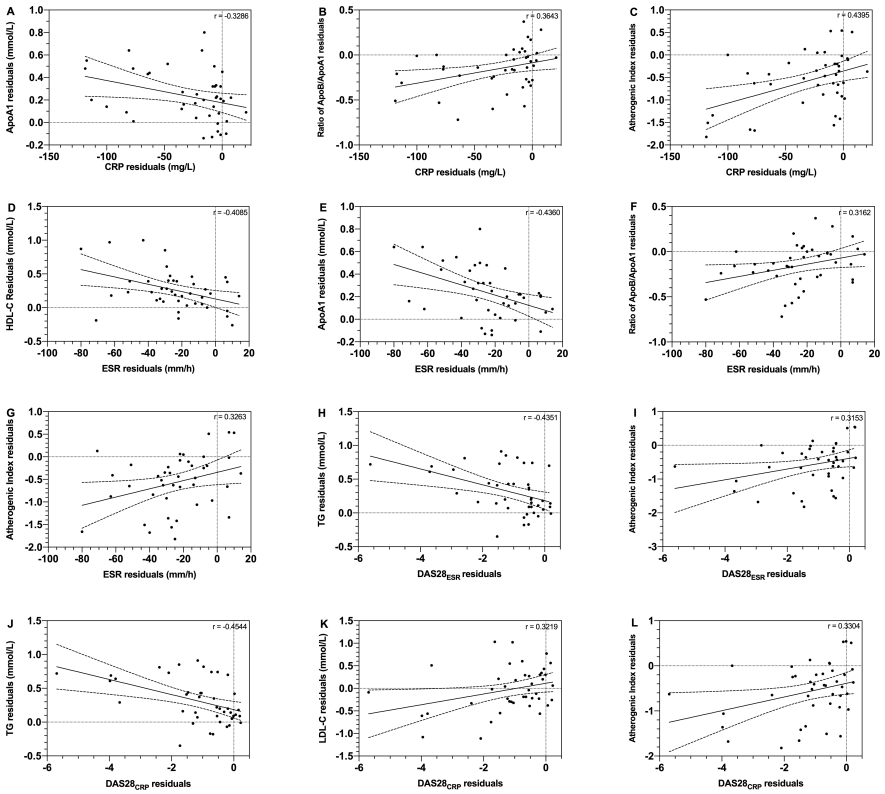

Figure 4 The correlation of between inflammation markers and lipid profile in the group of ^{99}Tc & GC by line regression analysis CRP was inversely correlated with ApoA1, positively correlated with ratio of ApoB/ApoA1 and atherogenic index (A - C). ESR was negatively related to HDL-C, ApoA1 and positively related to ratio of ApoB/ApoA1, atherogenic index (D - G). $DAS28_{ESR}$ was negatively related to TG and positively related to atherogenic index (H & I). $DAS28_{CRP}$ was negatively related to TG and positively related to LDL-C and atherogenic index (J - L). r is correlation coefficient presented at the top right corner in every figure in this panel.

Supplementary data

Supplementary Table 1 Usage of DMARDs in the two groups of^{99}Tc and ^{99}Tc & GC

Supplementary Table 2 The inflammatory markers and disease activities of the patients with RA between before & after treatment in the two groups of ^{99}Tc and ^{99}Tc & GC

Supplementary Table 3 The correlations of between inflammatory markers and lipid profiles in the group of ^{99}Tc by non-parameter spearman correlation analysis

Supplementary Table 4 The correlations of between inflammatory markers and lipid profiles in the group of ^{99}Tc & GC by non-parameter spearman correlation analysis