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Original Article

# Green tea and exercise interventions as nondrug remedies in geriatric patients with rheumatoid arthritis

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**Abstract. [Purpose]** This study aimed to evaluate the effects of green tea and supervised exercise training interventions on improvement of disease activity and bone metabolism markers in rheumatoid arthritis patients. [Subjects and Methods] One-hundred and twenty subjects who had a mean age of (60.7 ± 2.53 years) and had been diagnosed with rheumatoid arthritis at least ten years previously were randomly included in this study. Patients were treated with infliximab, green tea, or a supervised exercise program for six months. Disease activity markers as well as antioxidant activity of green tea extracts were estimated before supplementation using in vitro assays. [Results] Rheumatoid arthritis patients treated with green tea for 6 months alone or in combination with infliximab or an exercise program showed significant improvement in disease activity parameters, including C-reactive protein, and erythrocyte sedimentation rate, swollen and tender joints counts, and modified Stanford Health Assessment Questionnaire score, along with an increase in serum levels of bone resorption markers, i.e., deoxypyridinoline, amino-terminal telopeptide of type 1 collagen, and bone alkaline phosphatase, at 6 months of after initial treatment. The European League Against Rheumatism and American College of Rheumatology scores revealed more clinical improvement in the disease activity of rheumatoid arthritis patients treated with green tea along with exercise compared with rheumatoid arthritis patients treated with infliximab or exercise combinations. This may have been due to the higher potential antioxidant activity of green tea (89.6% to 96.5%). [Conclusion] Both exercise and green tea interventions appeared to be beneficial as nondrug modulates for rheumatoid arthritis disorders.

**Key words:** Aerobic exercise, Rheumatoid arthritis, Green tea

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## INTRODUCTION

Chronic joint inflammation and severe pain along with functional impairment and disability are reported in all patients with rheumatoid arthritis (RA)[1, 2)], especially older patients of both genders, but the severity, such as impaired physical function and reduced muscle strength with severe pain is most often 5 times higher in women[3, 4)]. Previous research has reported that severe synovium inflammation is the main feature of RA, with subsequent release of proinflammatory cytokines[5)]. Therefore, confirmation of the earliest stages of disease might be helpful in minimizing disease activity and reducing joint damage through targeted therapeutic interventions[6)], such as those using molecular marker technology, which evaluates the anti-rheumatic therapy effects on rheumatic tissues[7)].

Previously, it was reported that specific markers that reflect the turnover of cartilage, synovium, and bone should be evaluated to better explain the pathophysiology of joint tissues in RA[8)]. Urinary excretion of pyridinium cross-links, especially deoxypyridinoline (DPD), cross-linked N-telopeptides of type I collagen (NTX), and cartilage oligomeric matrix protein

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were significantly reported as markers to reflect cartilage and synovium tissue turnover among patients with RA[9]. Although the clinical importance remains uncertain[10], patients with RA[11] and patients with osteoarthritis[12], reportedly exhibited a reduction in the excretion of total PYD and total DPD, which indicates the degree of joint degradation among patients with RA, and the levels of both PYD and DPD were significantly correlated with disease activity markers[13]. Thus, these markers might be helpful as a potential markers of joint degradation that reflect both bone resorption and formation among patients with RA[14]. As both DPD and NTX have been validated as markers for bone resorption, bone alkaline phosphatase (BAP) has been suggested to be a candidate marker for bone formation and as an early marker of osteoblast differentiation[15, 16]. Furthermore, although chemotherapy has been shown to improve disease outcome, it has more severe side effects.

Infliximab, one of the most antagonist tumor necrosis factor (TNF) drugs recently, has recently been shown to be highly successful in treatment of patients with RA. However, it is postulated to cause cell lysis via antibody-dependent cell-mediated cytotoxicity or complement activation[17, 18].

Thus new strategies based of nondrug treatment modalities such as exercise and physical activity, along with natural plant products have received significant attention in the treatment of RA[19, 20].

In patients with RA, supervised exercise interventions have been shown to improve physical performance, cardiorespiratory fitness, and muscle strength without worsening of joint inflammation. Also, they result in a significant reduction in the level of RA disease activity as measured by the number of swollen or tender joints[21, 22]. It has reported that participating in moderate intensity exercise for at least 30 minutes five days per week was of significant benefits, especially for the healthy adult population[23]. Exercise has also shown to decrease the risk of coronary artery disease and improve cardiovascular health[24], reduce adiposity[25], and increase muscle strength, which supports exercise health benefits among patients with RA[26, 27]. Furthermore, it has been reported that exercise of high intensity that fell within a physiologic range was more effective in increasing physical function when compared with low intensity exercise[26, 27].

Most studies based on in vitro and in vivo animal models have placed much interest on the use of green tea (*Camellia sinensis*) or its active polyphenols (GTPs) as nondrug therapy against RA[28, 29]. The data from these studies show that supplementation of drinking water with GTPs in mice greatly minimized disease activity markers and reduced the expression of collagen-induced arthritis[30]. This may be due to the anti-inflammatory and antioxidant activities of green tea constituents such as epigallocatechin-3-gallate (EGCG), which inhibit inflammatory mediators that promote bone degradation[31]. The biological activities of green tea as a nondrug therapy for rheumatic disease are due to the antioxidants and anti-inflammatory properties of its polyphenolic compounds[32]. Currently, there is no cure for rheumatoid arthritis, and treatment strategies involve a combination of drugs as well as non-pharmacologic treatments such as exercise and physical therapy[33]. Therefore, this study aimed to evaluate the effects of green tea and supervised exercise training interventions on improvement of disease activity and bone metabolism markers in patients with RA.

## SUBJECTS AND METHODS

A total of 120 Saudi patients who had a mean age of 60.7 ± 2.53 years and had been diagnosed with RA according to the criteria of the American College of Rheumatology (ACR) and radiographic analysis at least 10 years previously were randomly selected for participation in this study[34]. Patients with a physical disability, or a history of receiving anti-inflammatory drugs or oral glucocorticoids were excluded from this study. Also, patients were excluded if they took any drugs or received any injections 3 months prior to enrolment or during the study period. Dietary information was obtained from each participant and carefully examined to avoid elimination diets[35]. All participants were instructed not to change their normal eating habits during the period of data collection and to record accurately the amounts and types of foods and fluids consumed. According to sample power calculations (90%) with an estimated difference of 5% between groups and the type of treatment, the patients were classified into six groups (20 patients/each group). After obtaining written informed consent, demographic, clinical, and biochemical analysis were performed for all patients at baseline, 6 weeks and 6 months after the initial treatment. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was reviewed and approved by ethical committee of Rehabilitation Research Chair (RRC), King Saud University, KSA.

Infliximab was administered by intravenous infusion at a dose of 3 mg/kg at baseline, at 2 and 6 weeks later, and then every 8 weeks. Green tea was supplemented at a dose of 4–6 cups/day (60 to 125 mg catechins) for six months.

Patients with RA participated in a supervised aerobic exercise program for 45–60 minutes three times per week for 6 months using a treadmill. The exercise program had a moderate intensity and was shown to be suitable for most sedentary subjects, especially those with RA. The maximum exercise intensity of each participant was calculated as the training heart rate according to Karvonen's formula[36] and was set at a level that produced physical activity resulting in 30–45% of maximum oxygen uptake ($VO_2max$)[37].

Disease activity was examined in all patients by radiographic analysis, estimation of C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) along with assessment of self-reported functional status using a pre-validated modified Stanford Health Assessment Questionnaire (mHAQ) score and DAS28-ESR score analysis[38, 39]. Scores of less than 0.3 are considered normal for mHAQ. Scores for the DAS28-ESR were calculated from ESR values and the clinical data of both hands and feet of the RA patients measured by radiographs at baseline and following 6 months of treatment. The clinical severity of RA patients was classified according to DAS28-ESR scores as follows: highly active (≥4.1), moderate (2.7 to

**Table 1.** Demographics and baseline characteristics of the patients with rheumatoid arthritis (RA) enrolled in this study

| Parameters | I | GT | EX | I + GT | I + EX | GT + EX |
|---|---|---|---|---|---|---|
| No. of patients | 20 | 20 | 20 | 20 | 20 | 20 |
| Gender (M/F) | (16/4) | (15/5) | (17/3) | (12/8) | (13/7) | (14/6) |
| Mean Age (yrs) | 55.6 ± 12.41 | 57.3 ± 11.2 | 52.6 ± 9.4 | 48.9 ± 7.1 | 45.9 ± 6.3 | 51.6 ± 3.8 |
| BMI (kg/m$^2$) | 24.6 ± 2.18 | 23.9 ± 3.2 | 24.3 ± 1.2 | 24.6 ± 3.15 | 25.2 ± 3.2 | 22.9 ± 4.13 |
| Duration of RA (yrs) | 12.9 ± 3.01 | 11.9 ± 2.03 | 13.1 ± 1.03 | 12.5 ± 4.05 | 10.8 ± 3.02 | 12.3 ± 2.01 |
| DAS28-ESR | 6.6 ± 0.65 | 5.4 ± 0.43 | 6.7 ± 0.23 | 5.7 ± 0.31 | 5.1 ± 0.40 | 6.2 ± 0.37 |
| mHAQ score | 4.5 ± 1.38 | 5.1.3 ± 3.5 | 7.1 ± 3.21 | 6.9 ± 1.27 | 8.1 ± 2.1 | 9.5 ± 1.4 |

DAS28: Disease Activity Score-28; mHAQ: modified Stanford Health Assessment Questionnaire score; BMI: body mass index; I: infliximab group; GT: green tea group; EX: exercise group; I + GT: infliximab + green tea; I + EX:infliximab + exercise group; GT + EX: green tea + exercise group

<4.1), low active (≥2.3 to <2.7), and normal (<2.3).

The response or improvement in disease activity of RA patients following nondrug interventions using exercise and green tea was reported using European League Against Rheumatism (EULAR) response criteria and the American College of Rheumatology 20%, 50%, and 70% (ACR20, ACR50, ACR70) response criteria currently reported in RA clinical trials[33]. EULAR response criteria were calculated form the data of DAS28-ESR scores of each participant. The clinical improvement in disease activity of RA patients following green tea and/or exercise treatment was classified according to EULAR scores as good (>1.2), moderate (0.6 to 1.2), and no response (<0.6).

Phenolic compounds of aqueous green tea extracts (GTEs) were determined in 100 mg of the extract using gas-liquid chromatography with an HP1050 (Hewlett-Packard, Palo Alto, CA, USA) equipped with an ODS C18 column and UV detector as previously reported[38–40].

In vitro analyses were performed to estimate the antioxidant activity of green tea extracts as free radical scavenging activity using both DPPH and NBT assays as previously reported in the literature[41, 42]. Antioxidant activity of GTEs resulting from the reaction between green tea polyphenols with the produced superoxide free radicals which leads to a significant inhibition in the color of DPPH and NBT reagents. The change in color absorbance was estimated at the wavelengths of 517 nm and 560 nm respectively.

The levels of both NTX and DPD were estimated in urine samples of the participating patients using enzyme immunoassay techniques. The levels were measured with ELISA kits (Osteomark, Ostex International, Seattle, WA, USA) for NTX and enzyme immunoassay kits (Metra Biosystems, Mountain View, CA, USA) for DPD respectively. Serum BAP (sBAP) was measured in the serum of the participants using an enzyme immunoassay kit (Alka phase, Metra Biosystems).

The data obtained were statistically analyzed using SPSS for widows, version 10 (SPSS Inc, Chicago, IL, USA). All data were expressed as the mean ± SD. Wilcoxon's matched-pairs test and single regression analysis were performed to evaluate comparisons and correlations of the changes in measurements between before and after treatment. A p-value of $< 0.05$ was considered significant.

## RESULTS

Patients were diagnosed with RA according to the criteria of the American College of Rheumatology (ACR), DAS28-ESR, radiographic analysis, and RA biomarkers. They were classified into 6 groups (20 patients per group) according to the type of RA treatment. The demographic data, duration of disease, and disease activity parameters of each group are shown in Table 1.

Liquid chromatography analysis was performed to evaluate the active constituents of green tea extracts. The data obtained showed that green tea contains high amounts of catechins (589 mg/g), caffeine (96 mg/g), chlorogenic acid (25.34 mg/g), and pyrogallol (18.5 mg/g) along with low quantities of vanillic, synergic, salycillic, benzoic, and ferulic acids, as shown in Table2. The biological antioxidant activity of these polyphenols was estimated in vitro using DPPH/NBT scavenging colorimetric assays and measured in relation to the inhibition of DPPH and NBT free radicals. Aqueous green tea extracts (AGTEs) showed high free radical scavenging activities (96.5 and 89.6% for DPPH and NBT free radicals respectively) at concentration of 64 µg ml$^{-1}$ (Table 2).

Significant improvement in clinical and biochemical parameters was observed in the patients after treatment with green tea, infliximab, or supervised aerobic exercise for 6 months. A significant decrease ($p<0.01$) in disease activity parameters (CRP, ESR, and DAS28-ESR) was observed in patients treated with green tea compared with those treated with infliximab or the exercise program. When patients were subjected to combined treatment modalities, patients treated with green tea plus the supervised training program showed a significant ($p<0.01$) improvement in disease activity parameters (CRP, ESR, and DAS28-ESR) after 6 months compared with patients treated with infliximab plus exercise or green tea. In addition, the

**Table 2.** Phenolic compounds content (mg/g) and free-radical scavenging activities of 350 mL aqueous green tea extract (AGTE) using liquid chromatography and spectrophotometry analysis

| Parameters | Phenolic contents (mg/g) |
|---|---|
| Phenolic components: | |
| Catechins (EGCG, ECG) | 589 |
| Caffeine | 96 |
| Chlorogenic acid | 25.34 |
| Pyrogallol | 18.5 |
| Vanillic acid | 6.8 |
| Synergic acid | 4.5 |
| Salycillic acid | 3.58 |
| POH Benzoic acid | 0.91 |
| Ferulic acid | 0.74 |
| P-Coumaric acid | 0.16 |
| Coumarin | 0.18 |
| Naringenin | 2.1 |
| AGTE scavenging activities: | Free-radical scavenging activities at 64 µg/ml |
| Percentage of inhibition of DPPH reagent | 96.50% |
| Percentage of inhibition of NBT/ Riboflavin reagent | 89.60% |

**Table 3.** Biomarkers and disease activity levels of RA patients receiving infliximab, green tea therapy, and/or exercise training

| Parameters | Treatment groups | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | I (n=20) | | GT (n=20) | | EX (n=20) | | I+GT (n=20) | | I+EX (n=20) | | GT+EX (n=20) | |
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| CRP | 5.29 ± 0.7 | 2.84 ± 0.8$^b$ | 6.2 ± 0.52 | 2.5 ± 0.7$^b$ | 7.1 ± 0.45 | 4.9 ± 0.7$^b$ | 6.9 ± 0.5 | 1.9 ± 0.4$^b$ | 9.2 ± 0.7 | 3.9 ± 0.5$^b$ | 6.2 ± 0.5 | 1.8 ± 0.4$^b$ |
| ESR | 68.7 ± 9.09 | 45.9 ± 8.7$^b$ | 65.7 ± 11.1 | 42.4 ± 6.8$^b$ | 71.5 ± 13.1 | 56.4 ± 9.3$^b$ | 78.5 ± 10.1 | 36.4 ± 6.3$^b$ | 65.5 ± 11.3 | 51.4 ± 7.4$^b$ | 60.7 ± 11.1 | 32.2 ± 3.6$^b$ |
| DAS28 | 6.6 ± 0.7 | 4.9 ± 0.4$^b$ | 5.4 ± 0.3 | 2.1 ± 0.3$^b$ | 6.7 ± 0.2 | 5.3 ± 0.5$^b$ | 5.7 ± 0.3 | 3.5 ± 0.42$^b$ | 5.1 ± 0.40 | 4.5 ± 0.6$^b$ | 6.2 ± 0.4 | 2.5 ± 0.41$^b$ |
| SJC | 14.3 ± 2.8 | 9.6 ± 1.62$^b$ | 13.2 ± 2.5 | 8.5 ± 1.3$^b$ | 12.7 ± 2.9 | 10.5 ± 1.3$^b$ | 11.2 ± 1.5 | 7.5 ± 1.2$^b$ | 11.8 ± 2.3 | 9.7 ± 1.7$^b$ | 11.2 ± 1.5 | 6.5 ± 1.21$^b$ |
| TJC | 7.12 ± 1.8 | 4.35 ± 0.9$^a$ | 6.7 ± 1.9 | 4.2 ± 0.8$^b$ | 8.5 ± 3.6 | 5.8 ± 0.5$^b$ | 8.3 ± 3.9 | 3.9 ± 0.6$^b$ | 8.65 ± 3.6 | 4.6 ± 0.5$^b$ | 7.9 ± 2.9 | 3.6 ± 0.6$^b$ |
| mHAQ | 4.8 ± 1.4 | 2.9 ± 0.9$^b$ | 5.1 ± 3.5 | 1.9 ± 1.4$^b$ | 5.4 ± 3.2 | 3.2 ± 1.3$^b$ | 6.9 ± 1.5 | 3.2 ± 1.2$^b$ | 7.2 ± 2.1 | 5.4 ± 2.6$^b$ | 7.3 ± 1.4 | 2.7 ± 2.3$^b$ |
| NTX | 87.1 ± 16.0 | 56.5 ± 5.1$^b$ | 82.1 ± 11.0 | 47.5 ± 3.6$^b$ | 89.5 ± 18.0 | 68 ± 6.2$^b$ | 79.3 ± 12.0 | 37.4 ± 8.2$^b$ | 69.5 ± 12.3 | 51.9 ± 4.2$^b$ | 85.4 ± 11.9 | 36.8 ± 5.8$^b$ |
| DPD | 11.22 ± 0.9 | 8.38 ± 0.7$^b$ | 10.6 ± 0.6 | 7.4 ± 0.4$^b$ | 12.8 ± 0.5 | 9.4 ± 0.3$^b$ | 10.5 ± 0.9 | 6.6 ± 0.3$^b$ | 13.2 ± 0.4 | 7.6 ± 0.3$^b$ | 11.8 ± 0.7 | 4.5 ± 0.5$^b$ |
| sBAP | 15.66 ± 6.2 | 16.5 ± 5.5$^a$ | 18.7.6 ± 7.5 | 24.6 ± 4.5$^a$ | 16.1 ± 6.3 | 18.1 ± 3.0$^a$ | 15.7 ± 5.9 | 26.5 ± 7.0$^a$ | 12.8 ± 5.7 | 19.6 ± 4.2$^a$ | 18.3 ± 3.7 | 35.3 ± 4.5$^a$ |

Data are shown as mean ± SD values. $^a$p<0.05 vs. pre (before treatment or baseline)., $^b$p<0.01 vs. pre (before treatment or baseline). DAS28: Disease Activity Score-28; mHAQ: modified Stanford Health Assessment Questionnaire score; BMI: body mass index; I: infliximab group; GT: green tea group; EX: exercise group; I + GT: infliximab + green tea; I + EX, infliximab + exercise group; GT + EX, green tea + exercise group. SJC: swollen joints counts; TJC: tender joints count. DPD (nM/MCl): deoxypyridinoline; NTX (nM BCE/mM Cr): cross-linked N-telopeptides of type I collagen; sBAP(U/l): serum bone alkaline phosphatase. CRP (mg/dl): C-reactive protein; ESR (mm): erythrocyte sedimentation rate

mHAQ score, tender joint count (TJC) and swollen joint count (SJC) were significantly decreased after 6 months of therapy (Table 3).

The mean NTX levels decreased significantly in all treated groups. A significant decrease (p<0.01) in NTX levels was observed in patients treated with green tea (47.5 ± 3.6 vs. 82.1±11.0) for 6 months compared with those infliximab (56.5 ± 5.11 vs. 87.1 ± 16.0) or exercise (67.9 ± 6.2 vs. 89.5 ± 18.0) (Table 3). Also, a significant decrease (p<0.01) in NTX levels was observed in patients treated with infliximab + green tea (36.4 ± 8.2 vs. 79.3 ± 12.0) or green tea plus exercise (37.8 ± 5.8 vs. 85.4 ± 11.9) compared with patients treated with infliximab plus exercise (51.9 ± 4.2 vs. 69.5 ± 12.3) (Table 3).

Patients treated with green tea or infliximab plus green for 6 months showed a significant decrease (p<0.01) in mean DPD level (7.4 ± 0.45 vs. 10.6 ± 0.61 and 4.6 ± 0.32 vs. 10.5± 0.81, respectively). The data obtained showed significant decreases when compared with the other patient groups, as shown in Table 3.

The mean sBAP levels (48.3 ± 3.7 vs. 26.3 ± 4.5) decreased significantly (p<0.05) in patients treated with green tea plus the supervised exercise program for 6 months. The data obtained were significantly correlated when compared with the other patient groups, as shown in Table 3.

**Table 4.** Correlation between the bone resorption markers and the changes in disease activity of RA patients treated with infliximab, green tea, or a supervised aerobic training program

| Parameters | I group (n=20) | | GT group (n=20) | | EX group (n=20) | | I + GT (n=20) | | I + EX (n=20) | | GT +EX (n=20) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NTX | DPD | NTX | DPD | NTX | DPD | NTX | DPD | NTX | DPD | NTX | DPD |
| | R | R | R | R | R | R | R | R | R | R | R | R |
| CRP | 0.045[a] | 0.067 [b] | 0.123[a] | 0.078[b] | 0.118[a] | 0.008[b] | 0.138[a] | 0.029[b] | 0.149[a] | 0.039[b] | 0.228[a] | 0.078[b] |
| ESR | 0.050[a] | 0.221[b] | 0.231[a] | 0.125[b] | 0.125[a] | 0.005[b] | 0.175[a] | 0.015[b] | 0.195[a] | 0.045[b] | 0.345[a] | 0.085[b] |
| SJC | 0.635[a] | 0.165[b] | 0.550[a] | 0.240[b] | 0.130[a] | 0.125[b] | 0.230[a] | 0.185[b] | 0.180[a] | 0.295[b] | 0.180[a] | 0.035[b] |
| TJC | 0.124[a] | 0.004[b] | 0.347[a] | 0.255[b] | 0.147[a] | 0.058[b] | 0.167[a] | 0.098[b] | 0.189[a] | 0.168[b] | 0.187[a] | 0.098[b] |
| mHAQ score | 0.475[a] | 0.457[b] | 0.175[a] | 0.132[b] | 0.158[a] | 0.039[b] | 0.179[a] | 0.082[b] | 0.289[a] | 0.172[b] | 0.218[a] | 0.085[b] |
| DAS28-ESR | 0.125[a] | 0.114[b] | 0.345[a] | 0.142[b] | 0.525[a] | 0.048[b] | 0.435[a] | 0.059[b] | 0.345[a] | 0.159[b] | 0.415[a] | 0.095[b] |

[a] Correlation is significant at ($p<0.01$). [b] Correlation is significant at ($p<0.001$). I: infliximab group; GT: green tea group; EX: exercise group; I + GT: infliximab + green tea; I + EX: infliximab + exercise group; GT + EX: green tea + exercise group. SJC: swollen joints counts; TJC: tender joints counts. DPD (nM/MCl): deoxypyridinoline; NTX (nM BCE/mM Cr): cross-linked N-telopeptides of type I collagen; CRP (mg/dl): C-reactive protein; ESR (mm): erythrocyte sedimentation rate

**Table 5.** Summary of therapeutic responses criteria at week 24

| Clinical end point | Treatment groups | | | | | |
|---|---|---|---|---|---|---|
| | I (n=20) | GT (n=20) | EX (n=20) | I+GT (n=20) | I+EX (n=20) | GT+EX (n=20) |
| ACR20 | | | | | | |
| n (%) | 10 (50%) | 5 (25%) | 8 (40%) | 2 (10%) | 10 (50%) | 2 (10%) |
| ACR50 | | | | | | |
| n (%) | 7 (35%) | 6 (30%) | 9 (45%) | 7 (35%) | 2 (10%) | 6 (30%) |
| ACR70 | | | | | | |
| n (%) | 3 (15%) | 9 (45%) | 3 (15%) | 11 (55%) | 8 (40%) | 12 (60%) |
| EULAR response score | | | | | | |
| Good (>1.2%): | 9 (45%) | 10 (50%) | 9 (45%) | 11 (55%) | 12 (60%) | 15 (75%) |
| Moderate (0.6 to −1.2%) | 5 (25%) | 9 (45%) | 5 (25%) | 8 (44%) | 3 (15%) | 4 (20%) |
| No response (>0.6%) | 6 (30%) | 1 (5%) | 6 (30%) | 1 (5%) | 5 (25%) | 1 (5%) |

ACR20: American College of Rheumatology 20% improvement; ACR50: American College of Rheumatology 50% improvement; ACR70: American College of Rheumatology 70% improvement. I: infliximab group; GT: green tea group; EX: exercise group; I + GT: infliximab + green tea; I + EX: infliximab + exercise group; GT + EX: green tea + exercise group; EULAR: European League Against Rheumatism

Significant positive ($p=0.01$ and $p=0.001$) correlation was observed between bone resorption markers (NTX and DPD levels) and improvements in RA disease activity markers. NTX and DPD levels were statistically correlated with SJC, TJC, CRP, ESR mHAQ score, and DAS28-ESR (Table 4).

After 24 weeks, 50% of infliximab-treated patients achieved an ACR20 response, whereas 35% and 15% achieved ACR50 and ACR70 responses, respectively. In green tea-treated patients, 25%, 30%, and 45% of patients achieved ACR20, ACR50, and ACR70 responses, respectively. More ACR20 and ACR50 responses were observed in exercise-treated patients than green tea treated patients (ACR20, 40% vs. 25%; ACR50,45% vs. 30%); however, green tea-treated patients showed more ACR70 response (45%) compared with infliximab- or exercise-treated patients (Table 5). Similar supporting results were obtained when comparing moderate or good EULAR scores of each group. In green tea-treated groups, patients showed moderate to good improvement (45–50%) in disease activity parameters (DAS28-ESR, CRP, ESR, and mHAQ score) compared with infliximab- or exercise-treated patients (25–45%), as shown in Tables 3 and 5.

In patients treated with infliximab plus green tea, ACR20 was achieved in 10% of the patients, whereas 35%, and 55% of the patients achieved ACR50, and ACR70 responses, respectively. ACR20 response was achieved in 50% of patients who received infliximab plus supervised exercise, whereas ACR50 and ACR70 responses were achieved by 10% and 40% of the patients, respectively. On the other hand, in patients treated with green tea plus the supervised exercise program, ACR20 was achieved by 10% of the treated patients, whereas 30% and 60% of patients achieved ACR50 and ACR70 responses, respectively (Table 5). According to the EULAR improvement scores, patients treated with green tea plus exercise showed moderate to good responses in disease activity markers and significant improvement (20–75%) in DAS28-ESR and mHAQ scores compared with the other treated groups, as shown in Tables 3 and 5.

## DISCUSSION

Generalized and near joint osteoporosis are most often devolving in rheumatoid arthritis patients, with a subsequent increase in bone loss[43]. In most cases, generalized bone loss may be increased as a result of inflammation[44] or as a result of extensive treatments with corticosteroids[43–45]. A wide range of biochemical markers relating to bone resorption (DPD, NTX) and formation (sBAP) have been validated as useful markers of bone metabolism[14–16].

Nondrug treatments of plant origin for arthritis have been shown to be effective for the inflammation associated with the disease and to provide a significant reduction in the level of pain and swelling among RA patients[46–48]. Although, these treatment modalities do not have the ability to completely protect bone cartilage from this ongoing degenerative process, they suppress the destruction of joints via modification or reduction of the release of cartilage oligomeric matrix protein (COMP) and hyaluronic acid (HA), which are biomarkers of joint status in RA[49, 50]. Thus, traditional herbal substances of plant origin that have shown the ability to substantially protect or regulate of RA might be of considerable medical intrrest[19]. Previous research studies have also reported that exercise interventions used as alternative therapies were shown to have a specific health benefits for patients with RA[27, 32].

For the abovementioned reasons, we measured urinary excretion levels of NTX and DPD and sBAP levels as bone metabolism markers and measured disease activity markers in 120 patients with RA treated with green tea and a supervised exercise program as nondrug modalities.

In the present study, in vitro studies were performed to estimate active polyphenolic contents and antioxidant activity of green tea extracts before studying their anti-rheumatic activity using liquid chromatography and DPPH/NBT. The data obtained showed that green tea contains high amounts of catechins (589 mg/g), caffeine (96 mg/g), chlorogenic acid (25.34 mg/g), and pyrogallol (18.5 mg/g) along with low amounts of other active polyphenols such as vanillic, synergic, salycillic, benzoic, and ferulic acids. Also, AGTEs showed high free radical scavenging activities (96.5 and 89.6% for DPPH and NBT free radicals, respectively) at a concentration of 64 µg $ml^{-1}$. The data matched those of Hoff and Singleton[49], who reported the same levels of polyphenolic compounds. Furthermore, another previous research study reported that green tea, the most popular consumed beverage worldwide, has higher levels of active phenolic compounds such as catechins like EGCG, EGCG and these compounds were shown to have a potential anti-rheumatic activity[50]. The levels of polyphenol content vary according to type of tea, brewing, commercial brand, and producing country, as reported by Khokhar and Magnusdottir[51], who estimated the polyphenol contents of black and green tea leaves to be 80.5 to 134.9 mg/g and 65.8 to 106.2 mg/g, respectively. Also, AGTEs showed high antioxidant activities against DPPH and NBT radicals (96.5 and 89.6% for DPPH and NBT free radicals, respectively) at a concentration of 64 µg $ml^{-1}$. These results are in agreement with previous research works that reported high antioxidant activity of green tea extracts[52–54].

In the present study, 20 patients with RA were supplemented with 4–6 cups of green tea per day for 6 months. Each cup contained 60 to 125 mg catechins in the form of EGCG, as previously mentioned[54]. The patients showed significant reductions in the levels of disease activity parameters such as the ESR, CRP, SJC and TJC, and significant improvements in mHAQ scores following 6 months of treatment. There were also significant decreases in the levels of NTX and DPD, biomarkers of bone resorption and sBAP, a marker of bone formation, after the initial treatment with green tea.

The decreases in the bone resorption markers (NTX and DPD) were found to be significantly ($p=0.01$ and $p=0.001$) correlated with the improvements in disease activity markers and represented promising data compared with the data for patients treated with infliximab for 6 months. On the other hand, green tea polyphenols were shown to prevent bone loss and the joint degenerative process via an increase in antioxidant capacity and/or a decrease in oxidative stress damage[55] or to preserve or protect the integrity of bone cartilage via a reduction in the release of COMP and HA biomarkers[56]. Recent research has suggested that BMD is positively associated with tea consumption, which may optimize bone health. The bioactive components in tea may benefit bone health in terms of maintaining a higher bone mineral density[57, 58]. Furthermore, green tea or its bioactive EGCG component has been shown to reduce RA via an improvement in the bone resorption process, which ultimately reduces the release of both NTX and DPD in serum or urine samples[59–61]. The high EGCG contents of our green tea extract were shown to be responsible for the anti-rheumatic and other biological activities of green tea, and EGCG possesses about 25–100 times more antioxidant potential than vitamins C and E[62–64].

Certain pathways have been proposed to support the protective effect of green tea against RA, the most popular of these pathways previously reported, are the ability of green tea to regulate the endocrine system, redox status, and regulation of TNF–α gene expression, which suppresses the release of TNF-α, IL-1, and IL-6[65, 66]. These proinflammatory cytokines play a significant role in the pathogenesis of RA via cartilage and bone degradation by synovial inflammation. Thus, green tea preserves the integrity of cartilage and prevents the release of cartilage and collagen degradation markers, which increase during progressive cartilage degradation in OA and RA[67–69].

Much interest has been expressed among health professionals with respect to improvement of health care trials among patients with severe RA. Thus more studies have been performed on the use of exercise interventions for improvement of joint function, mobility, strength, endurance, and cardiovascular fitness[67, 68].

From this regard, a trial of exercise therapy interventions was one of the main targets of this study to evaluate the benefits of exercise on RA disease activity. The patients were subjected to a supervised exercise program (45 min, 2–3 times, week

for 6 month). The data obtained showed positive reliable changes in disease activity parameters, taking into account the TJC, SJC, and physical status of the subjects. Application of the exercise therapies for 6 months appeared to assist in control of the disease activity, as the TJC, SJC, mHAQ score, ESR, CRP, and DAS28-ESR were reduced in all subjects with a varying ACR response rate. Also, the mean levels of bone resorption markers (NTX and DPD) and sBAP decreased significantly ($p=0.01$ and $p=0.001$). This unique trial demonstrates the efficacy of alternative exercise modalities in maintaining bone health while providing further evidence that lack of an osteogenic stimulus via physical inactivity results in more rapid bone deterioration in patients with RA[4, 69]. The data also were in accordance with previous research work that reported a significant improvement in bone metabolism indices and bone mineral density following 12 weeks of moderate aerobic exercise, and concluded that moderate exercise supports the bone formation process and minimizes the rate of bone resorption, which might assist in the prevention of bone loss or osteoporosis[70].

In the exercise group, the changes in NTX, DPD, and BAP from baseline were statistically correlated with the disease activity markers (ESR, CRP, TJC, SJC, mHAQ score, and DAS28-ESR). The data obtained matched those of other studies that reported superior changes in bone resorption and BAP markers[71–73] and that the positive effects reported in patients with RA following aerobic exercise depend mainly on increases in aerobic capacity parameters, which in turn maintain joint mobility, muscle strength[74, 75], stabilization of the joints, and prevention of joint angulation, and later osteoarthrosis[76, 77].

It has also been reported that endurance training exercise suppresses inflammatory processes via deactivation of the release of basal inflammatory mediators and consequently prevents progressive cartilage degradation and bone degradation[78, 79].

In this study, the patients who received green tea plus the supervised exercise program as combined nondrug modalities showed significant improvements in disease activity parameters (ESR, CRP, TJC, SJC, mHAQ score, and DAS28-ESR.) beginning after the initial treatment compared with the patients treated either with infliximab plus green tea or exercise only. The mean levels of NTX, DPD, and sBAP were significantly correlated with the improvements in disease activity parameters, which matched the data of another study in which infliximab therapy was used for other data during management of RA.

In this study, clinical improvements of all patients were evaluated using EULAR and American College of Rheumatology scores. At week 24, the achievement with respect to ACR20, ACR50, and ACR70 responses and EULAR scores were different in all treatment trials. In green tea-treated patients, 25%, 30%, and 45% of patients achieved ACR20, ACR50 and ACR70 responses, respectively, whereas, 50%, 35%, and 15% of patients did so in the infliximab group, and 40%, 45%, and 50% of patients did so in the exercise-treated group. In the green tea and exercise groups, patients showed a tendency towards a reduction in all disease activity parameters and significant improvement in all ACR parameters, especially in the green tea group. These data were supported by the results of comparing the moderate or good EULAR scores of each group. Green tea- treated patients showed moderate to good improvement (45–50%) in disease activity parameters (DAS28-ESR, CRP, ESR, and mHAQ scores) compared with infliximab or exercise treated-patients (25–45%). The data obtained were in line with other studies that reported significant improvement in disease activity, health quality, bone markers, and integrity of bone cartilage[38, 50, 75].

In the combination therapy interventions, 10%, 30%, and 60% of patients treated with green tea plus supervised exercise achieved ACR20, ACR50, and ACR70 responses, respectively whereas 10%, 35%, and 55% of the patients did so in the infliximab plus green tea group, and 50%,10%, and 40% of the patients did so in the infliximab plus exercise group. According to EULAR improvement scores, patients treated with green tea plus exercise interventions showed moderate to good responses in disease activity markers and significant improvements (20–75%) in DAS28-ESR and mHAQ scores compared with the other groups. The improvements in disease activity among our patients revealed that exercise has significant positive effects on bone health and bone mineral density, as shown in the literature[76–78]. These findings have also been reported by Shen et al.[80], who concluded that Tai Chi exercise and green tea polypehonols alone or in combination result in significant improvement in bone formation biomarkers and improved muscle strength and bone turnover rate.

Finally, this study showed that green tea and exercise either alone or in combination provide positive effects on disease activity among patients with RA. The possible mechanism(s) might be related to the potential antioxidant activity and anti-inflammatory of both green tea polyphenols and exercise and their effects of preservation of cartilage integrity and suppression of the bone loss process.

In conclusion, in the present study, clinical improvements in disease activity, health quality, and bone resorption and formation biomarkers were observed in all RA patients following green tea and exercise therapy interventions. The data suggested that green tea and exercise might be of interest in RA therapy depending on to the patient's needs and disease activity status. This needs for further research with larger samples, so that comparisons can be made among various modes of exercises and tea to evaluate the long-term effects.

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