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IMPACT OF VARIOUS RHEUMATOID ARTHRITIS TREATMENTS ON BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN

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Abstract

Aim: The objective of this study was to evaluate the impact of various treatment options on bone mineral density (BMD) in postmenopausal women with rheumatoid arthritis (RA).

Material and Methods: A retrospective analysis was conducted on the data of 163 postmenopausal women, including 121 RA patients meeting the 2010 American College of Rheumatology/European League Against Rheumatism criteria and 42 healthy controls. RA patients were categorized into four groups based on their treatment regimens: Group 1, receiving conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) alone; Group 2, receiving csDMARDs in combination with glucocorticosteroids (GCs); Group 3, receiving csDMARDs with GCs and biological/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs); and Group 4, receiving b/tsDMARDs combined with methotrexate. Data collected included demographic information, BMD T-scores at lumbar spine (L1-L4), femoral neck, total hip, and serum calcium, and vitamin D levels.

Results: RA patients had significantly lower BMD T-scores at L1-L4, femoral neck, and total hip compared to controls ($p=0.041$, $p=0.026$, and $p=0.003$, respectively). Among treatment groups, patients receiving csDMARDs with GCs exhibited greater bone loss, particularly in femoral neck scores, compared to other regimens (all $p\leq0.005$). Conversely, b/tsDMARDs showed a protective effect on BMD, mitigating bone loss despite the use of low-dose GCs.

Conclusion: This study demonstrates that RA treatments significantly influence BMD in postmenopausal women. b/tsDMARDs appear to mitigate the adverse effects of GCs on bone health, while prolonged GC use is associated with greater bone loss, especially in the csDMARDs group.

Keywords: Rheumatoid arthritis, postmenopausal women, biologic therapies, corticosteroids, DMARDs, bone mineral density

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder primarily characterised by joint inflammation and systemic involvement, including significant skeletal complications (1). Beyond joint pathology, RA is related with lower bone mass, decreased bone mineral density (BMD), and a heightened risk of osteoporosis and fractures. These fractures, considered among the most severe complications of RA, significantly impair quality of life and may shorten life expectancy (2).

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The pathways leading to bone loss in RA involve a complex interplay of inflammatory mechanisms. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, and IL-17 stimulate osteoclastogenesis through the receptor activator of nuclear factor-κB ligand (RANKL)-RANK-osteoprotegerin (OPG) pathway, thereby increasing bone breakdown while concurrently suppressing osteoblast function. Autoimmune responses associated with RA further exacerbate bone loss by altering Wnt signalling and other pathways essential for maintaining bone homeostasis. Additionally, systemic factors such as glucocorticosteroids (GCs) therapy, reduced physical activity due to joint pain, and chronic systemic inflammation intensify bone deterioration (3,4).

The treatment of RA involves conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate (MTX), hydroxychloroquine (HCQ), and sulfasalazine, alongside biological/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) TNF-α, IL-6, and Janus kinases (JAK) inhibitors (upadacitinib, baricitinib). Combination approaches using synthetic and bDMARDs are also effective in managing the disease (5).

This study aims to evaluate the impact of diverse RA treatment regimens on bone health in postmenopausal women, and to provide observations on how biologic therapies may affect the adverse effects of long-term GC use.

MATERIAL AND METHODS

This retrospective study was approved by the Clinical Research Ethics Committee of Mersin University (approval number: 2024/987, dated: 16.10.2024). Patient data collected between January 1, 2021, and September 30, 2024, was analyzed. In the retrospectively analyzed data, only cases in which disease activity scores 28 (DAS28), BMD measurements, calcium, and vitamin D levels were recorded during the same clinical visit were included in the study. Only RA patients who remained on the same treatment regimen for at least 24 months were included in the study. The study involved a total of 163 postmenopausal women aged over 50 years. Of these, 121 were identified as having RA and were included in the RA group, while 42 healthy, RA-negative individuals with similar demographic characteristics formed the control group.

Patients in the RA group were required to meet the following criteria: a confirmed RA diagnosis based on the 2010 American College of Rheumatology and European League Against Rheumatism (EULAR) classification criteria (6), postmenopausal status, availability of bone densitometry (DXA) results, and serum measurements of calcium and vitamin D in the hospital automation system. For the control group, inclusion required postmenopausal status, an absence of RA, and the availability of bone DXA together with serum vitamin D and calcium levels. Exclusion criteria applied to both groups included the existence of chronic infections, systemic inflammatory diseases other than RA, malignancies, prior treatment with osteoporosis medications (e.g., bisphosphonates, denosumab, teriparatide, romosozumab), other conditions leading to osteoporosis, such as hyperthyroidism, hyperparathyroidism, liver failure, or kidney failure, and the presence of medical implants or devices that could interfere with DXA results.

RA patients were categorized into five groups according to their treatment protocols: (1) those treated with csDMARDs (MTX and HCQ); (2) those treated with csDMARDs (MTX + HCQ) in combination with GC (e.g., prednisolone), characterized by low-dose steroid use (≤7.5 mg/day) administered over a long duration (≥3 months); (3) those treated with csDMARDs, GC, and b/tsDMARDs (including anti-TNF drugs such as etanercept, adalimumab, golimumab, infliximab, and certolizumab; JAK inhibitors such as upadacitinib, baricitinib, and tofacitinib; or the anti-IL-6 agent tocilizumab), with steroid use matching the low-dose, long-duration criteria; (4) those treated exclusively with b/tsDMARDs (e.g., anti-TNF drugs, JAK inhibitors, or the anti-IL-6 agent) combined with MTX (a csDMARD); and (5) a control group of RA-negative postmenopausal individuals matched for demographic characteristics. Each group consisted of participants as follows: Group 1 (28); Group 2 (43); Group 3 and 4 (25 each); and Group 5 (42), yielding a total of 163 participants across the five groups. Data were retrieved from the hospital's electronic database. Recorded information included demographic details such as age, weight, and height. Bone health measurements included T-scores of the L1-L4 region, the hip (total) and the neck of the femur, obtained from DXA scans. Laboratory parameters such as serum levels of vitamin D and calcium at the point of DXA measurement were also recorded.

Statistical Analysis

The statistical analysis was conducted to summarize the data, presenting continuous variables as mean ± standard deviation or median (minimum-maximum), depending on the distribution. The Shapiro-Wilk test was utilized to examine the normality of the data. Parametric tests were applied to data sets with normal distributions, whereas non-parametric tests were used for those that did not meet normality assumptions. For comparisons between two groups, the independent samples t-test or Mann-Whitney U test was employed. For multiple-group comparisons, one-way analysis of variance (ANOVA) or the

Kruskal-Wallis test was applied. Significant outcomes from one-way ANOVA were further assessed using the Tukey's post-hoc test, while significant results from the Kruskal-Wallis test underwent additional analysis with Bonferroni-adjusted pairwise Mann-Whitney U tests. The analysis of the distribution of bone health statuses among five patient groups was conducted using Fisher's exact test. Subsequently, post-hoc analysis was performed using Z-scores obtained from crosstabulation to further evaluate pairwise comparisons between groups. A Z-score threshold of ±1.96 was used, corresponding to a 95% confidence interval, to determine whether the observed counts significantly deviated from the expected counts in each category. Statistical analyses were performed using SPSS version 22.

RESULTS

Age, weight, height, body mass index (BMI), calcium, and vitamin D levels showed statistical similarity across the groups (p>0.05). However, significant differences were identified among the groups for T-score of L1-L4 (p=0.041), femoral neck (p=0.026), and hip (p=0.003) parameters (Table 1).

The five subgroups were statistically similar in terms of age, weight, height, and BMI (p>0.05). The disease duration among RA subgroups was also similar (p=0.568). Calcium and vitamin D levels did not differ significantly across the groups (p=0.420 and p=0.115, respectively). However, the DAS28 scores of each RA subgroup were statistically different (p<0.001). Significant differences were observed among the groups for T-score of L1-L4 (p=0.015), femoral neck (p<0.001), and total hip (p<0.001). T-scores of the femoral neck, and the total hip differed significantly between Groups 1 and 2 (p<0.001), and between Groups 2 and 3 (p=0.005 and p=0.004, respectively). Additionally, Groups 2 and 5 showed differences in T-scores of femoral neck, total hip (both p <0.001), and L1-L4 (p=0.005). Between Groups 4 and 2, only femoral neck T score was significantly different (p=0.004) (Table 2). Other BMD parameters were similar between the groups. Specifically, the direct comparative data of Group 2 and Group 3 at L1-L4 did not show a significant difference, (p=0.615).

Table 1. Demographic and laboratory parameters of the patient and healthy groups

	Patient group	Control group	p-value
Age (years), mean ± SD	61.96±9.29	61.73±8.01	0.879
Weight (kg), mean ± SD	73.47±14.71	76.28±11.74	0.216
Height (meter), mean ± SD	1.58±0.06	1.58±0.04	0.432
BMI (kg/m^2), mean ± SD	29.24±5.15	30.23±4.71	0.253
Disease duration (years), mean ± SD	9.88±5.86	N/A	-
Calcium, mean ± SD	9.18±0.55	9.30±0.39	0.115
Vitamin D (ng/dL), mean ± SD	19.22±9.26	19.25±8.40	0.983
LI-L4 T score, mean ± SD	-1.56±0.98	-1.06±1.40	**0.041**
Femoral neck T score, mean ± SD	-1.40±0.98	-1.02±0.90	**0.026**
Total hip T score, mean ± SD	-1.05±1.09	-0.48±1.04	**0.003**

SD: Standard deviation, kg: Kilogram, m: Meter, BMI: Body mass index, N/A: Not applicable

A significant statistical difference was observed in the bone health status of patients across different groups (p=0.008). The adjusted residuals indicated that Group 5 had a statistically higher number of healthy patients in terms of bone health than expected (Z-score =+3.3). Similarly, Group 3's observed osteopenic count was significantly higher than expected (z-score =+2.0), whereas Group 5 had fewer osteopenic patients than anticipated (z-score =-2.7). For osteoporotic patients, the adjusted residuals indicated that Group 2 had significantly more cases than expected (z-score =+2.5) (Table 3).

No correlation was observed between T-scores and DAS28 scores (all p>0.05).

DISCUSSION

The present study investigates the significant impact of RA and its treatment regimens on BMD in postmenopausal women. The RA patient group exhibited reduced T-scores in all bone density parameters relative to the healthy control group. Moreover, this study demonstrated that treatment regimens for RA significantly affect BMD in postmenopausal women. It showed that GC + csDMARDs treatment was associated with worse T-scores in the femoral neck and hip regions compared to csDMARDs treatment alone, or csDMARD + GC + b/tsDMARDs treatment. Additionally, the study showed that the femoral neck scores of the b/tsDMARDs + MTX treatment group were higher than those of the csDMARDs + GC treatment group.

Osteoporosis is a chronic skeletal condition characterized by reduced bone density and structural degradation, which result in increased bone fragility and a heightened risk of fractures (7).

Bone remodeling is an essential physiological process regulated by pathways like RANK-RANKL, OPG and the wingless-related integration site (Wnt) signaling, which are influenced by immune cells and cytokines. In RA, elevated proinflammatory cytokines

Table 2. Demographic and laboratory parameters of the groups

	Group 1 csDMARDs n=28	Group 2 csDMARDs + GCs n=43	Group 3 csDMARDs + GCs + b/tsDMARDs n=25	Group 4 b/tsDMARDs + MTX n=25	Group 5 Healthy n=42	p-value
Age (years), mean ± SD	61.79±10.14	63.91±9.71	60.08±7.61	60.72±9.0	61.73±8.01	0.461
Weight (kg), mean ± SD	76.39±15.82	70.30±14.74	73.92±14.21	73.80±14.27	76.28±11.74	0.549
Height (meter), mean ± SD	1.58±0.07	1.58±0.06	1.59±0.05	1.59±0.06	1.58±0.04	0.731
BMI (kg/m^2), mean ± SD	30.61±5.28	28.95±5.32	28.49±5.13	28.97±4.76	30.23±4.71	0.406
Disease duration (years), mean ± SD	9.11±7.05	9.93±5.29	9.32±4.64	11.24±6.62	NA	0.568*
DAS28 score, mean ± SD	1.39±0.73	2.67±0.61	3.53±0.71	4.20±0.78	NA	**p<0.001***
Calcium, med. (min.-max.)	9.40 (7.60, 10.90)	9.20 (7.70, 9.70)	9.20 (7.80, 10.10)	9.15 (8.00-10.60)	9.30 (8.50-10.20)	0.420
Vitamin D (ng/dL), mean ± SD	22.50±11.62	19.12±9.47	19.18±8.31	15.76±5.04	19.25±8.40	0.115
L1-L4 T score, med. (min.-max.)	-1.3 (-2.7, 0.3)	-1.9 (-4.0, 0.8)	-1.6 (-4.4, -0.5)	-1.1 (-3.5, 1.7)	-1.1 (-4.9, 2.2)	0.015
Femoral neck T score, med. (min.-max.)	-0.85 (-3.5, 0.6)	-1.8 (-4.2, 1.2)	-1.3 (-3.8, -0.4)	-1.3 (-2.7, 1.6)	-0.95 (-2.7, 1.1)	**p<0.001**
Total hip T score, med. (min.-max.)	-0.3 (-3.5, 1.6)	-1.6 (-4.9, 1.6)	-1.0 (-3.0, 1.3)	-0.7 (-2.7, 0.6)	-0.35 (-2.8, 2.4)	**p<0.001**

*p-value for comparisons among patient subgroups. SD: Standard deviation, kg: Kilogram, m: Meter, BMI: Body mass index, N/A: Not applicable, med.: Median, min.-max.: Minimum-maximum, DAS28 score: Disease activity score 28, csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs, GCs: Glucocorticoids, b/tsDMARDs: Biologic or targeted synthetic disease-modifying anti-rheumatic drugs, MTX: Methotrexate

such as TNF-α, IL-1β, IL-6, and IL-17 enhance osteoclastogenesis and bone resorption, contributing to bone loss (3,8).

Besides chronic systemic inflammation, the frequently lower serum vitamin D concentrations in RA patients compared to healthy individuals may exacerbate bone health deterioration (9,10). According to the literature, patients with RA generally show lower vitamin D levels compared to the control group, and these reduced levels are often associated with higher disease activity (11,12). However, we observed in our study similar vitamin D levels between the RA group and controls. This discrepancy may be explained by our study's retrospective nature, as some patients might have been using vitamin D supplements or related compounds either regularly and prior to their assessment.

RA treatment aims to control inflammation and prevent disease progression through various pharmacological strategies. These include non-steroidal anti-inflammatory drugs and GCs, which provide symptomatic relief. csDMARDs, such as MTX, leflunomide, HCQ, and sulfasalazine, remain the cornerstone of RA management. tsDMARDs, including JAK inhibitors like tofacitinib and baricitinib, offer a more focused approach by modulating specific intracellular signaling pathways. Furthermore, bDMARDs, including anti-TNF medications (etanercept, golimumab, adalimumab, infliximab, and certolizumab) and IL-6 inhibitors such as tocilizumab, target key cytokines in the inflammatory cascade, representing significant advancements in RA therapy (13).

Most csDMARDs used in the treatment of RA are believed to exert a beneficial impact on bone density and metabolism, primarily through their ability to suppress systemic inflammation. Despite their potential to modulate inflammation, evidence supporting the efficacy of csDMARDs in reducing bone loss remains limited (3).

In a study evaluating the effects of MTX on bone mass in patients with RA, it was found that BMD in the neck of the femur and lumbar bones remained unchanged following long-term MTX use (14). Another study found that MTX does not seem to detrimentally change BMD among premenopausal early RA patients, comparable to sulfasalazine, after 12 months of treatment (15). A study reported that HCQ use does not significantly affect the risk of osteoporosis in patients with RA (16).

Short-term GCs therapy remains part of the 2023 EULAR recommendations for RA management, with a strong emphasis on tapering and discontinuation as quickly as clinically feasible. Despite this, approximately 10% of patients continue GC use at

Table 3. Comparison of bone health status of patients in different groups

Status of bone health		Group 1 csDMARDs n=28	Group 2 csDMARDs + GCs n=43	Group 3 csDMARDs + GCs + b/tsDMARDs n=25	Group 4 b/tsDMARDs + MTX n=25	Group 5 healthy n=42
Healthy	Count	6	5	2	4	16
	Expected count	5.7	8.7	5.1	5.1	8.5
	% within grup	21.4%	11.6%	8.0%	16.0%	38.1%
	Adjusted residual	0.2	-1.6	-1.7	-0.6	3.3
Osteopenic	Count	18	23	19	18	17
	Expected count	16.3	25.1	14.6	14.6	24.5
	% within grup	64.3%	53.5%	76.0%	72.0%	40.5%
	Adjusted residual	0.7	-0.7	2.0	1.5	-2.7
Osteoporotic	Count	4	15	4	3	9
	Expected count	6.0	9.2	5.4	5.4	9.0
	% within grup	14.3%	34.9%	16.0%	12.0%	21.4%
	Adjusted residual	-1.0	2.5	-0.7	-1.3	0.0

*Fisher's exact test p-value for this analysis: 0.008. csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs, GCs: Glucocorticoids, b/tsDMARDs: Biologic or targeted synthetic disease-modifying anti-rheumatic drugs, MTX: Methotrexate

6, 12, or even 24 months, highlighting challenges in achieving optimal disease control and discontinuing GCs in clinical practice (17). GCs disrupt bone remodeling by suppressing osteoblast function through downregulation of Wnt signaling and insulin-like growth factor-1 (IGF-1), enhancing osteoclast activity via RANKL/OPG imbalance, inducing osteocyte apoptosis, and reducing vascular endothelial growth factor (VEGF)-mediated vascular support (18). Despite this well-established and widely accepted knowledge, the influence of low-dose GCs on bone health in RA remains a topic of ongoing debate. While their use is linked to a higher risk of bone loss and fractures, they simultaneously play a critical role in mitigating systemic inflammation (19). Some randomized controlled trials have found evidence that these beneficial effects of GCs may offset their potential harm to bone health. The randomized controlled trial conducted by Haugeberg et al. (20) demonstrated a significant reduction in bone loss in the hands of RA patients treated with 7.5 mg of prednisolone daily compared to those receiving a placebo. Engvall et al. (21) observed that over a two-year follow-up, treatment with DMARDs combined with low-dose GC was more effective in preserving femoral BMD in patients with early RA compared to DMARD therapy alone. However, they also noted that this regimen failed to prevent a decline in lumbar spine BMD, particularly in postmenopausal women. In contrast, our findings indicate that GC + csDMARD therapy was linked to lower BMD scores compared to csDMARD therapy alone, especially in femur neck and total hip scores.

Abtahi et al. (22) found that low daily doses of GCs in RA patients increased vertebral fractures but not non-vertebral ones. Kroot et al. (23) highlighted that prednisone use is consistently associated with bone loss in patients with RA and underscored the importance of carefully monitoring and managing GC use to mitigate the risk of osteoporosis and other bone-related complications over time. The conflicting evidence regarding the effects of low-dose daily oral GC use on bone health in RA, coupled with the uncertainty over whether these effects are predominantly beneficial or harmful, highlights the need for a more detailed investigation of this relationship. Our study makes a significant contribution to the literature by addressing this gap and providing new insights into the dual role of GCs.

bDMARDs, particularly TNF-α inhibitors, positively impact bone health in RA by inhibiting osteoclast-mediated bone resorption and promoting osteoblast activity. TNF-α inhibitors achieve this by reducing RANKL expression, increasing OPG, and lowering the RANKL/OPG ratio, which suppresses osteoclastogenesis. Additionally, they enhance osteoblastogenesis by decreasing Dickkopf-1, a key inhibitor of bone formation (3). In their study on RA patients, Marotte et al. (24) found that over a one-year follow-up, femoral neck and spine BMD decreased in the MTX + GC treatment group, whereas the addition of infliximab to MTX + GC therapy successfully prevented bone loss. The majority of patients in both groups (over 60%) were also receiving a daily GC dose of approximately 5 mg. In line with the findings of Marotte et al. (24), our study also highlights that while

csDMARD combined with low-dose GC therapy may result in decreased BMD, the addition of BA to csDMARD and low-dose GC therapy effectively prevents bone loss. Similarly, the study by Chen et al. (25) observed that RA patients treated with csDMARDs experienced greater bone loss compared to those receiving b/tsDMARDs. Interestingly, GC use was observed in approximately 85% of patients in both groups in this study. Based on the 24-year analysis conducted by Oelzner et al. (26), RA patients with a disease duration exceeding two years displayed higher BMD when receiving biologic therapies, despite the elevated cumulative GC exposure. This study clearly indicates that biological treatments can play a protective role against the negative effects of GCs on bone. In our study, despite the use of GCs in Group 3, BMD values did not differ significantly between Group 3 and Group 4. This finding may be attributed to the potential protective effects of b/tsDMARDs on bone health.

Glucocorticoid drugs induce hypophosphatemia by reducing phosphate reabsorption in the kidneys (27). In contrast, vitamin D enhances phosphate absorption in both the kidneys and intestines (28). Steroid use and vitamin D deficiency are both associated with hypophosphatemia, which may contribute to increased bone resorption (27-29). However, due to the retrospective design of our study, phosphate levels were not available in the records of some patients, and these values could not be included in our analysis.

In our study, DAS28 scores, which reflect disease activity and the level of acute phase reactants (30), were statistically different between the groups. This variation may be attributed to differences in disease activity and treatment regimens among the groups. While it is expected that osteoporosis would be more prevalent in RA patients with high DAS28 scores, bone health is influenced by multiple factors, including disease activity, GCs' use, cDMARDs, and biologic agents, which can complicate the interpretation. The absence of a direct relationship between T-scores and DAS28 scores in our study may be a result of this multifactorial interplay of both protective and detrimental factors.

Preserved BMD levels observed in Groups 3 and 4 were thought to be associated with the use of biologic therapies. Conversely, the maintained BMD levels in Group 1 may be attributed to low disease activity (indicating reduced inflammation) and a relatively lower utilisation of GCs compared to other groups. Patients in Group 2, who showed significant bone loss compared to other groups, may benefit from reassessing their treatment. If there are no contraindications and the patient agrees to switch, initiating biologic therapy could help reduce the adverse effects of prolonged steroid use.

Study Limitations

Although this study provides important findings, it has some limitations. The retrospective design, small sample size, heterogeneity in treatment agents, and inadequate details about dose and duration regarding GC use and other RA treatment agents are the main study limitations. Despite patients remaining on the same treatment for at least 24 months, the study duration of approximately 10 years and the treatment switches made during this period in some patients make it difficult to present consistent data. Insufficient data on adherence to treatment and inadequate control of other osteoporosis risks, like dietary habits, physical activity levels, and the assessment of vitamin D and calcium supplementation, are additional limitations of the study. Finally, the absence of data on phosphate levels is another limitation.

CONCLUSION

BMD seems to be higher in patients receiving b/tsDMARDs, with or without GCs, compared to those receiving cDMARDs with GCs. In the context of csDMARDs treatment, the prolonged use of low-dose GCs is associated with marked adverse effects on bone health. Optimizing treatment regimens by minimizing GC exposure and incorporating b/tsDMARDs may help preserve bone health in RA patients.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Mersin University (approval number: 2024/987, dated: 16.10.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.U., A.N.D., U.G.D., Concept: A.U., A.N.D., U.G.D., Design: A.U., A.N.D., U.G.D., Data Collection or Processing: A.U., A.N.D., U.G.D., Analysis or Interpretation: A.U., A.N.D., Literature Search: A.U., A.N.D., U.G.D., Writing: A.U., A.N.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

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