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ORIGINAL ARTICLE

Vitamin D levels and bone mass in rheumatoid arthritis

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Abstract Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease with high prevalence of osteoporosis. Previous evidence indicates an association between vitamin D deficiency and autoimmune diseases. The aim of this study was to evaluate serum 25 hydroxyvitamin D [25(OH)D] levels, bone mineral density (BMD) and disease activity in RA patients living in Argentina. We studied 34 RA women and 41 healthy women as a control group. RA patients had lower 25(OH)D levels (20.4 ± 0.9 ng/ml) than controls (26.3 ± 1.9 ng/ml; $p < 0.05$). No significant differences were found in lumbar spine BMD between premenopausal (preM) or postmenopausal (postM) patients, but femoral neck BMD was significantly lower in postM RA patients (T score −2.5 ± 0.4) than in postM control subjects (T score −0.9 ± 0.3, $p = 0.014$). Although no linear correlation between 25(OH)D levels and disease activity (DAS-28) was found, patients with moderate-high disease activity had lower 25(OH)D levels than those with low disease activity: DAS-28 >3.2: 19.5 ± 0.88 ng/ml; DAS-28 ≤3.2: 23.7 ± 2.8 ng/ml ($p = 0.047$). After 1 year of vitamin D treatment 25(OH)D levels were increased while DAS-28 were decreased ($n = 25$; $p < 0.05$). We conclude that patients with RA had lower 25(OH)D levels than the control group. Low levels of 25(OH)D were associated with moderate-high disease activity suggesting the importance of optimal 25(OH)D levels in RA patients. Femoral neck BMD was lower in postM RA patients. No differences in lumbar BMD were found between preM and postM RA patients, suggesting that bone mass evaluation in RA patients should include femoral neck BMD regardless of age.

Keywords Vitamin D · Bone mass · Rheumatoid arthritis · Disease activity

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Introduction

Rheumatoid arthritis (RA) is a common chronic systemic inflammatory autoimmune disease. The synovial tissue in RA patients is characterized by hyperplasia and inflammatory cells, which produce several proinflammatory mediators and proteases that affect cartilage and bone. RA leads to progressive joint destruction, deformation and progressive disability, systemic complications and early death. Additionally, it is a bone-destructive disease and a risk factor for the development of local and systemic osteoporosis [1].

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Previous evidence indicates an association between vitamin D deficiency and an increased incidence of autoimmune diseases [2]. Additionally, it has been reported that the levels of 25-hydroxyvitamin D [25(OH)D] are negatively correlated with RA activity, measured by the Disease Activity Score (DAS-28) and other scores of mobility in daily living activities [3–5]. Interestingly, a study found a significant negative correlation between 25(OH)D and DAS-28 in Italian patients during the summer and in Estonian patients during the winter [6]. In addition, significantly lower 25(OH)D levels have been found in patients without disease remission or responding poorly to treatment [7]. After 3 months of high-dose oral therapy with alpha-calcidiol, 89 % of patients showed an improvement in RA symptoms, with 45 % of patients achieving complete remission [8]. In Chinese RA patients not taking glucocorticoids (GC), low serum 25(OH)D levels correlated with low bone mineral density (BMD) and high disease activity [9].

Osteoporosis-related fragility fractures represent one of the most important complications in patients with rheumatic diseases. RA patients have a high prevalence of fractures [10], with an increased risk of both vertebral and non-vertebral fractures due to the frequent use of GC but also to the negative effect of the disease itself on bone health. Disease activity, immobilization and treatment with GC are the main factors increasing the risk of osteoporotic fractures. Doses as low as 2.5 mg prednisone per day or equivalent for longer than 3 months increase the risk of vertebral fractures [11]. These fractures may cause an important decrease in quality of life and an increase in morbidity, mortality and health care costs. Therefore, the appropriate control of the disease activity may be a protective factor against bone fragility [12].

In RA, the expression of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are increased. In turn, TNF-α increases the production of cytokines, chemokines and endothelial-cell adhesion molecules; it also increases angiogenesis and decreases the number of regulatory T cells. IL-6 produces local leukocyte activation and mediates systemic effects that promote acute-phase responses [13]. The proinflammatory cytokines TNF-α, IL-1, IL-6 and potentially IL-17 contribute to local and systemic bone loss in RA via osteoclast activation [14].

The aim of this study was to evaluate serum 25(OH)D and bone mass in patients with RA and to evaluate whether 25(OH)D levels correlate with disease activity and health status in patients with RA in a Latin American population.

Patients and methods

We studied 42 Caucasian women who fulfilled the RA classification criteria of the 2010 American College of Rheumatology/European League Against Rheumatism [15] and 48 healthy female volunteers matched for age and body mass index (BMI) as a control group. Body weight and height were recorded and the BMI (kg/m^2) was calculated in all subjects. To be included, patients referred to the Department of Rheumatology, Centenario Hospital, Rosario (Argentina), had to be women older than 18 years, and have RA diagnosed at least 1 year before. Patients were excluded if they had a previous history of neoplasia or had taken drugs that affect bone metabolism, including bisphosphonates, calcium and vitamin D supplements in the last 12 months or were receiving oral GC (>10 mg/day prednisone or equivalent) in the last 3 months.

Patients were also interviewed to find out whether they were receiving or had received any other specific RA treatment as disease-modifying anti-rheumatic drugs (DMARDs) or anti-TNFα therapy. The erythrocyte sedimentation rate, the number of swollen and tender joints and a visual analog scale (VAS) were recorded to evaluate disease activity. Disease activity in RA patients was assessed according to DAS-28 [16], including the number of swollen and tender joints (28 joints), erythrocyte sedimentation rate and a VAS ≤3.2 as low disease activity, 3.2 to ≤5.1 as moderate disease activity and >5.1 as high disease activity. A value of <2.6 was considered the threshold for remission. The functional status was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI) [17].

Additionally, after 1 year of treatment with 100,000 IU of vitamin D_3 every 1–3 months according to basal 25(OH)D levels (average 2,200 IU/day), 25(OH)D levels and DAS-28 were reevaluated.

Biochemical measurements

Serum levels of total calcium (mg/dl), inorganic phosphate (mg/dl), alkaline phosphatase (IU/l) and creatinine were measured. Calciuria (mg/24-h), phosphaturia (mg/24-h) and urinary creatinine excretion (mg/24-h) were also determined by standard techniques. Parathyroid hormone (PTH, pg/ml) was measured by immunoassay (Cobas, Roche Basel, Switzerland), C-reactive protein (CRP, mg/l) by an immunoturbidimetric assay and erythrocyte sedimentation rate (ESR, mm/h) by the Westergren method. Rheumatoid factor (RF, IU/ml) was also determined by an immunoturbidimetric assay, and a RF > 20 IU/ml was defined as positive. Anti-citrullinated peptide antibody (anti-CCP, IU/ml) (defined as positive when ≥20 UI/ml) was determined by ELISA. Total serum 25(OH)D levels were measured by chemiluminescence (Vitamin D Total, Roche; Basel, Switzerland). Vitamin D deficiency was defined as 25(OH)D levels <20 ng/ml (50 nmol/l), insufficiency as 25(OH)D levels between 20 and 30 ng/ml (50–75 nmol/l) and optimal levels as 25(OH)D levels >30 ng/ml [18, 19].

BMD was determined by dual-energy X-ray absorptiometry (DXA) in a Norland densitometer (XR-26, using the software Illuminatus 2008) in the lumbar spine (L2-L4) in patients under 60 years of age and in the femoral neck in patients over 60 years of age. According to the BMD, osteoporosis was diagnosed when the *T* score was −2.5 SD or lower and osteopenia when the *T* score was between −1.0 and −2.5 SD in postmenopausal (postM) women. In premenopausal (preM) women, low bone mass for age was defined when the *Z* score was −2.0 SD or lower [20, 21].

Radiographic films of hands and feet were taken to determine the presence of erosion. Thoracic and lumbar spine lateral X-ray films were obtained to determine the presence of vertebral fractures.

The study was approved by the Ethics Committee of the Centenario Hospital and the Ethics Committee of the School of Medical Sciences, Rosario National University (Argentina) and conducted in compliance with the Declaration of Helsinki. All patients gave written informed consent to participate and each participant was identified by a number in order to keep their identity confidential.

All the patients were from the city of Rosario (32º 52′18′ S), located in the Pampa Region, a region with UV sunlight able to photoproduce vitamin D. The study was carried out in October and November (spring in the Southern hemisphere).

Statistical analysis

Date are expressed as mean ± SEM. Differences between groups were analyzed using the unpaired Mann–Whitney test, the Kruskal–Wallis test or Wilcoxon matched pairs test. The Chi square test was used to analyze categorical variables. Correlations were performed with Spearman's correlation test. The difference was considered significant if $p < 0.05$.

Results

A total of 34 female RA patients between 21 and 75 years of age, and 41 healthy female volunteers aged 25–75 years (controls) were included in the study. The subjects were matched for BMI and other demographic characteristics. Additionally, no differences were found in time of menopause and percentage of preM and postM women between groups. Table 1 shows the main characteristics of the study population.

Eight RA patients and seven controls were not included because of exclusion criteria: two had history of neoplasia, whereas the others had taken vitamin D supplements or other drugs capable of affecting bone mass in the previous 12 months, or GC >10 mg/day prednisone or equivalent in the previous 3 months.

The overall mean level of 25(OH)D was 26.3 ± 1.9 ng/ml in the control group and 20.4 ± 0.9 ng/ml in the RA group (Fig. 1, Mann–Whitney test, $p = 0.009$).

Both the RA and control groups had similar percentages of 25(OH)D deficiency (control: 41.5 %; RA: 35.3 %). However, the RA group showed a higher percentage of 25(OH)D insufficiency (control: 31.7 %; RA: 55.9 %) and a lower percentage of 25(OH)D in the optimal range (control: 26.8 %; RA: 8.8 %) (Table 2; Chi square test, $p = 0.043$). Serum and urine calcium and phosphate values were not different between groups, while alkaline phosphatase was significantly higher in the RA group, although it remained within the normal range. No significant differences were found in lumbar spine BMD between preM or postM patients, but femoral neck BMD was significantly lower in postM RA patients (0.651 ± 0.026 g/cm^2; *T* score −2.5 ± 0.4) than in postM control subjects (0.769 ± 0.030 g/cm^2; *T* score −0.9 ± 0.3]) (Table 2, Mann–Whitney test, $p = 0.014$). Moreover, femoral neck BMD showed that 41.6 % of the RA patients had osteoporosis while 5.9 % of the control subjects had a *T* score <−2.5. No prevalent vertebral fractures were observed in the spine X-rays in either group.

Serum 25(OH)D levels were analyzed as a function of RA activity (DAS-28) and no linear correlation between 25(OH)D levels and disease activity was found. Patients with low disease activity ($n = 7$) had 23.7 ± 2.8 ng/ml of 25(OH)D, patients with moderate disease activity ($n = 20$) had 19.9 ± 1.2 ng/ml and patients with high disease activity ($n = 7$) had 18.4 ± 0.5 ng/ml of 25(OH)D levels. No differences were found between the three groups (Kruskal–Wallis test, $p > 0.05$). However, when the data of patients with low disease activity (DAS-28 ≤ 3.2) were compared with those of patients with moderate-high disease activity (DAS-28 > 3.2), significantly lower levels of 25(OH)D were found in the latter (Fig. 2): low disease activity (20.6 %): 23.7 ± 2.8 ng/ml; moderate-high disease activity (79.4 %): 19.5 ± 0.88 ng/ml (Mann–Whitney test, $p = 0.047$). The 25(OH)D levels did not correlate with BMD or HAQ-DI (Spearman's correlation test, $p > 0.05$).

After 1 year of treatment with oral vitamin D, 25(OH)D levels and RA activity (DAS-28) were evaluated in 25/34 RA patients. After the treatment (Fig. 3), 25(OH)D levels were significantly increased (basal = 20.37 ± 2.06; post-treatment = 35.22 ± 6.56; Wilcoxon matched pairs test, $p = 0.043$) and DAS-28 was decreased (basal = 3.92 ± 0.19; post-treatment = 3.47 ± 0.24; Wilcoxon matched pairs test, $p = 0.032$).

Discussion

In this study, we found a high prevalence of 25(OH)D values below 30 ng/ml in both RA patients and the control

Table 1 Main characteristics of the study population

	Control ($n = 41$)	RA ($n = 34$)	Mann–Whitney test
Age (years [range])	54.8 ± 1.7 [25–71]	52.2 ± 1.9 [21–71]	ns
BMI (kg/m^2)	27.2 ± 0.9	26.2 ± 0.9	ns
Menopause age (years)	48.2 ± 0.6	44.8 ± 1.5	ns
PreM/PostM (%)	24.4/75.6	29.4/70.6	ns
Disease duration (years)	–	7.6 ± 1.4	–
GC treatment duration (years)	–	4.9 ± 1.0	–
Bone erosion		32.3 %	–
Swollen joint count (range 0–28)	–	9.1 ± 1.0	–
Tender joint count (range 0–28)	–	6.1 ± 1.3	–
DAS-28	–	4.0 ± 0.2	–
Inactive	–	7/34 (20.6 %)	–
Moderate	–	20/34 (58.8 %)	–
Very active	–	7/34 (20.6 %)	–
HAQ score (range 0 to 3)	–	1.3 ± 0.2	–
Serum rheumatoid factor positive	–	61.8 %	–
Serum anti-CCP positive	–	64.7 %	–
GC therapy			
<7.5 mg prednisone or equivalent	–	15/34 (44.1 %)	–
≥7.5 mg prednisone or equivalent	–	19/34 (55.9 %)	–
DMARDs therapy	–	29/34 (85.3 %)	–
Anti-TNF therapy	–	3/34 (8.8 %)	–

BMI body mass index, *PreM* premenopausal, *PostM* postmenopausal, *GC* glucocorticoids, *DAS* Disease Activity Score, *HAQ* Health Assessment Questionnaire Disability Index, *anti-CCP* anti-citrullinated peptide antibody, DMARDs Disease-modifying drugs, *anti-TNF* anti- tumor necrosis factor, *ns* not significant

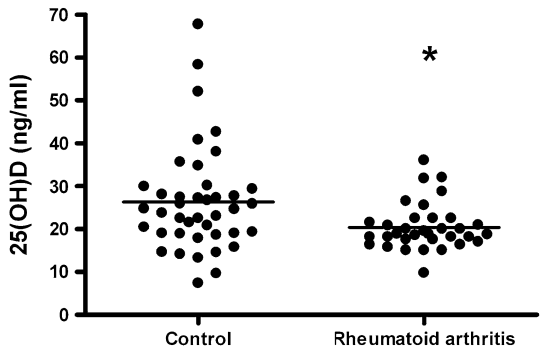

Fig. 1 25(OH)D level in control and RA patients. *Asterisk* indicates significant differences ($p < 0.05$)

group, although the deficiency was more pronounced in the RA group, with a high percentage of patients with insufficiency levels. Therefore, RA patients showed lower 25(OH)D levels than the control group (Fig. 1), similarly to data reported in previous papers [3, 7] but not in others, where 25(OH)D levels in patients with RA were similar to those in the control groups [3, 5, 6]. Although no linear correlation was found between 25(OH)D levels and disease activity (DAS-28), patients with higher DAS-28 values showed lower 25(OH)D levels. Although not all studies have found this association [22–25], the low number of patients in our study might have been insufficient to obtain statistically significant values. Regarding this issue, a previous study [7] with 1,191 RA patients and 1,019 controls showed 25(OH)D levels similar to those of our study. When the data were analyzed comparing low disease activity (DAS-28 $\leq$ 3.2) versus moderate-high disease activity (DAS-28 > 3.2), we found lower levels of 25(OH)D among patients with higher disease activity. Moreover, after 1 year of vitamin D supplementation and without significant changes in RA treatment, DAS-28 decreased in parallel with an increase in 25(OH)D levels. Minor changes in RA treatment as modifications in GC doses cannot state that the improvement in DAS-28 was only due to the increase in 25(OH)D levels.

A recent study showed vitamin D deficiency in 90.9 % of RA patients ($n = 55$), with 72 % prevalence of insufficiency levels, but no correlation between serum 25(OH)D levels and disease activity [3]. Another study found that RA patients ($n = 302$) with severe 25(OH)D deficiency had high percentage of disease activity [22]. A meta-analysis which included eight studies about the association between serum 25(OH)D levels and RA activity showed that in all studies, except one, vitamin D levels were inversely associated with RA activity. In the present study, perhaps the high incidence of vitamin D deficiency influenced the outcome of RA patients. Individuals with high vitamin D intake have 24 % lower risk of developing RA than individuals with low vitamin D intake [26]. Moreover, in African American early RA patients ($n = 266$), 25(OH)D levels were found to be inversely associated with DAS-28 [27].

Table 2 Biochemical and densitometric determinations

	Control	RA	Mann–Whitney test
Serum 25(OH)D (ng/ml)	26.3 ± 1.9	20.4 ± 0.9	$p = 0.009$
Deficiency (*n*, %)	17 (41.5 %)	12 (35.3 %)	–
Insufficiency (*n*, %)	13 (31.7 %)	19 (55.9 %)	–
Optimal (*n*, %)	11 (26.8 %)	3 (8.8 %)	–
Serum calcium (mg/dl, range: 8.5–10.5)	9.4 ± 0.08	9.3 ± 0.09	ns
Serum phosphate (mg/dl, range 2.5–4.5)	3.5 ± 0.1	3.3 ± 0.1	ns
Urine calcium (mg/24 h, range 100–250)	169.7 ± 15.5	199.2 ± 30.4	ns
Urine phosphate (mg/24 h, range 400–1300)	611.9 ± 56.2	613.0 ± 45.8	ns
PTH (pg/ml, range 15–65)	35.1 ± 3.4	40.3 ± 3.8	ns
AP (UI/L, range 90–270)	99.4 ± 8.6	191.3 ± 14.5	$p < 0.0001$
PreM lumbar spine BMD (g/cm^2) [*Z* score]	1.051 ± 0.043 [−0.2 ± 0.4] ($n = 10$)	0.992 ± 0.0312 [−0.4 ± 0.2] ($n = 10$)	ns
PostM lumbar spine BMD (g/cm^2) [*T* score]	0.888 ± 0.0572 [−1.6 ± 0.5] ($n = 14$)	0.874 ± 0.032 [−1.9 ± 0.3] ($n = 12$)	ns
PostM femoral neck BMD (g/cm^2) [*T* score]	0.769 ± 0.030 [−0.9 ± 0.3] ($n = 17$)	0.651 ± 0.026 [−2.5 ± 0.4] ($n = 12$)	$p = 0.014$

25(OH)D 25 hydroxyvitamin D, *PTH* parathyroid hormone, *AP* alkaline phosphatase, *PreM* premenopausal; *PostM* postmenopausal, *BMD* bone mineral density, *ns* not significant

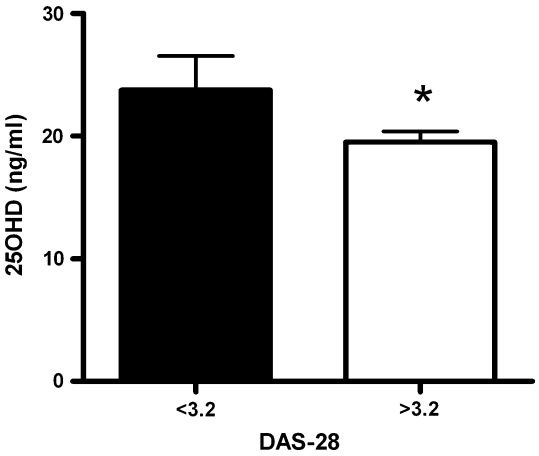

Fig. 2 25(OH)D levels in RA patients with moderate disease activity and high disease activity. *Asterisk* indicates significant differences ($p < 0.05$)

Levels of 25(OH)D above 20 ng/ml are needed for better muscle function and strength in women over 65 years of age [28]. In RA patients, the VAS, a DAS-28 component, is a patient's perception of symptoms and is inversely related to 25(OH)D levels. RA patients may perceive themselves or be perceived by assessors as having responded less well to disease in the presence of 25(OH)D deficiency [25]. Moreover, besides DAS scores, 25(OH)D deficiency has been associated with pain and disability [29]. It has also been demonstrated that vitamin D polymorphisms may contribute to the high prevalence of RA in North American natives [30].

Glucocorticoids have indirect effects on bone by inhibiting gastrointestinal calcium absorption and decreasing renal tubular reabsorption of calcium, and direct effects on bone cells. GC decrease bone remodeling and bone formation, leading to diminished bone quality and density with increased fracture

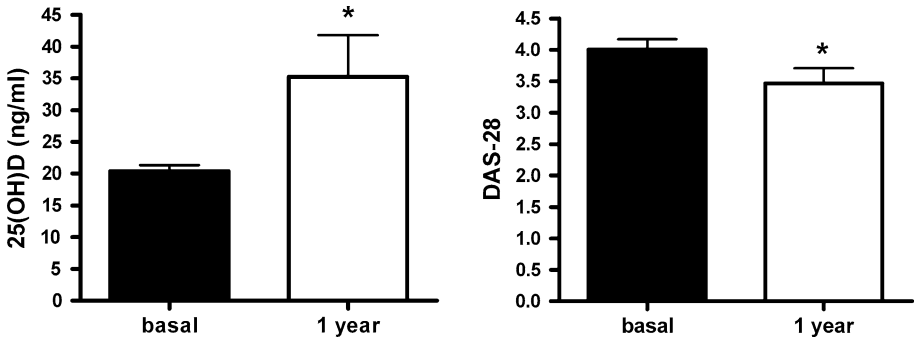

Fig. 3 25(OH)D levels and DAS-28 in RA patients, both before (basal) and after 1 year of vitamin D supplementation *Asterisk* indicates significant differences ($p < 0.05$) versus basal

risk [31–33]. It is also possible that GC increase fracture risk through other mechanisms, such as steroid myopathy, which could induce an increased risk of falls.

In the present study, we found no significant differences in lumbar spine BMD between preM and postM patients, but femoral BMD was lower in postM RA patients than in control subjects (Table 2). A previous study found an association between moderate RA activity and low BMD in the femoral neck rather than in the spine [34]. Moreover, patients with other chronic rheumatic diseases (such as systemic lupus erythematosus and rheumatic polymyalgia) receiving GC have been shown to have lower BMD values both in the lumbar spine and in the hip [35, 36]. However, in RA patients, the decrease in BMD is due to the disease activity, immobilization and treatments with GC, vitamin D levels or other treatments.

The association between joint damage and low BMD suggests that some of the pathophysiological processes causing generalized osteoporosis appear to be similar to those causing local bone loss (juxta-articular osteoporosis and bone erosions [1]). Vis et al. [10] followed 150 women with RA for 5 years and found a high annual incidence of vertebral and nonvertebral fractures: 3.7 % patient/years and 3.2 % patient/years, respectively. In another study, after a 5-year follow-up, vertebral fractures were observed in 41/275 RA patients (15 %). Patients with vertebral fractures have greater functional disability over time and higher disease activity, suggesting that vertebral fractures may be prevented by optimal disease activity suppression [37]. In a large cohort of patients with RA ($n = 603$), the prevalence of vertebral fracture was found to be 12.77 % [38]. No vertebral fractures were found in our study.

The main limitation of this study was the relatively small group of patients and the heterogeneity in disease duration. Additionally, this study only included women with RA, so the results cannot be extrapolated to men. On the other hand, the strengths of this study are that it had a control group, a fact not observed in every previously published study, and that it included BMD measurement in all patients.

Conclusions

We conclude that patients with RA had lower 25(OH)D levels than the control group and that low levels of 25(OH)D were related to moderate-high disease activity. After 1 year of treatment with vitamin D, DAS-28 decreased in parallel with an increase in 25(OH)D levels, suggesting the importance of obtaining and maintaining adequate 25(OH)D levels in these patients. Bone mass in RA patients was lower in postM patients in the femoral neck. No differences were found in spine BMD between preM and postM patients, suggesting that bone mass evaluation in RA patients should include femoral neck BMD regardless of age.

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Conflict of interest All authors have no conflict of interests.

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