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ORIGINAL RESEARCH

Association Between Chronic Hepatitis C Virus Infection and Bone Mineral Density

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Abstract Whether chronic hepatitis C virus (HCV) infection is a risk factor for the development of bone disease has long been controversial. For this reason, chronic HCV-infected participants ($n = 69$) were recruited into a prospective cohort study and underwent dual-energy X-ray absorptiometry for determination of bone mineral density (BMD). Fibrosis staging was evaluated according to the noninvasive index FIB-4. T scores at the femoral neck and lumbar spine were used as the primary outcome variables to assess the association between degree of liver disease and BMD. The study cohort was 41 % male with a mean age of 53.6 years. The mean BMD, Z score, and T score values of lumbar spine in chronic hepatitis C (CHC) patients were significantly lower than those in healthy controls ($p < 0.001$). The rate of osteoporosis for CHC patients aged 45–54 years was significantly higher than that of the control group ($p = 0.011$). Bone alkaline phosphatase and C-terminal cross-linking telopeptide of type I collagen levels were also significantly higher in CHC patients with reduced BMD. Patients with more advanced liver fibrosis had significantly lower BMD. In conclusion, reduced BMD is common in this population of chronic HCV-infected patients and associated with liver disease severity. This extrahepatic manifestation is probably secondary to increased bone turnover in osteodystrophy pathogenesis.

Keywords Bone mineral density · Osteodystrophy · Osteoporosis · Viral hepatitis

The authors have stated that they have no conflict of interest.

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Introduction

Osteoporosis is a disease characterized by systemic loss of bone mineral and is considered to be one of the major public health problems today [1]. The term "hepatic osteodystrophy" encompasses bone disease associated with chronic liver disease and includes osteopenia/osteoporosis and, more rarely, osteomalacia [2, 3]. It is a metabolic bone disease secondary to reduced formation and increased resorption of bone [2]. The etiology of these disorders is complex and multifactorial [2, 4]. The incidence of osteoporosis in chronic liver diseases varies widely, depending on the patient population and the underlying liver disease and its severity [3, 5–7]. In addition to severe cholestatic liver disease, significant osteoporosis is generally reported in patients with cirrhosis, especially secondary to hepatitis C [3, 4, 8].

Hepatitis C is a global health problem caused by infection with the hepatitis C virus (HCV); it is estimated that as many as 170 million persons worldwide may be

infected with HCV [9]. The late sequelae of chronic HCV infection result in serious public-health consequences, such as chronic hepatitis, cirrhosis, and hepatocellular carcinoma [9]. Moreover, chronic HCV infection is associated with a number of extrahepatic manifestations [9]. However, only few data from smaller studies reporting bone loss in noncirrhotic patients with chronic HCV infection are available [10–16]. The risk for bone depletion in the earlier stages of chronic HCV infection in this context is not yet fully elucidated and remains a matter of debate [10–16].

To determine whether those in earlier stages of chronic HCV infection are at increased risk of developing low bone mass, we conducted a thorough investigation of bone turnover markers and bone mineral density (BMD) in a homogenous cohort of patients with noncirrhotic chronic HCV infection.

Materials and Methods

Patients

From January 2009 to December 2011, a total of 69 consecutive, ambulatory, ethnic Chinese, treatment-naive hepatitis C patients were assessed. They were recruited at the outpatient clinic of the Division of Gastroenterology of Tri-Service General Hospital, a medical teaching hospital belonging to the National Defense Medical Center in Taipei, Taiwan. This group of research subjects fulfilled all inclusion and exclusion criteria detailed later in the article. Chronic HCV infection was defined as positivity of anti-HCV and serum HCV RNA for more than 6 months, with persistently abnormal alanine aminotransferase. Exclusion criteria were liver cirrhosis (Child-Pugh score $\geq$6); presence of hepatocellular carcinoma; human immunodeficiency virus (HIV) coinfection; hepatitis B virus coinfection; autoimmune liver disease defined according to validated diagnostic criteria [17]; genetic liver disease (e.g., Wilson disease, hemochromatosis); concomitant use of drugs known to affect bone metabolism such as hormone replacement therapy, vitamin D, corticosteroids, calcitonin, or bisphosphonates; and active intravenous drug use. We selected only patients whose previous alcohol consumption had not exceeded three drinks per week. For the analysis of BMD, 275 healthy age- and gender-matched controls were randomly selected from the Health Management Center of our hospital for lumbar spine assessment in health checkups and had no risk factors for liver disease. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (sixth revision, 2008) as approved by the hospital institutional review board and ethical committees. All patients gave written informed consent to participate in the study.

Variable Definition

Demographics, history of occurrence of fractures, lifestyle, and menopause status were collected by interviewers face-to-face from participants at the research visit. Smoking was categorized by whether participants were nonsmokers or smokers. Menopause was designated if there had been complete cessation of menses for more than 12 months.

Laboratory Evaluations

Patients had standard laboratory assessments performed by licensed clinical laboratories, including a complete blood cell count, serum aspartate transaminase (AST), alanine transaminase (ALT), total calcium, phosphate, magnesium, albumin, total bilirubin, total alkaline phosphatase, creatinine, 25-hydroxyvitamin D, intact parathyroid hormone, bone alkaline phosphatase (BAP), C-terminal cross-linking telopeptide of type I collagen (CTX), prothrombin time, and international normalized ratio. BAP reflects enzymatic activity of osteoblastic cells and is widely accepted as a marker for osteoblastic activity and bone formation [18], whereas serum CTX, as a collagen-degradation product, is a marker of bone resorption [19]. HCV genotype testing was performed using reverse-transcriptase polymerase chain reaction.

Noninvasive Biomarkers for Liver Fibrosis

The noninvasive index FIB-4, age (years) $\times$ AST [U/L]/(platelets [10^9/L] $\times$ (ALT [U/L])$^{1/2}$, was calculated from laboratory results in all patients [20]. We defined low (<1.45), intermediate (1.45–3.25), and high FIB-4 (>3.25) as previously established [20].

Body Composition and BMD

Because there exists the possibility of ambiguity when attempting to achieve accuracy within dual-energy X-ray absorptiometry (DXA) [21, 22], we used a simple method of body mass index (BMI) to assess body composition. BMI was defined as weight (kilograms) divided by height (meters) squared. A wall-mounted stadiometer was used to measure height. Each participant was weighed while wearing minimal clothing. All patients underwent DXA scans to determine the BMD in the lumbar spine (L1–L4) and the left femoral neck. A single technician certified by the International Society of Clinical Densitometry performed all DXA scans on a fan-beam bone densitometer

(QDR-4500A; Hologic, Waltham, MA) [23]. DXA data for age- and sex-matched controls were obtained from the DXA manufacturer's reference population and comprised the BMD reference in this study. For descriptive analyses, osteoporosis was defined as a T score ≤ -2.5. Osteopenia was defined as $-2.5 <$ T score ≤ -1.0. Low BMD was defined as Z score ≤ -2.0.

Table 1 Patient characteristics

	Patients with chronic hepatitis C ($n = 69$)
Age (years)	53.6 ± 12.7
Gender (male/female)	28/41
Body mass index (kg/m^2)	24.4 ± 3.6
HCV RNA (IU/mL × 10^6)	6.4 ± 15.5
HCV genotype 1 (*n*)	45
International normalized ratio	1.02 ± 0.09
Alanine aminotransferase (IU/L)	72.2 ± 51.1
Bilirubin (mg/dL)	0.6 ± 0.3
Albumin (g/dL)	4.5 ± 0.3
Parathyroid hormone (pg/mL)	35.1 ± 27.4
Serum calcium (mg/dL)	9.4 ± 0.5
Alkaline phosphatase (U/L)	93.5 ± 36.4
Serum phosphate (mg/dL)	3.7 ± 0.6
25(OH)vitamin D (ng/mL)	21.5 ± 5.7
Thyroid-stimulating hormone (μIU/mL)	1.9 ± 1.1
Cigarette smoking (*n*)	11
Postmenopausal women (*n*)	32
FIB-4 > 3.25 (*n*)	21
Number with fractures (%)	2 (2.9%)

All values are given as mean ± SD unless indicated otherwise. *Normal ranges* alanine aminotransferase, 0–31 U/L; bilirubin, <1.2 mg/dL; albumin, 3.97–4.94 g/dL; parathyroid hormone, 10–69 mg/dL; serum calcium, 8.62–10.2 mg/dL; alkaline phosphatase, 38–126 U/L; serum phosphate, 2.7–4.5 mg/dL; 25(OH) vitamin D, 20–40 ng/mL; thyroid stimulating hormone 0.25–5 μIU/mL

HCV hepatitis C virus

Statistical Analysis

Chi-squared tests were used to evaluate the prevalence of osteoporosis, osteopenia, and low BMD between male, premenopausal, and postmenopausal female patients. We compared the BMD, T score, and Z score between study groups and healthy age-matched control groups using *t*-tests. One-way ANOVAs were used to compare site-specific BMD and Z scores between male, premenopausal, and postmenopausal female patients and to compare site-specific BMD and T score between different FIB-4 values. $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed by SPSS (SPSS, Inc., Chicago, IL).

Results

Characteristics of Study Population

The demographic and clinical characteristics of the study population are presented in Table 1. The mean age was 53.6 ± 12.7 years (range 22–79), 41 % were male, and 19 % had a history of smoking. The mean BMI was 24.4 ± 3.6 kg/m^2 (range 18.4–35.3). Sixty-five percent were infected with HCV genotype 1. Of the 69 cases, 22 had low FIB-4, 26 had intermediate FIB-4, and 21 had high FIB-4. The prevalence of overall fracture history was 2.9 % (two patients). One of them had vertebral fractures. The other one had fractures resulting from a road traffic accident.

BMD Comparison of Study Group and Control Group

BMD values (g/cm^2), Z scores, and T scores of the lumbar spine in patients and controls are summarized in Table 2. In postmenopausal patients with chronic HCV infection, the mean BMD values ($p < 0.001$), Z-score values ($p < 0.001$), and T-score values ($p < 0.001$) of the lumbar spine were

Table 2 Comparison of BMD, T scores, and Z scores at the lumbar spine between the study groups and healthy age-matched controls

	Men			Premenopausal women			Postmenopausal women		
	Controls ($n = 138$)	Patients ($n = 28$)	*p*	Controls ($n = 44$)	Patients ($n = 9$)	*p*	Controls ($n = 93$)	Patients ($n = 32$)	*p*
BMD mean (g/cm^2), (SD)	1.20 (0.20)	0.95 (0.09)	<0.001	1.18 (0.14)	0.92 (0.12)	<0.001	1.11 (0.15)	0.84 (0.137)	<0.001
Z score, mean (SD)	1.20 (1.38)	–0.1 (0.61)	<0.001	0.64 (1.12)	–0.54 (1.0)	0.005	0.98 (1.10)	0.177 (0.801)	<0.001
Low BMD, *n* (%)	1 (0.7 %)	0 (0 %)	0.651	1 (2.3 %)	1 (11 %)	0.205	0 (0 %)	0 (0 %)	–
T score, mean (SD)	0.91 (1.38)	–0.61 (0.78)	<0.001	0.46 (1.15)	–0.78 (1.03)	0.004	–0.14 (1.18)	–1.49 (1.20)	<0.001
Osteopenia, *n* (%)	12 (8.7)	9 (32 %)	0.001	4 (9.1 %)	3 (33 %)	0.05	18 (19.4 %)	15 (47 %)	0.002
Osteoporosis, *n* (%)	0 (0 %)	0 (0 %)	–	1 (2.3 %)	0 (0 %)	0.648	4 (4.3 %)	5 (16 %)	0.033

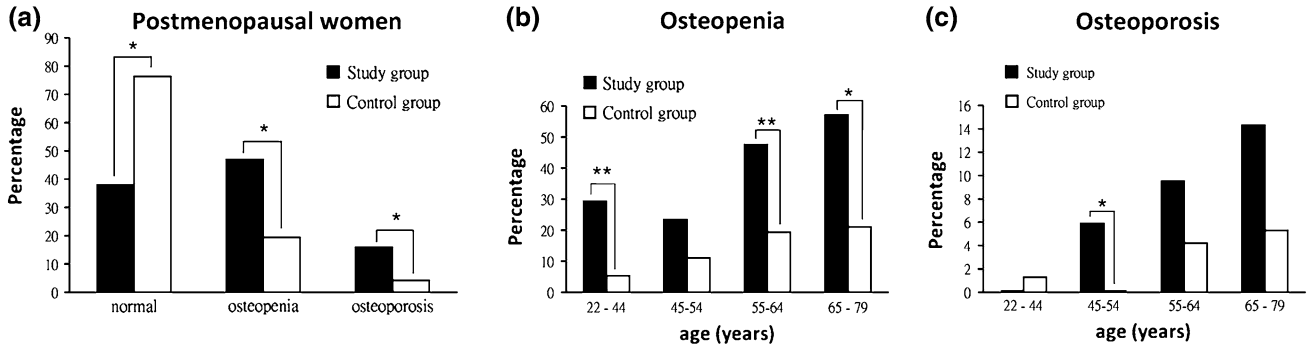

Fig. 1 Comparison of the prevalence of reduced bone mineral density between CHC patients and health controls. **a** Ratios of postmenopausal patients with or without osteopenia/osteoporosis according to T-score values. **b** Prevalence of osteopenia in patients with CHC and controls according to ranges of age. **c** Prevalence of osteoporosis in patients with CHC and controls according to ranges of age. $*p < 0.05$, $**p < 0.001$

Table 3 BMD measures

	Male patients ($n = 28$)	Premenopausal female patients ($n = 9$)	Postmenopausal female patients ($n = 32$)	p
Overall (i.e., femoral neck or lumbar spine)				
Osteopenia, *n* (%)	12 (43 %)	3 (33 %)	20 (63 %)	0.169
Osteoporosis, *n* (%)	1 (3.6 %)	1 (11.1 %)	8 (25 %)	0.06
Low BMD, *n* (%)	0 (0 %)	2 (22 %)	0 (0 %)	0.001
Site-specific data				
Femoral neck				
BMD mean (g/cm^2), (SD)	0.78 (0.11)	0.72 (0.12)	0.66 (0.12)	0.001
Z score, mean (SD)	0.11 (0.75)	−0.44 (1.07)	0.08 (0.96)	0.247
Low BMD, *n* (%)	0 (0 %)	1 (11 %)	0 (0 %)	0.034
T score, mean (SD)	−0.61 (0.79)	−0.86 (1.11)	−1.35 (1.09)	0.019
Osteopenia, *n* (%)	7 (25 %)	2 (22 %)	13 (41 %)	0.346
Osteoporosis, *n* (%)	1 (3.6 %)	1 (11.1 %)	7 (21.9 %)	0.108
Lumbar spine				
BMD mean (g/cm^2), (SD)	0.95 (0.09)	0.92 (0.12)	0.84 (0.137)	0.002
Z score, mean (SD)	−0.1 (0.61)	−0.54 (1.0)	0.177 (0.801)	0.041
Low BMD, *n* (%)	0 (0 %)	1 (11 %)	0 (0 %)	0.034
T score, mean (SD)	−0.61 (0.78)	−0.78 (1.03)	−1.49 (1.20)	0.005
Osteopenia, *n* (%)	9 (32 %)	3 (33 %)	15 (47 %)	0.471
Osteoporosis, *n* (%)	0 (0 %)	0 (0 %)	5 (16 %)	0.044

significantly lower than those in the control group; in men and premenopausal women, we also found a significant difference in mean lumbar spine BMD values, Z-score values, and T-score values when comparing the study group with healthy age-matched controls. In postmenopausal women, five patients (16 %) in the study group and four (4.3 %) in the control group had osteoporosis. This difference was significant ($p = 0.033$) (Fig. 1a). When the prevalence of osteopenia and osteoporosis was evaluated according to ranges of age, all categories showed higher rates of osteopenia than the control group, with a statistically significant difference for patients aged 22–44 years ($p = 0.002$), 55–64 years ($p = 0.009$), and 65–79 years ($p = 0.033$) (Fig. 1b). However, the rate of osteoporosis for patients 45–54 years old was significantly higher than that of the control group (Fig. 1c, $p = 0.011$).

Increased Frequency of Low BMD in Premenopausal Women with Chronic HCV Infection

BMD measures and prevalence of osteoporosis, osteopenia, and low BMD, stratified by sex, are presented in Table 3. Overall, 3.6 % (1/28) of men, 11.1 % (1/9) of premenopausal women, and 25 % (8/32) of postmenopausal women had osteoporosis (i.e., T scores ≤ -2.5 at either of the two sites). The prevalence of osteoporosis seemed greater

among postmenopausal women at each of the two sites. Mean Z scores of the lumbar spine were significantly lower for premenopausal women (−0.54, $p = 0.041$). The prevalence of low BMD (Z score ≤ -2.0 at either site) was higher among premenopausal women (22 %, $p = 0.001$). Mean T scores of both sites were, significantly, lowest for postmenopausal female patients and highest for male patients.

Elevated BAP and CTX in Patients with Reduced BMD

The clinical and laboratory data of CHC patients with or without osteopenia/osteoporosis are summarized in Table 4. Osteopenic/osteoporotic patients had significantly higher BAP and CTX values than the nonosteopenic/non-osteoporotic group. In addition, the proportion of female patients and the prevalence of high FIB-4 (>3.25) were higher in osteopenic/osteoporotic patients ($p < 0.05$).

Correlations of Bone Measures with Hepatic Fibrosis

As depicted in Table 4, we found a statistically significant difference between low and high FIB-4, which is described in Table 5. BMD of the femoral neck ($p = 0.009$) or lumbar spine ($p = 0.011$) was lower in the high FIB-4 group. A similar effect was seen in T scores of the femoral neck ($p = 0.008$) and lumbar spine ($p = 0.011$).

Table 4 Clinical, biological, and densitometric data in patients with osteopenia/osteoporosis (T score ≤ -1) versus without osteopenia/osteoporosis (T score > -1)

	T score ≤ -1 (24/69)	T score > -1 (45/69)	p
Age (years)	57.9 ± 13.3	51 ± 11.9	0.04
Female	79.2 %	48.9 %	0.015
Menopause	84.2 %	72.7 %	0.376
Body mass index (kg/m^2)	24 ± 3.4	25 ± 3.7	0.431
HCV RNA (IU/mL × 10^6)	5.4 ± 7.3	7.0 ± 18.6	0.679
HCV genotype 1	75 %	60 %	0.213
FIB-4 > 3.25	50 %	20 %	0.01
International normalized ratio	1.04 ± 0.11	1.01 ± 0.08	0.25
Parathyroid hormone (pg/mL)	41.4 ± 35.6	31.2 ± 20.3	0.156
Serum calcium (mg/dL)	9.4 ± 0.6	9.4 ± 0.4	0.848
Serum phosphate (mg/dL)	3.7 ± 0.5	3.6 ± 0.6	0.103
25(OH)vitamin D (ng/mL)	20.9 ± 4.4	21.8 ± 6.3	0.536
Thyroid-stimulating hormone (μIU/mL)	2 ± 1.1	1.9 ± 1.1	0.72
Cigarette smoking (%)	10 %	23.7 %	0.206
BAP (U/L)	50.2 ± 36.2	36.5 ± 17.4	0.039
CTX (ng/mL)	0.26 ± 0.19	0.18 ± 0.12	0.037

All values are given as mean ± SD unless indicated otherwise

HCV hepatitis C virus, *BAP* bone alkaline phosphatase, *CTX* C-terminal cross-linking telopeptide of type I collagen, *N.S.* not significant

Discussion

Metabolic bone disease occurring in individuals with chronic liver disease, particularly in those with cholestasis, is known as hepatic osteodystrophy [4]. Established cirrhosis is generally associated with lower BMD [4], whereas the relation between reduced BMD and noncirrhotic CHC patients who are not cholestatic or hypogonadal is still a matter of debate [10–13, 15]. Luchi and colleagues [11] used BMD and biochemical markers to evaluate bone metabolism in male patients with CHC and in healthy male controls. In the hepatitis group, 56 % of the patients proved that bone depletion increased as the histological score of CHC increased. These authors believe that hepatitis C is a risk factor for bone depletion. Similarly, a previous study described an association between noncirrhotic viral hepatitis (predominately CHC) and osteopenia/osteoporosis [12]. However, there was no control group and no details were given of concurrent alcohol intake. In contrast, Yenice et al. [13] and Yucel et al. [10] suggested that chronic HCV infection was not a significant risk factor for low BMD. Moreover, a small case–control study found that chronic HCV infection did not increase the risk of development of metabolic bone disease in postmenopausal women with chronic HCV infection [15]. Furthermore, Lo Re et al. [14] found that viral hepatitis (predominantly CHC) increased the risk of low BMD among HIV-infected female patients, whereas a high prevalence of osteoporosis was found in patients with HIV/HCV coinfection in a more

Table 5 Lumbar spine and femoral neck BMD and T score by FIB-4 ($n = 69$)

	FIB-4 < 1.45, no or minimal fibrosis ($n = 22$)	FIB-4 ≥ 1.45 and ≤3.25 ($n = 26$)	FIB-4 > 3.25, significant fibrosis ($n = 21$)	p
Femoral neck				
BMD mean (g/cm^2) (SD)	0.77 (0.10)	0.72 (0.13)	0.66 (0.13)	0.009
T score, mean (SD)	−0.56 (0.84)	−0.91 (1.03)	−1.52 (1.00)	0.008
Lumbar spine				
BMD mean (g/cm^2) (SD)	0.94 (0.11)	0.90 (0.13)	0.83 (0.11)	0.011
T score, mean (SD)	−0.61 (0.98)	−0.94 (1.13)	−1.58 (0.97)	0.011

recent study but not related to the severity of liver fibrosis [16]. Direct comparisons could not be performed within previous studies due to the heterogeneity of the liver diseases and subjects [10–16]; thus, it was not clear whether chronic HCV infection per se affects the incidence and severity of osteoporosis in noncirrhotic patients. Our study is the first report in the literature to focus on a homogenous cohort of patients with noncirrhotic chronic HCV infection. We have shown that patients with CHC had lower BMD than healthy controls and found a high prevalence of metabolic bone disease. In addition, there was a relation between the severity of liver disease and the degree of bone loss at the spine or the femoral neck.

We found that mean T-score values and BMD values at both sites were lowest for postmenopausal female patients and highest for male patients and that the proportion of female patients was higher in the osteopenic/osteoporotic group. These results suggested greater reduction in BMD in female CHC patients compared with male patients. A Z score of −2.0 or lower may suggest the presence of a secondary cause of osteoporosis. Z scores are used preferentially to assess bone loss in premenopausal females [24]. Therefore, as shown in Table 3, we observed a tendency toward higher a prevalence of low BMD in premenopausal female patients. Nanda et al. [15] reported that chronic HCV infection does not lead to discernible metabolic bone disease in postmenopausal women. Taken together, these observations suggested that chronic HCV infection may increase the risk of osteodystrophy development, mainly in premenopausal women rather than in postmenopausal women.

Some studies suggest that lower bone density in patients with chronic liver disease results from reduced bone formation ("low-turnover" osteoporosis), whereas others report it is secondary to increased resorption ("high-turnover" osteoporosis) [25, 26]. Previous reports indicate serum BAP and CTX levels were higher in the osteoporotic patients [18, 27–30]. Nanda et al. [15] observed a tendency toward higher levels of BAP in postmenopausal CHC women, which did not reach statistical significance as a result of the relatively small number of studied patients. In this study, we observed higher serum BAP and CTX levels in CHC patients with osteopenia or osteoporosis. These results may mean that the bone loss in earlier stages of CHC patients is not due to diminished bone synthesis, but rather, is secondary to the increased bone resorption.

There were some limitations or defects in this study. First, a larger population with noncirrhotic hepatitis C would be needed to demonstrate whether chronic HCV infection per se has a role in BMD loss; this is particularly the case for premenopausal women. Second, because the precise time of becoming infected with HCV was difficult to determine, we did not analyze the correlation between BMD and the duration of chronic HCV infection. Third, all measurements were not performed in the same season. Fourth, the values of the control group for the main variables of bone metabolism were not studied.

In conclusion, our study shows that chronic HCV infection does increase the risk of development of metabolic bone disease in this cohort. Indeed, greater reduction of BMD occurs in advanced liver fibrosis. The bone loss in earlier stages of CHC is likely to result from increased bone resorption rather than in decreased bone formation. Overall, these observations suggest an important role for chronic HCV infection in increased bone turnover in osteodystrophy pathogenesis.

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