Turk J Gastroenterol 2006; 17 (4): 260-266

Assessment of bone metabolism and mineral density in chronic viral hepatitis

Kronik viral hepatitlerde kemik metabolizması ve kemik mineral yoğunluğunun değerlendirilmesi

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Background/aims: *The aim of the study was to assess bone metabolism and impact of disease on bone mineral density in patients with non-cirrhotic chronic hepatitis B or C.* ***Methods:*** *105 patients with chronic hepatitis B or C receiving antiviral agents and 60 healthy controls were included. Subgroups (n=15) were defined on the basis of age (males) or menopausal status (females). Bone mineral density; serum parathyroid hormone (PTH), calcium (Ca), phosphorus (P), total alkaline phosphatase, and 25-hydroxy vitamin D levels; 24-hour urinary levels of Ca and P; and urinary telopeptide (NTX) were measured. Statistical comparisons were made between patient groups and the matched controls.* ***Results:*** *Compared to controls, the average serum levels of PTH were lower and 24-hour urinary mean Ca levels and T scores were higher in chronic hepatitis B patients between 20 and 40 years of age. Men with chronic hepatitis B and aged 40 - 65 years had lower mean serum P concentrations. Postmenopausal women with chronic hepatitis B had significantly higher NTX levels. Men with chronic hepatitis C had significantly elevated levels of 24-hour mean urinary P levels. The serum 25 OH vitamin D levels were significantly higher in premenopausal women with chronic hepatitis C. Postmenopausal women with chronic hepatitis C had significantly lower serum P concentrations. Other parameters and T scores did not differ significantly between patient groups and matched controls.* ***Conclusion:*** *Our results suggest that chronic hepatitis B and C infections do not pose a risk for osteoporosis and low bone mineral density.*

Key words: Bone mineral density, chronic hepatitis B, chronic hepatitis C, osteoporosis, calcium

Amaç: *Bu çalışmanın amacı sirotik olmayan kronik B ve kronik C hepatitli hastalarda kemik metabolizmasını değerlendirmek ve hastalığın kemik mineral yoğunluğu üzerine etkisini araştırmaktır.* ***Yöntem:*** *Çalışmaya, antiviral ilaçlarla tedavi edilen, nonsirotik 105 kronik B ve C hepatitli hasta ile 60 sağlıklı kişi kontrol grubu alındı. Hastalar; kronik B hepatit, kronik C hepatit ve sağlıklı kontrol grubu olmak üzere 3 ana gruba ayrıldı. Subgruplar (n=15) yaşa (Erkek), menapozal duruma (kadın) göre tanımlandı. Kemik mineral dansitesi ,serum paratiroid hormon, kalsiyum, fosfor, total alkalen fosfataz, 25 hidroksi D vitamini ve 24 saatlik idrar kalsiyum ve fosfor, üriner telopeptid (NTX) düzeyleri tespit edildi. Tüm hasta grupları ile kontrol grupları bu paremetreler açısından kıyaslanarak istatistiksel olarak anlamlı fark arandı.* ***Bulgular:*** *Kontrol grubu ile karşılaştırıldığında, 20-40 yaş arası kronik B hepatitli hastaların serum PTH değeri ortalaması daha düşük, 24 saatlik üriner Ca değeri ortalaması daha yüksek ve T skoru ortalaması da daha yüksek bulundu. 40-65 yaş arası erkek kronik B hepatitli hastaların serum P değeri ortalaması daha düşüktü. Postmenapoz kronik B hepatitli hastaların üriner NTX düzeyi anlamlı derecede yüksekti Kronik C hepatitli erkek hastaların 24 saatlik üriner P düzeyi ortalaması anlamlı olarak yüksekti. Premenapoz kronik C hepatitli hastaların serum 25 OH D vitamini düzeyi ortalaması kontrol grubuna göre anlamlı derecede yüksek bulundu. Postmenapoz kronik C hepatitli hastaların serum P düzeyi ortalaması postmenapoz kontrol grubundakinden anlamlı olarak düşük bulundu. Diğer laboratuvar parametreler ve T skoru ölçümleri kontrol grupları ile kıyaslandığında istatistiksel olarak anlamlı fark tespit edilmedi.* ***Sonuç:*** *Çalışma kronik C hepatit ve kronik B hepatitin osteoporoz ve düşük kemik mineral yoğunluğu için bir risk faktörü olmadığını göstermiştir.*

Anahtar kelimeler: Kemik mineral yoğunluğu, kronik hepatit B, kronik hepatit C, osteoporoz, kalsiyum

INTRODUCTION

In chronic diseases of the liver, particularly in hepatic cirrhosis and cholestatic liver disease (regardless of the cause), a decrease in bone mineral density (BMD) is observed (1-4). Osteoporosis, osteomalacia or deficiency of vitamin D, or a combination of these factors may be responsible for the

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Manuscript received: 01.11.2005 **Accepted:** 16.08.2006

observed decrease in BMD (5, 6). Several studies have shown that bone formation is diminished in chronic diseases of the liver (7). In such patients, osteomalacia may also lead to a decrease in BMD; however, hepatic osteomalacia demonstrated by histomorphometric methods is very rare (8). The most common reason for the decrease in BMD in these conditions is the decreased absorption of vitamin D from the small intestine (5, 6, 9, 10). Since functions of enzymes responsible for 25-hyroxylation of vitamin D may be impaired in liver disease, an increased incidence of secondary osteoporosis or osteopenia is expected (10-12). In the literature, there are many clinical studies that have denoted the decrease in BMD among cirrhotic patients (1-5, 7-15, 24). In contrast with the other studies, in this study we included chronic hepatitis B and C patients whose liver biopsy showed moderate and severe hepatitis activation, and we assessed bone metabolism and BMD in patients with non-cirrhotic chronic hepatitis B and C.

MATERIALS AND METHODS

A total of 105 patients with a history of chronic hepatitis for ≤ 4 years who were diagnosed with liver biopsy which showed moderate and severe hepatitis activation, with elevated serum AST and ALT levels (1.5-2 times higher than normal limits), serological tests, and who were followed at the Hepatology Outpatient Clinic, 3rd Department of Internal Medicine, Okmeydani Training and Research Hospital were included in this study. Only patients with no clinical or histological signs of cirrhosis were eligible. The control group consisted of 60 healthy individuals. Interferon or antiviral agents were being used in all patients, and patients were included in the study irrespective of the stage of treatment. Informed consent was obtained from all patients and controls. This study was approved by the local ethics committee and conducted in concordance with the Declaration of Helsinki. Patients were assigned into the following three groups: chronic hepatitis B group, chronic hepatitis C group, and healthy controls. Subgroups, each consisting of 15 patients, were defined on the basis of age (male participants) or menopausal status (female participants). Only one subgroup was defined for male patients with chronic hepatitis C due to the limited number of subjects between the ages of 20 and 40. Systemic diseases other than chronic viral hepatitis (diabetes, chronic renal disease, metabolic bone diseases, thyroid diseases, parathyroid diseases, neoplasias), current or previous history of alcohol abuse, osteoporosis previously diagnosed with BMD measurement, and use of medical treatment for osteoporosis precluded participation in the study.

Group 1: A) Men between 20 and 40 years of age with chronic hepatitis B (n=15; mean age: 31.67±5.69) B) Men between 40 and 65 years of age with chronic hepatitis B (n=15; mean age: 54±7.34) C) Premenopausal women with chronic hepatitis B (n=15; mean age: 32.33±8.68) D) Postmenopausal women with chronic hepatitis B (n=15; mean age: 50.33±7.36).

Group 2: A) Men with chronic hepatitis C (n=15; mean age: 55.07±8.51) B) Premenopausal women with chronic hepatitis C (n=15; mean age: 41.47±4.34) C) Postmenopausal women with chronic hepatitis C (n=15; mean age: 54.27±6.27).

Group 3: A) Healthy men between 20 and 40 years of age (n=15; mean age: 29.40±5) B) Healthy men between 40 and 65 years of age (n=15; mean age: 49.47±7.75) C) Premenopausal healthy women (n=15; mean age: 37.87±8.96) D) Postmenopausal healthy women (n=15; mean age: 54.07±5.93).

In all patients, calcium (Ca), phosphorus (P), and total alkaline phosphatase (ALP) measurements were performed at the Biochemistry Laboratory, Okmeydani Research and Training Hospital; parathyroid hormone (PTH), 24-hour urinary Ca and P, urinary telopeptide (NTX) and serum 25 OH vitamin D measurements were done at the Biochemistry Laboratory, Istanbul University Medical School. All blood samples were obtained after 12 hours of fasting. The results were expressed as pg/ml for PTH, mg/dl for serum Ca and P, U/L for ALP, mg/24-h for urinary Ca and P, ng/ml for 25 OH vitamin D, and nM BCE/mmol creatinine for urinary NTX.

Bone mineral density measurements were performed using an ALARA metriScan device by digital radiographic photon absorptiometry at the medial phalanxes of the 2nd, 3rd and 4th fingers of the non-dominant hand. The T score was calculated by using the average value obtained at three different fingers and comparing the measurements with the reference values. Z score was disregarded. The T score was considered normal, osteopenic, or osteoporotic for scores between 1 SD and -1 SD, -1 SD and -2.5 SD, or < -2.5 SD, respectively.

Student's *t* test, Mann-Whitney U, ANOVA and Tukey HSD were used for comparisons between

groups. Serum Ca, P, ALP, PTH, 25 OH vitamin D, urinary NTX, and 24-hour urinary Ca and P levels were compared between matching age groups in male patients and according to matching menopausal status in female patients among groups (chronic hepatitis B, chronic hepatitis C, healthy controls). A p value less than 0.05 was considered statistically significant. PTH measurements in two patients were excluded from these analyses due to abnormally elevated concentrations, one in Group 1B (chronic hepatitis B, 40-65 y) and one in Group 1C (premenopausal women with chronic hepatitis B).

RESULTS

Comparison of T scores

There was a statistically significant difference in T scores between Group 1A (mean ± SD=1.30 ± 1.09) and Group 3A (mean ± SD=0.23 ± 1.46) ($p < 0.05$) (Figure 1).

The comparison between other groups and healthy controls with respect to T scores did not reveal any significant differences.

Comparison of serum PTH

Serum PTH (mean ± SD) levels in men with chronic hepatitis B between 20 and 40 years of age (Group 1A) and in healthy controls (Group 3A) were 31.93±7.54 and 38.20±9.12, respectively, with a statistically significant difference ($p < 0.05$) (Table 1).

There were no significant differences with respect to serum PTH levels between other groups and healthy controls.

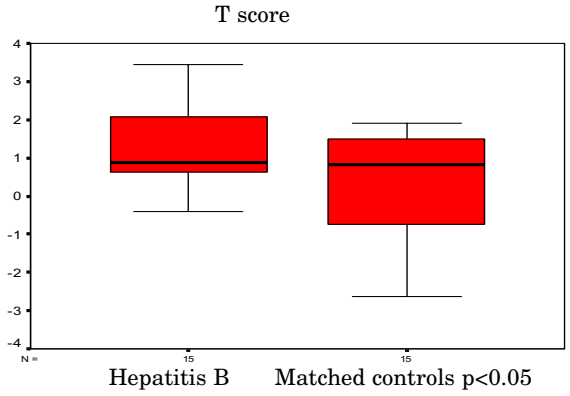

Figure 1. Selected comparisons among groups in terms of laboratory parameters regarding bone metabolism and bone mineral density

Comparison of serum Ca, P, and ALP

Serum P concentrations (mean ± SD) in Group 1B and Group 3B were 3.00±0.48 and 3.42±.58, and the difference was statistically significant ($p < 0.05$) (Table 1).

Serum P concentrations (mean ± SD) in Group 2C and Group 3D were 3.34±0.70 and 3.83±0.55, respectively, with a significant difference ($p < 0.05$) (Table 1).

Serum Ca concentrations in combined Group 1A plus Group 1B and in Group 2A were 9.82±0.60 and 9.42±0.46, respectively, again with a significant difference ($p < 0.05$) (Table 1).

The comparison between other groups and healthy controls with regard to serum Ca and P concentrations did not show any significant difference. Also, serum ALP levels were similar across all patient groups and healthy controls.

Comparison of serum 25 OH vitamin D

Serum 25 OH vitamin D levels (mean ± SD) in Group 2B and Group 3C were 17.01±7.21 and 11.32±3.86, respectively, demonstrating a significant difference ($p < 0.05$) (Table 1).

Serum 25 OH vitamin D levels were similar between other groups and healthy controls.

Comparison of 24-hour urinary Ca and P

The 24-hour urinary Ca levels (mean ± SD) in Group 1A and Group 3A were 295.93±104.82 and 227±69.68, respectively, with a significant difference ($p < 0.05$) (Table 1).

The 24-hour urinary P levels in Group 2A and Group 3A + 3B combination were 0.75±0.3 and 0.49±0.22, respectively, and this difference was significant ($p < 0.05$) (Table 1).

There were no significant differences with respect to 24-hour urinary Ca and P concentrations between other groups and healthy controls.

Comparison of urinary NTX

A significant difference existed between Group 1D and Group 3D with regard to mean urinary NTX levels (32.26 ± 13.74 and 21.94 ± 7.84, respectively) ($p < 0.05$) (Table 1).

Mean urinary NTX levels in Group 1A plus Group 1B combination and in Group 2A were 26.86 ± 15.32 and 19.96 ± 5.05, respectively, and the difference was not significant ($p < 0.05$) (Table 1).

Urinary NTX levels were similar between other groups and healthy controls.

Table 1. Laboratory parameters that mean sense statistically

	Group	n	Mean	SD	p
PTH (pg/ml)	20-40 years Male Hepatitis B	15	31.93	7.54	0.05
	20-40 years Male Control Group	15	38.20	9.12	
Urinary Ca (mg/24 h)	20-40 years Male Hepatitis B	15	295.93	104.82	<0.05
	20-40 years Male Control Group	15	227.73	69.68	
P (mg/dl)	40-65 years Male Hepatitis B	15	3.00	0.48	<0.05
	40-65 years Male Control Group	15	3.42	0.58	
	Hepatitis C Postmenopause	15	3.34	0.70	
	Postmenopause Control Group	15	3.83	0.55	
Urinary NTx (nM BCE/mmol creatinine)	Hepatitis B Postmenopause	15	32.26	13.74	<0.05
	Postmenopause Control Group	15	21.94	7.84	
	Hepatitis B Male	30	26.86	15.32	
	Hepatitis C Male	15	19.96	5.05	
Urinary P (g/24 saat)	Hepatitis C Male	15	0.75	0.30	<0.05
	Total Male Control Group	30	0.49	0.22	
25-OH D3 (ng/ml)	Hepatitis C Premenopause	15	17.01	7.21	<0.05
	Premenopause Control Group	15	11.32	3.86	
Ca (mg/dl)	Hepatitis B Male	30	9.82	0.60	<0.05
	Hepatitis C Male	15	9.42	0.46	

DISCUSSION

Three underlying mechanisms for the bone mineral loss observed in chronic liver diseases have been postulated: osteoporosis, osteomalacia and vitamin D deficiency (5, 6). Although increased bone resorption even without presence of osteoporosis has been shown in patients with chronic liver disease, decreased bone formation also has been reported (7). Osteomalacia can lead to a decreased bone density as well. The alterations in clinical biochemistry parameters in osteomalacia include hypocalcemia, hypophosphatemia, increased PTH, and increased bone-specific ALP levels. However, serum levels of Ca and P are usually within normal limits. Histomorphometrically established hepatic osteomalacia is very rare (5, 8). Osteomalacia could not be demonstrated in bone biopsies of 60 patients awaiting liver transplantation (13). Deficiency of vitamin D results in impaired bone mineralization as well as osteoid accumulation, which is another feature of osteomalacia (12). Several studies have shown that serum 25 OH vitamin D levels decrease in patients with chronic liver disease and that this decrease is accentuated as the condition progresses toward cirrhosis (14-16).

The risk of osteoporosis and associated fractures has been shown to increase in cirrhosis (irrespective of the etiology), primary biliary cirrhosis, cholestatic liver diseases such as sclerosing cholangitis, and hemochromatosis (17-19). Alcohol is an independent risk factor for osteoporosis (20, 21).

Serum or urinary markers of bone formation and resorption are used to assess the bone metabolism.

BMD is evaluated by bone densitometry measurements. Since decreased BMD and T score is a consistent finding in cirrhosis, such cases were excluded from our study, and only patients receiving various antiviral agents or interferon alpha 2a or 2b with no histological findings suggestive of cirrhosis in needle biopsy were included. Different treatments were not taken into account while defining the study groups. Treatment received by patients may have either positive or negative effects on bone metabolism. Previous studies determined that ribavirin does not increase the bone loss (22). Interferon may affect bone metabolism positively however proof of this information with more comprehensive studies is required (23-25).

In another study evaluating bone metabolism in chronic liver disease (n=100; 49 non-cirrhotic, 51 cirrhotic), Ca, PTH, bone specific ALP, 25 OH D3, and urinary NTX levels were assessed and BMD was measured with DXA at lumber vertebrae, Ward's triangle and femoral neck, demonstrating a decreased BMD in patients with chronic liver disease compared to a healthy population (8). In contrast to ours, a study in Germany that included non-cirrhotic 30 chronic hepatitis C and 13 chronic hepatitis B patients determined a decrease in BMD and increase in the levels of intact PTH and bone specific ALP (25).

Tsuneoka et al. (1) reported a significantly decreased BMD in cirrhotic patients whose urinary pyridinoline (a bone resorption marker) levels were significantly elevated. In that study, it was concluded that osteogenesis was decreased and the decrease in BMD was a reflection of the impaired liver functions.

An Italian study evaluated BMD with DXA method in 27 postmenopausal cirrhotic women and found a significantly decreased BMD in these patients (3).

Carey et al. (4) looked at clinical, biochemical, radiological and bone densitometry measurements in 207 patients who had undergone liver transplantation due to chronic hepatitis C, alcohol, or both, and found lower basal mean T scores for patients with chronic hepatitis C compared to the alcohol group.

Contrary to all these studies in which bone metabolism in cirrhotic patients was evaluated, our study exclusively included patients with chronic liver disease with no clinical or histological findings of cirrhosis. A total of 105 patients with chronic hepatitis B or C were assigned into subgroups consisting of 15 patients each on the basis of age, gender and menopausal status; Ca, P, total ALP, serum 25 OH D3, 24-hour urinary Ca and P excretion, and fasting urinary NTX (second urine sample of the day) were measured to assess bone metabolism. Other resorption markers such as urinary hydroxyproline, proline, deoxyproline, hydroxylysine and formation markers such as bone specific ALP and osteocalcin were not measured due to economic limitations of the study. Unlike other studies, BMD was measured in the medial phalanxes of the 2^{nd}, 3^{rd}, and 4^{th} fingers of the non-dominant hand by digital radiographic absorption method. Although the most common sites of measurement for BMD are lumber vertebrae and left femoral neck, we preferred a device exposing the patient to minimal radiation that was easily operated without the assistance of a radiologist. The comparison between patients with hepatitis B or C and age- and gender-matched healthy controls with respect to T scores did not reveal any significant differences. Interestingly, the T score in men with chronic hepatitis B between 20 and 40 years of age was significantly higher compared to the healthy controls in the same age range ($p < 0.05$). But this difference was not considered clinically meaningful, since this age range is not associated with increased risk of osteoporosis. Postmenopausal women deserve most attention from the standpoint of osteoporosis, and the average T score in postmenopausal women with chronic hepatitis B, chronic hepatitis C and healthy postmenopausal women were -0.66, -1.33 and -0.54, respectively, showing normal bone density (according to WHO osteoporosis criteria) for postmenopausal women with chronic hepatitis B and controls, but osteopenia for postmenopausal women with chronic hepatitis C; however, the difference when compared to controls was not significant.

When we assess the situation according to the laboratory data, all laboratory data need to be evaluated in relation to each other in order to reach the result that bone metabolism is affected in patients. One data alone found statistically significant does not mean that all bone metabolisms are affected. For example, osteoporosis can be mentioned when BMD T score is measured as low, together with an increase in the levels of serum PTH, Ca and ALP, decrease in the levels of serum 25 OH D3 and increase in urinary NTX levels in the same patient group.

PTH and 24-hour urinary Ca levels were significantly higher (although within normal range) in men between 20 and 40 years of age with chronic hepatitis B compared to age-matched healthy controls. However, this finding was not interpreted as a sign of increased bone turnover, because serum Ca and 25 OH D3 were not significantly decreased and ALP was not elevated. In men between 40 and 65 years of age, serum P levels were significantly lower compared to age-matched controls ($p<0.05$). Similarly, postmenopausal women with chronic hepatitis C had significantly lower serum P levels compared to age-matched postmenopausal healthy controls ($p<0.05$). On the other hand, other parameters including 24-hour urinary P, serum Ca and ALP were not significantly altered. The increase observed in serum P concentration was also not considered meaningful. Twenty-four hour urinary P levels were significantly higher in men with chronic hepatitis C compared to corresponding healthy controls. However, serum P levels were normal, and no significant abnormality was observed in the associated laboratory parameters. Individual increase in the 24-hour urinary P level was not indicative of any metabolic bone disease. Serum fasting 25 OH vitamin D was significantly higher in premenopausal women with chronic hepatitis C compared to healthy premenopausal women, in disagreement with other studies. In patients with chronic liver disease, serum 25 OH D3 levels are expected to decrease due to the fact that 25 hydroxylation of vitamin D takes place in the liver. There are two possible explanations for our results. First, our patients were not cirrhotic, and therefore 25 hydroxylation may not have been influenced. Secondly, women with chronic hepatitis C were probably more likely to pay attention to their health status compared to premenopausal women in the normal population, and thus were more likely to take vitamin D- containing over-the-counter medications to prevent osteoporosis, though not stated in their history. Menopause is a risk factor for osteoporosis, and postmenopausal women with chronic hepatitis B had significantly higher urinary NTX levels compared to healthy postmenopausal women, although no difference between these patients and women with chronic hepatitis C was detected in terms of urinary NTX. Average urinary NTX levels were 32.26 nM BCE/mmol creatinine, 27.10 nM BCE/mmol creatinine, and 21.94 nM BCE/mmol creatinine in postmenopausal women with chronic hepatitis B, in postmenopausal women with chronic hepatitis C, and in healthy postmenopausal controls, respectively. All these values were above the upper limit of the reference range of the laboratory, but the only significant difference was observed between postmenopausal women with chronic hepatitis B and healthy postmenopausal women. The increased resorption of bone reflected by the increased urinary NTX levels in postmenopausal women with chronic hepatitis B was not associated with a concurrent decrease in the BMD.

In this study, we compared patients with chronic hepatitis B and C with respect to markers of bone metabolism and T scores. Hepatitis C virus, a virus with well-established extra-hepatic manifestations and association with immunologic disorders, had no significant impact on bone metabolism and the risk of osteoporosis. The comparison between premenopausal and postmenopausal women with chronic hepatitis B did not reveal any significant differences in terms of serum Ca, P, ALP, urinary Ca and P, urinary NTX and BMD. On the other hand, men with chronic hepatitis B had significantly higher serum Ca and urinary NTX levels compared to men with chronic hepatitis C, without a concomitant increase in serum PTH and 25 OH vitamin D levels. The average T score was 0.86 and 0.34 in men with chronic hepatitis B and men with chronic hepatitis C, respectively. However, these T scores were similar and within the normal range reported by the WHO. The increased urinary NTX was not associated with a decrease in BMD.

Our findings are not in total agreement with previous studies (1-4, 9, 10, 26). No significant association between chronic viral hepatitis and decreased BMD could be found. Although the objective of our study was partly different, the study by Yucel et al. (27) from Turkey reported supportive findings. In that study, the association between chronic hepatitis C, osteoporosis and osteopenia was explored, with no significant difference in BMD between patients with or without chronic hepatitis C. Our findings are also supported by results of an Australian study, in which serum levels of vitamin D metabolites were not significantly decreased in chronic hepatitis patients in contrast with cirrhotic patients (28).

To our knowledge, this is the only study that has investigated bone metabolism in non-cirrhotic chronic patients with viral hepatitis but no other systemic disease. Our study suggests that

non-cirrhotic chronic hepatitis B and C are not significant risk factors for low BMD. Also, laboratory parameters should not be judged individually and a diagnosis of impaired bone metabolism should only be made on the basis of multiple parameters. It should be kept in mind that hepatic osteomalacia is a rare entity which requires a bone biopsy for a diagnosis. Though unlikely, the technique used for the measurement of BMD and the anatomical location of measurements may also have influenced our results. To adjust for this difference, DXA measurements at the lumber vertebrae and femoral neck may be used to present comparative results, as done in our reference studies.

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