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Original Article

Estimation of bone mineral density and its correlations with homocysteine, and various other biochemical bone markers in postmenopausal women

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ABSTRACT: Introduction- Homocysteine (Hcy) prevents collagen cross-linking and activates osteoclast function within the bones. Bone mineral density (BMD) may be affected by Hyperhomocysteinemia via Cathepsin K. **Aim**- To find the correlation of BMD with biochemical bone markers. **Methods**- BMD was investigated by the DXA scan with the help of the Hologic QDR1000 system. As per WHO guidelines, subjects were divided into three different subsets with; normal bone mass, osteopenia, and osteoporosis. Every subject underwent routine biochemical laboratory investigations, Hcy, Vitamin B12, and folic acid levels. **Results**- Among 355 postmenopausal women, 69% (245) had osteoporosis while 11.27% (40) had normal BMD (mean age, 53 ± 8.35 years) and 19.72% (70) had osteopenia (mean age 52.86 ± 7.93 years). The mean age in the osteoporotic group was 56.49 ± 6.65 years. The mean levels of Hcy in the three groups were 15.58± 7.92 µmol/L, 16.13± 7.34µmol/L and 17.05± 5.13µmol/L, respectively. Hip BMD showed a strong inverse correlation with age (r=-0.360, p=0.002), while no significant correlations were found between weight and BMI. PTH was consistently seen to be negatively correlated with BMD at Spine (r=-0.0339, p=0.004), Forearm (r=-0.267, p=0.027), and Hip (r=-0.224, p=0.064). **Conclusion**- Low BMD is an important problem in postmenopausal female patients. Age and duration of menopause are independent risk predictors for the development of osteoporosis. Vitamin D levels do not predict low BMD in postmenopausal females. Weight is protective for osteoporosis especially at spine and forearm BMD. Vitamin B12 and Hcy levels did not correlate with low BMD.

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INTRODUCTION

Estrogen plays an important role in bone remodeling. It acts as an anabolic hormone and increases osteoblast differentiation as well as modulates the differentiation of osteoclasts. Estrogen is also reported to regulate cytokines that contribute to bone loss such as Tissue necrosis factor α(TNFα), Interleukin 1β (IL-1β), IL-6, macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (G-CSF) and prostaglandin-E2 (PGE2) [1]. It also up-regulates TGF-β which decreases the activity of osteoclast and increases their apoptosis.

According to a hypothesis, the mechanism underlying the association between the homocysteine level and the risk of fracture may involve interference by homocysteine in collagen cross-linking [2].

MATERIALS AND METHODS

Study Design

The current prospective observational study was conducted for one year at King George's Medical University, Lucknow, Uttar Pradesh. The participants were recruited from the inpatient departments of the Department of Medicine, and Department of Orthopedic surgery and outpatient department (OPD) of Medicine and Endocrinology, King George's Medical University, Lucknow.

Ethics statement

Ethical approval for the study was obtained from the Institutional Ethics Committee. Before the start of the study, all the patients were given a verbal presentation of information on the study, together with a written document (in Hindi and English) describing the purpose and procedure of the study.

Study population

Post-menopausal females >45 years of age were included in the study after obtaining written informed consent. For the study, we considered the definition of menopause as the cessation of menses for more than one year [3]. Premature menopause (menopause at <40 years of age), patients of secondary osteoporosis, hyperparathyroidism, rheumatoid arthritis, history of ingestion of corticosteroids (prednisone equivalent of 5 mg/d for 3 months), subjects taking medication that includes the use of anticonvulsants, antitubercular, theophylline, oral contraceptives (within 6 months), subjects received vitamin B12 or folic acid supplements during the preceding one year were excluded from the study.

Methods

Participants of the study underwent detailed history regarding the duration of menopause, history of fracture, family history, and other details. Drug intake history in the past, such as anti-retroviral therapy, antitubercular treatment, anti-epileptics, calcium supplementation, food fortification with Vitamin D, and steroids were taken. World Health Organization classification system was used in classifying osteoporosis and osteopenia. Anthropometric variables, like height, were measured by standard stadiometer with the participant standing wearing no shoes, and it was recorded to the nearest centimeter in the Frankfurt plane. Weight was measured by an electronic scale and BMI was calculated for each.

Bone mineral density

At different sites of the body like hip, spine, and forearm bone mineral density (BMD) was measured in each patient by dual-energy X-ray absorptiometry (DEXA) using the Hologic QDR 1000 machine and was expressed in absolute values as grams of mineral content per square centimeters of bone area (g/cm^2).

Bone marker assessment

After 8 hours fasting, a peripheral venous blood sample was obtained and kept at -200C for analysis of parameters like complete hemogram, calcium, phosphate, parathyroid hormone (PTH), 25 hydroxyvitamin D or 25(OH)D, serum glutamic-oxaloacetic transaminase (SGOT)/ Serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP), protein/albumin, creatinine, Hcy level, vitamin B12, and folic acid using standard analytical techniques.

Statistical analysis

Descriptive statistics were examined for all study variables. Data analysis was done using SPSS version 20 (SPSS, Chicago, IL).

Kruskal Wallis test was used in analyzing patient's demographics and biochemical parameters, the difference in baseline between the three groups. The chi-square test for categorical variables was used for examining the baseline characteristics of each study group. Data are presented as mean ± standard deviation (SD). Non-parametric tests were applied because some variables did not present a normal distribution (Gaussian); due to data dispersion, the null hypothesis was rejected according to the Shapiro-Wilk test.

The measure of the correlation between BMD and study variables was done by using the Pearson correlation coefficient. Determination of the predictor of BMD at various parts (hip, spine, and forearm) was done by multiple linear regression analysis. BMD was entered as a dependent variable with serum ALP, calcium, phosphorus, vitamin D, PTH, Hcy, vitamin B12, and folic acid simultaneously as predictor variables.

A p-value of <0.05 was considered statistically significant for all analyses.

RESULTS

The present study was carried out to investigate whether levels of Hcy, along with folate, Vitamin D, PTH, calcium, phosphorus and Vitamin B12 are related to bone mineral density in postmenopausal women. 460 postmenopausal women were assessed for eligibility and out of them, 390 women who met the inclusion criteria and gave the consent, were included in the study.

All the cases included in the study were grouped into three divisions: postmenopausal women with osteoporosis (t-score < -2.5), postmenopausal women with osteopenia (t-score between -2.5 to -1), and postmenopausal women with normal BMD values (t score >-1). Out of 390 cases enrolled in the study, 35 cases did not complete the investigation so they were excluded from the analysis. Data from the remaining 355 subjects were analyzed. Of these 355 subjects, 245 patients (69.01%) were suffering from osteoporosis, 70 cases (19.72%) were osteopenic, while 40 cases (11.27%) had normal BMD.

The mean value of age, height, weight, and BMI were comparable between the three cohorts. Patients had significantly higher duration since menopause in the osteoporotic women compared to the control and osteopenic group ($p<0.007$). Haemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and platelet count (PC) were all comparable and within the normal limits in all the cases enrolled in the study (Table 1).

Table 1: Baseline characteristics of the postmenopausal women, divided on the basis of BMD values

Characteristics	Osteoporosis (n=245)	Osteopenia (n=70)	Normal (n=40)	Statistical Significance	
				H	P
Age (years)	56.49 ± 6.65	52.86 ± 7.93	53 ± 8.35	4.94	0.085
Height (cm)	149.48 ± 7.04	150.14 ± 5.76	154.38 ± 5.26	3.73	0.15
Weight (Kg)	60.03 ± 12.87	61.95 ± 11.07	68.94 ± 12.94	3.89	0.14
BMI (Kg/m^2)	26.75 ± 5.42	27.27 ± 3.85	28.85 ± 5.18	1.89	0.38
Duration of Menopause (years)	11.39 ± 6.08	7.21 ± 7.21	7.31 ± 8.32	9.79	0.007
Hb (g/dl)	11.20 ± 1.81	11.16 ± 2.23	12.59 ± 1.45	5.22	0.073
MCV (fl)	86.01 ± 6.89	85.67 ± 9.08	86.98 ± 5.35	0.77	0.678
MCH (pg)	28.55 ± 2.76	27.27 ± 3.79	28.80 ± 2.76	0.82	0.665
PC	1.85 ± 0.70	2.16 ± 0.84	2.09 ± 0.58	1.88	0.389
SGPT (U/L)	31.94 ± 31.54	35.01 ± 22.06	28.14 ± 14.72	3.68	0.15
SALP (U/L)	128.09 ± 68.22	95.94 ± 40.71	105.63 ± 31.18	2.86	0.23
Creatinine(mg/dl)	0.85 ± 0.37	0.75 ± 0.12	0.77 ± 0.29	0.126	0.93
Protein (g/dl)	7.45 ± 0.60	7.75 ± 0.39	6.84 ± 1.19	5.46	0.06
Albumin (g/dl)	4.11 ± 0.53	4.27 ± 0.50	3.74 ± 0.91	2.53	0.28
Calcium (mg/dl)	9.12 ± 0.58	9.44 ± 0.58	8.37 ± 1.86	3.58	0.16
Phosphorus (mg/dl)	3.91 ± 0.77	3.69 ± 0.57	5.12 ± 1.60	7.46	0.024
Vit D (ng/ml)	22.14 ± 15.79	21.44 ± 9.25	19.03 ± 15.18	0.856	0.65
PTH (pg/ml)	55.78 ± 32.12	38.98 ± 20.26	25.15 ± 27.19	8.69	0.013
T3 (ng/ml)	1.35 ± 0.40	1.27 ± 0.56	1.48 ± 0.53	1.69	0.42
T4 (ng/ml)	93.57 ± 32.47	109.51 ± 31.76	100.63 ± 21.90	2.19	0.33
TSH (µIU/ml)	4.56 ± 7.88	2.68 ± 2.3	4.78 ± 8.33	2.26	0.32

Data are Mean ± SD

Clinical and biochemical features from the study population were expressed in means ± SD. On comparison of the SGPT level among the three groups, no variation was found. SALP level in the osteoporotic group was 128.09 U/L which was higher than the normal group (105.63) and osteopenic group (95.94). However, it was not significantly different in the three groups. Similarly, the values of serum creatinine, protein, and albumin level were also found non-significant.

The osteoporotic and osteopenic groups had similar Calcium levels (9.12 and 9.44 mg/dl respectively) than normal group (8.37). In contrast, phosphorus level was significantly lower in osteoporotic (3.91 mg/dl) and osteopenic group (3.69 mg/dl) relative to normal group (5.12 mg/dl) (p=0.024)

Hormonal profile of the enrolled cases is shown in table 5. There was no significant difference in Vitamin D levels among osteoporotic, osteopenic, and normal groups (p=0.65). Similarly, the thyroid hormone levels in the three groups were equivalent, T3 (p=0.42), T4 (p=0.33), or the thyroid-stimulating hormone (TSH) levels (p=0.33). The PTH level in the osteoporotic group was significantly higher (p=0.013) than the osteopenic and normal group.

Intergroup comparisons of Hcy, Vit B12, and Folic acid

The total Hcy in the osteoporotic group was found to be 15.58; in the osteopenic group, 17.05, while in a normal group it was 16.13. However, there was no significant difference between these three groups.

The Vitamin B12 values were similar in the osteoporotic group, normal group, and osteopenic group, p=0.67. Similarly, the folic acid level was also not found significant between the three groups (p=0.36) (Table 2).

Table 2: Serum Hcy, Vitamin B12 and Folic acid level in postmenopausal women

	Osteoporosis (n=245)	Osteopenia (n=70)	Normal (n=40)	Statistical Significance	
				H value	P-value
Hcy (µmol/L)	15.58 ± 7.92	17.05 ± 5.13	16.13 ± 7.34	2.38	0.30
Vitamin B12 (pg/ml)	806.66 ± 609.4	571.14 ± 401.94	725.7 ± 607.99	0.77	0.67
Folic acid (ng/ml)	13.31 ± 5.87	11.05 ± 7.00	15.02 ± 7.18	2.03	0.36

Correlations between hip BMD, Hcy and other variables

Hip BMD showed a strong inverse correlation with age (r=-0.360, p=0.002), while no significant correlations were found between weight and BMI. Likewise, BMD was also inversely associated with the duration of menopause (r=-0.309, p=0.01). No significant associations were found between serum SGPT, creatinine, and albumin with BMD (p>0.05), although BMD did correlate inversely with total protein (r=-0.238, p=0.049).

Data did not show a negative association of hip BMD with SALP, creatinine, albumin, Vitamin D, Vitamin B12, folic acid, and calcium. PTH showed a weak inverse correlation with hip BMD which was statistically not significant (Table 3).

Table 3: Pearson's correlation between hip BMD and study variables

		Pearson correlation coefficient, r	P-value
BMD hip	Age	-0.360**	0.002
BMD hip	Weight	0.219	0.071
BMD hip	BMI	0.149	0.222
BMD hip	Duration of menopause	-0.309**	0.010
BMD hip	SGPT	0.005	0.967
BMD hip	SALP	-0.196	0.107
BMD hip	Creatinine	-0.039	0.751
BMD hip	Protein	-0.238*	0.049
BMD hip	Albumin	-0.194	0.111
BMD hip	Hcy	0.034	0.784
BMD hip	Vitamin D	-0.019	0.877
BMD hip	Vitamin B12	-0.098	0.425
BMD hip	Folic acid	-0.087	0.480
BMD hip	Calcium	-0.211	0.082
BMD hip	Phosphorus	0.187	0.124
BMD hip	PTH	-0.224	0.064

A significant correlation was found between the BMD and the variable *p<0.05; **p<0.01

Correlations between spine BMD, Hcy and other variables

Spine BMD was significantly negatively correlated with age (r=-0.236, p=0.05) and duration of menopause (r=-0.258, p=0.032) and positively with weight (r=0.248, p=0.04). Non-significant correlations were observed between spine BMD with BMI, SGPT, SALP, and creatinine.

Like Hip BMD, protein showed a strong significant inverse relation with spine BMD (r=-0.294, p=0.01). Hcy and folic acid did not show correlation with BMD, while phosphorus had a significant correlation with the spine BMD (r=0.314, p=0.009). Vitamin D and vitamin B12 also did not show a correlation with spine BMD. Interestingly, the PTH level showed a significant inverse correlation with spine BMD (r=-0.0339p=0.004) (Table 4).

Table 4: Pearson's correlation between spine BMD and study variables.

		Pearson correlation coefficient, r	P-value
BMD spine	Age	-0.236	0.051
BMD spine	Weight	0.248*	0.04
BMD spine	BMI	0.152	0.213
BMD spine	Duration of menopause	-0.258*	0.032
BMD spine	SGPT	0.051	0.676
BMD spine	SALP	-0.174	0.153
BMD spine	Creatinine	-0.015	0.904
BMD spine	Protein	-0.294*	0.014
BMD spine	Albumin	-0.224	0.064
BMD spine	Hcy	0.019	0.875
BMD spine	Vitamin D	-0.052	0.672
BMD spine	Vitamin B12	-0.091	0.457
BMD spine	Folic acid	0.032	0.792
BMD spine	Calcium	-0.286*	0.017
BMD spine	Phosphorus	0.314**	0.009
BMD spine	PTH	-0.0339**	0.004

A significant correlation was found between the BMD and the variable *p<0.05; **p<0.01

Correlations between forearm BMD, Hcy and other variables

Similar to the hip and spine BMD, forearm BMD had a significant inverse correlation with age (r=-0.393, p=0.001) and duration of menopause (r=-0.363, p=0.002). Interestingly, our data showed a strong significant positive correlation of forearm BMD with weight (r=0.381, p=0.001) and BMI (r=0.313, p=0.009).

PTH is also significantly negatively correlated with forearm BMD (r=-0.267, p=0.027) while regarding the other parameters no significant correlation was obtained which was in line with the above findings obtained with hip and spine BMD.

From the data PTH was consistently seen to be negatively correlated with BMD at Spine (r=-0.0339, p=0.004), Forearm (r=-0.267, p=0.027), and Hip (r=-0.224, p=0.064) (Table 5).

Table 5: Pearson's correlation between forearm BMD and study variables

		Pearson correlation coefficient, r	P-value
BMD forearm	Age	-0.393***	0.001
BMD forearm	Weight	0.381***	0.001
BMD forearm	BMI	0.313**	0.009
BMD forearm	Duration of menopause	-0.363**	0.002
BMD forearm	SGPT	0.056	0.65
BMD forearm	SALP	-0.172	0.159
BMD forearm	Creatinine	-0.061	0.617
BMD forearm	Protein	-0.042	0.730
BMD forearm	Albumin	0.024	0.846
BMD forearm	Hcy	0.114	0.352
BMD forearm	Vitamin D	0.111	0.365
BMD forearm	Vitamin B12	-0.170	0.163
BMD forearm	Folic acid	-0.084	0.492
BMD forearm	Calcium	-0.019	0.878
BMD forearm	Phosphorus	0.151	0.215
BMD forearm	PTH	-0.267*	0.027

Significant correlation was found between the BMD and the variable *p<0.05; **p<0.01; ***p<0.001

Multiple regression analysis of the predictors of hip, spine and forearm BMD

Hcy in osteoporotic women did not show any correlation with the hip BMD, spine BMD, or Forearm BMD. Hcy in osteopenic women showed a strong significant positive association with BMD at the spine (r=0.008), while at other sites, no significant correlation was seen.

The possible influence of selected variables including SALP, Calcium, Phosphorus, Vitamin D, PTH, Hcy, VitaminB12, and Folic acid in predicting BMD of postmenopausal women was assessed by multiple regression analysis shown in Table 6.

Regarding the hip BMD, a non-significant regression equation was found F (8,60) = 1.39; p= 0.219 with an r2 of 0.156.

Multiple regression analysis presented in Table 6 showed a significant regression equation with spine BMD F (8,60) = 3.001; p = 0.007 with an r2 of 0.286. From the data, we can conclude that the level of calcium and PTH were the main predictors of BMD at the spine. For every unit increase in PTH, BMD at the spine will decrease by 0.343 units (Table 6).

Similar to hip BMD, forearm BMD also had a non-significant regression equation F (8,60) = 1.22; p= 0.302

Table 6: Multiple regression analysis of the predictors of the hip, spine and forearm BMD

	BMD hip (r= 0.156; p= 0.219)		BMD spine (r= 0.286; p= 0.007)		BMD forearm (r= 0.140; p= 0.302)	
	β	*p value*	*β*	*p value*	*β*	*p value*
SALP	-0.196	0.112	-0.178	0.116	-0.149	0.228
Calcium	-0.180	0.156	-0.233	0.048	0.020	0.877
Phosphorus	0.084	0.547	0.178	0.170	0.080	0.571
Vitamin D	-0.108	0.408	-0.185	0.125	0.043	0.745
PTH	-0.237	0.087	-0.343**	0.008	-0.249	0.075
Hcy	0.016	0.918	-0.024	0.866	0.072	0.649
VitaminB12	-0.030	0.845	-0.061	0.665	-0.103	0.504
Folic Acid	-0.067	0.595	0.044	0.701	-0.067	0.594

A significant correlation was found between the BMD and the variable *p<0.05; **p<0.01.

DISCUSSION

A high prevalence of osteoporosis was seen in 355 postmenopausal females. The total overall prevalence of osteoporosis was 69% which is similar to that reported in previous studies. In a study conducted by Agarwal *et al.*, on Indian women, 53% of women had low BMD and they had reported a significant positive correlation between increasing age and low BMD [4]. Similar results were obtained with another study in which the prevalence of osteoporosis was found to be more than 40% of the women above 50 years in India [5]. In our study, only 11% of all women had normal BMD and around 1/5 had osteopenia. This has significant implications as 2/3 of all women in this age group were suffering from osteoporosis and thus were at high risk for fractures.

These results were in line with many other studies which show that with an increase in **age**, the risk of osteoporosis also increases [6].

Regarding the duration of **menopause,** there was a significant difference between all three groups. Women who had osteoporosis had longer duration menopause than the other two groups. Thus, the duration of menopause was a significant predictor for low BMD and osteoporosis in our study. There was no difference in height or weight between the three groups.

Serum **ALP** is a marker for bone formation. It is a ubiquitous enzyme that plays an important role in bone formation and bone mineralization. Serum ALP levels in our study did not show any significant difference between the osteoporotic, osteopenic, and normal BMD groups.

The group of females who had osteoporosis had lower **phosphorus** levels with higher **PTH.** Calcium and 25(OH)D levels were similar in all three groups. Despite similar 25(OH)D levels, there are unexplored factors that predispose some postmenopausal females to develop osteoporosis. Higher PTH levels were seen in osteopenic and osteoporotic groups, but this was not due to lower 25(OH)D levels as they were similar in all the groups.

The bone mineral phase is composed of calcium and phosphorus. When the bone is resorbed calcium and phosphorus ions are released into the ECF [7]. We observed a significant difference in phosphorus levels between osteoporosis and osteopenic as compared to the normal group. Phosphorus level was significantly lower in women of osteoporotic and osteopenic groups. However, the levels of calcium and 25(OH)D were similar in all the three groups.

Vitamin D is an important nutrient in the maintenance of bone health. The primary function of Vitamin D is the regulation of intestinal calcium absorption and the stimulation of bone resorption leading to the maintenance of serum calcium concentration. In Vitamin D deficiency states, decreased calcium absorption occurs from the intestines, causing increased osteoclast production, which enhances the mobilization of calcium from the bone [8]. In many cross-sectional studies, relationships between serum 25(OH)D and bone mineral density of the hip have been observed. A global study on Vitamin D status and BMD in 7441 postmenopausal women with osteoporosis showed a significant positive relationship between serum 25(OH)D and BMD in the trochanteric area of the hip [9].Contrary to these studies our study did not show any correlation of BMD with Vitamin D status in the Indian population [10,11].

Hcy has been a candidate risk factor for osteoporosis based on observations linking homocystinuria and skeletal abnormality. Though, the underlying mechanism of increased Hcy levels and osteoporosis may be a mechanistic link and may not be reflected in BMD and biochemical bone turnover markers. Few studies on Hcy and osteoporosis have resulted in defining a correlation of higher Hcy levels with lesser BMD [12] while in other studies it was failed [13,14] Many research studies resulted in defining increased osteoporotic fractures with higher Hcy levels [15], and collagen cross-linking may be the responsible mechanism [16]. In our study, Hcy levels were similar in all three groups and thus we postulate that Hcy may not play a significant role in the development of osteoporosis. A newer study concluded that osteoporotic postmenopausal women had increased plasma vitamin **B12** in comparison to those without osteoporosis [17,18] This finding was similar to the present study.

In the study of Tucker *et al.*, results were that in both sexes with vitaminB12 levels less than148 pmol/l had lesser average BMD in comparison to those with higher values. But this finding was significantly varying with the site of BMD measurement (men at the hip, women at the spine) [19]. The difference in results of the correlation of serum vitamin B12 and BMD may be described by population demographic differences, and, more specifically, the site of measurement of BMD. There was no difference in Vitamin B12 and folate levels between the three groups in our study.

Using Pearson's correlation coefficient, we were able to identify the age and duration of menopause as a significant predictor for low BMD at all three sites i.e hip, spine, and forearm.

Weight was protective for osteoporosis with higher BMD at the spine and forearm. It has been seen that bodyweight has a positive impact on BMD in women [20]. Interestingly, BMD at the spine is positively correlated with weight, while BMD at the forearm is positively correlated with both weight and BMI.

Thus, in our study to it was found that low BMD is related to low body weight which was by the study conducted by Shapses et al. [21].

Points strengthening this research were the use of the same DEXA machine (Hologic) with the same operator in calculating BMD and very few dropout rates (consistent with our group). The drawbacks of this research were a small sample size.

CONCLUSION

The main findings of this study were a high prevalence of osteoporosis in postmenopausal females of India. Age and duration of menopause are independent risk predictors for the development of osteoporosis. Vitamin D levels do not predict low BMD in postmenopausal females. Weight is protective for osteoporosis especially at spine and forearm BMD. Vitamin B12 and Hcy levels did not correlate with low BMD and thus may not play a significant role in the development of osteoporosis. PTH level was higher despite similar 25(OH)D levels in the osteoporotic group. This may be due to a pathway other than involving Vitamin D.

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Conflict of interest- None

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