Increases in Bone Density During Treatment of Men with Idiopathic Hypogonadotropic Hypogonadism*

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ABSTRACT. To assess the effects of gonadal steroid replacement on bone density in men with osteoporosis due to severe hypogonadism, we measured cortical bone density in the distal radius by 125I photon absorptiometry and trabecular bone density in the lumbar spine by quantitative computed tomography in 21 men with isolated GnRH deficiency while serum testosterone levels were maintained in the normal adult male range for 12–31 months (mean ± SE, 23.7 ± 1.1). In men who initially had fused epiphyses (n = 15), cortical bone density increased from 0.71 ± 0.02 to 0.74 ± 0.01 g/cm² (P < 0.01), while trabecular bone density did not change (116 ± 9 compared with 119 ± 7 mg/cm³). In men who initially had open epiphyses (n = 6), cortical bone density increased from 0.62 ± 0.01 to 0.70 ± 0.03 g/cm² (P < 0.01), while trabecular bone density increased from 96 ± 13 to 109 ± 12 mg/cm³ (P < 0.01). Cortical bone density increased 0.03 ± 0.01 g/cm² in men with fused epiphyses (n = 6), cortical bone density increased from 0.62 ± 0.01 to 0.70 ± 0.03 g/cm² (P < 0.01), while trabecular bone density increased from 96 ± 13 to 109 ± 12 mg/cm³ (P < 0.01). Cortical bone density increased 0.03 ± 0.01 g/cm² in men with fused epiphyses and 0.08 ± 0.02 g/cm² in men with open epiphyses (P < 0.05). Despite these increases, neither cortical nor trabecular bone density returned to normal levels. Histomorphometric analyses of iliac crest bone biopsies demonstrated that most of the men had low turnover osteoporosis, although some men had normal to high turnover osteoporosis. We conclude that bone density increases during gonadal steroid replacement of GnRH-deficient men, particularly in men who are skeletally immature. (J Clin Endocrinol Metab 69: 776, 1989)

OSTEOPOROSIS can cause significant morbidity in men, and hypogonadism is a major risk factor for its development (1–3). We have previously demonstrated that men with idiopathic hypogonadotropic hypogonadism (IHH), who are hypogonadal due to an isolated deficiency of hypothalamic GnRH, have marked decreases in both cortical and trabecular bone density compared to age-matched controls (4). Premature osteoporosis has also been reported in men with hypogonadism associated with hyperprolactinemia (5), anorexia nervosa (6), and Klinefelter's syndrome (7–9). Although few data exist regarding the effects of androgen replacement on the osteoporosis of hypogonadal men, cortical bone density increases in men with hyperprolactinemic hypogonadism when normal testicular function is restored (5, 10). Furthermore, testosterone therapy is associated with increases in bone formation in men with primary hypogonadism (11, 12). However, the effect of gonadal steroid restoration on cortical and trabecular bone densities in men with osteopenia due to isolated GnRH deficiency is unknown.

The osteopenia of hypogonadal men could be due to a decrease in the peak bone mass achieved during skeletal maturation, an accelerated loss of established bone, or both. Histomorphometric analyses of bone can be useful in assessing the mechanism of decreased bone mass in patients with osteopenia. However, analyses of bone biopsies from hypogonadal men have produced contradictory results regarding the cause of their osteopenia depending on the patients studied (11–13). These discrepancies may be related to heterogeneity within the patient populations, concomitant 1,25-dihydroxyvitamin D₃ deficiency in some of the study groups, or variability in the mechanism for osteopenia in hypogonadal men. Because men with isolated GnRH deficiency are a relatively homogeneous population, they are an excellent model in which to study androgen effects on bone density and metabolism.

To assess the effects of gonadal steroid replacement on cortical and trabecular bone density in 21 men with GnRH deficiency, we made serial measurements of cortical bone density in the shaft of the radius by 125I photon absorptiometry and trabecular bone density in the lumbar vertebral bodies by quantitative computed tomography (CT). To evaluate the relative importance of skeletal
maturation in the alteration in bone density occurring during gonadal steroid replacement, we compared the effect of androgen replacement therapy on bone density in 2 groups of GnRH-deficient men: those who had open epiphyses when initially studied, and those who had closed epiphyses. Finally, we performed quantitative histomorphometric analyses of iliac crest biopsies in a subset of 9 patients to determine the histological correlates of the changes in bone density that were observed during gonadal steroid replacement.

Materials and Methods

Subjects

Patients with IHH. Twenty-one caucasian men, 19–53 yr old (mean ± SE, 29 ± 2), were selected on the basis of the following criteria (14); 1) failure to undergo puberty by age 18 yr (n = 20) or isolated idiopathic loss of gonadotropin secretion after puberty (n = 1); 2) serum testosterone levels less than 3.5 nmol/L in the presence of low or normal circulating gonadotropin levels; 3) normal free T4 index; 4) normal levels of TSH and PRL at baseline and after the iv injection of 200 μg TRH; 5) normal GH and cortisol levels at baseline and in response to insulin-induced hypoglycemia; and 6) normal CT scan of the hypothalamic-pituitary region. None of the patients had a history of hyperparathyroidism, Cushing’s syndrome, liver disease, renal disease, or other chronic illness. No patients had received corticosteroids, anticonvulsants, calcium, or vitamin D supplements, and all patients had normal levels of serum calcium, inorganic phosphate, and PTH. Fifteen of the 21 patients consumed alcohol. In 12 of these men, the amount of alcohol ingested was less than 30 mL (1 oz)/day. The other 3 men consumed about 60 mL (2 oz) alcohol/day. Ten men smoked cigarettes, with a range of consumption from 7–25 pack-yr. No patients were involved in regular vigorous exercise.

Patients were divided into two groups on the basis of their bone ages (15) at the time of their initial investigations. Group I consisted of 15 patients with fused epiphyseal plates (bone age of 18 yr or more); group II consisted of 6 patients with open epiphyses (mean bone age ± SE, 16.1 ± 0.4 yr). The baseline clinical, hormonal, and bone density data for these men have been reported in our previous study (4).

Controls. For patients with fused epiphyses (group I), cortical bone density measurements were compared with our previously established normative data from chronological age-matched men (4). For patients with open epiphyses (group II), cortical bone density measurements were compared to those from control patients who were matched for bone age (16). Because the published data for trabecular bone density in normal adolescents (17) are insufficiently detailed to compare with our data on the basis of bone age, trabecular bone density was compared with normative data for adult men (18) for all patients (groups I and II).

Protocol

Patients were admitted to the Mallinkrodt General Clinical Research Center at the Massachusetts General Hospital for the following studies: a complete history and physical examination, radiographs of the hand and wrist for bone age using the method of Tanner and Whitehouse (15), determination of cortical and trabecular bone density, and measurements of serum concentrations of testosterone, PTH, 25-hydroxyvitamin D3, 1,25-dihydroxyvitamin D3, and alkaline phosphatase. Initial serum hormone levels were determined by previously described RIAs (19–22) on pools of equal aliquots of blood specimens that were drawn every 10 min for 24 h during an admission to the General Clinical Research Center when the patients were receiving no hormone replacement therapy. Subsequent levels of serum testosterone, PTH, 25-hydroxyvitamin D3, 1,25-dihydroxyvitamin D3, and alkaline phosphatase were determined during therapy on blood samples drawn on the same day that bone density measurements were made. Daily oral calcium intake was estimated from a detailed retrospective dietary history performed by a research dietician at the center.

Seventeen of the 21 patients (all men in group I and 2 of 6 men in group II) had received prior androgen replacement therapy and were sexually mature (i.e. Tanner stage V genitalia) at the time of their initial bone density studies. The mean duration of prior therapy was 3.2 ± 0.7 yr in group I and 0.2 ± 0.1 yr in group II. Subsequent treatment in these patients and in the 4 others was with im testosterone enanthate (3 patients), hCG (8 patients), or pulsatile GnRH (10 patients) (23, 24) in doses titrated to maintain serum testosterone levels within the normal adult male range. The patients were followed prospectively and underwent an identical set of studies after serum testosterone levels had been sustained in the normal adult male range for at least 1 yr (range, 12–31 months; mean, 23.7 ± 1.1). This protocol was approved by the Subcommittee on Human Studies at the Massachusetts General Hospital, and all patients provided written informed consent.

Bone density determinations

Cortical bone density was determined by 125I photon absorptiometry (25, 26) using a Norland model 278A bone densitometer (Norland Instruments, Fort Atkinson, WI). Quadruplicate readings were obtained from the junction of the proximal two thirds and distal one third of the nondominant radius, a site that contains greater than 90% cortical bone. Our coefficient of variation for replicate patient measurements on the same day is 1.5–2.0%, and that for long term instrumental stability (assessed by daily measurements of an aluminum cortical bone phantom) is 1.0%. Previous studies have demonstrated that the reproducibility of single photon absorptiometry at the midshaft site is 2.4% for measurements made with this instrument over a 3-yr period (27). Trabecular bone density was measured with a General Electric model 8800 CT scanner (General Electric Co., Schenectady, NY), as described previously (28), and results are expressed in terms of milligrams of K2HPO4 standard per cm³. Axial scans were obtained through the midbody of the first four lumbar vertebrae, and their trabecular bone density
was then measured and averaged. The likelihood that a duplicate average would fall within 10 CT units was greater than 95%.

**Iliac crest bone biopsies**

Nine unselected patients (6 from group I and 3 from group II) underwent biconical iliac crest biopsy under local anesthesia at a time when serum testosterone levels had been normal for at least 1 yr. Eight of these men had received a double tetracycline label before the biopsy. The undecalcified specimens were embedded in methylmethacrylate, and 3-μm sections were stained with von Kossa, Toluidine blue, and Goldner trichrome. Ten-micron unstained sections were used for quantitative fluorescent analysis. Histomorphometric analysis was performed by Nichols Institute (San Juan Capistrano, CA) using a previously described method (29, 30). This same technique was used to establish normal data in 21 healthy men, aged 20–42 yr (kindly provided by Dr. Dennis Andrews, University of Washington). The following histological indices were assessed: osteoid surface (as a percentage of the total surface), osteoblastic surface (cuboidal or plump osteoblasts, as a percentage of the total surface), bone apposition rate (microns per day), daily rate of bone formation at the tissue level (square microns per mm² tissue/day), resorbing surface (as a percentage of total bone surfaces), osteoid width (microns), osteoid area (as a percentage of the total bone area), and mineralization lag time (days). The bone formation rate at the tissue level was determined by multiplying the bone apposition rate (distance between the 2 tetracycline labels divided by the number of days of tetracycline administration) by the total length of bone surface occupied by double tetracycline labels, and then normalizing by the total bone area. The mineralization lag time was determined by dividing the osteoid width by the bone apposition rate.

**Statistical analyses**

Comparisons of all parameters between patients and controls or between groups I and II were made by Student's nonpaired t test or, for data that were nonnormally distributed, a Mann-Whitney test. Comparisons of all baseline and follow-up parameters within each group were made by Student's paired t test. The amount of change in cortical and trabecular bone density was compared between patients treated with hCG and pulsatile GnRH using Student's nonpaired t test. Because only 3 men were treated with testosterone enanthate, the amount of change in bone density in these men was not compared statistically with that in the other patients. Multiple linear regression analyses with the method of least squares were used to assess the relationship between the patient's chronological age, age at the onset of therapy, duration of therapy, oral calcium intake, and serum alkaline phosphatase level with changes in cortical or trabecular bone density for the entire group of patients. Parameters of bone histomorphometry were compared by Student's nonpaired t test with data from 21 normal men. All results are expressed as the mean ± SE.

**Results**

**Clinical characteristics**

At the time of the initial bone density measurements the 15 men with fused epiphyses (group I) were 24–52 yr old (mean, 32 ± 2), had serum testosterone levels of 0.6–3.3 nmol/L (mean, 1.7 ± 0.2; normal adult male range 11.4–33.6 nmol/L) (31), and had an adult bone age (4). The 6 patients with open epiphyses (group II) were 19–26 yr old (mean, 21 ± 1; P < 0.01 compared with group I), had serum testosterone levels of 0.5–3.1 nmol/L (mean, 1.4 ± 0.4), and had bone ages between 14.3–17.1 yr (mean, 16.1 ± 0.4) at the time of the initial evaluation (4). At the time of the final evaluation during therapy serum testosterone levels had been in the normal adult male range for 15–31 months (mean, 25.2 ± 1.0 months) in the patients in group I and for 12–25 months (mean, 20.0 ± 2.4 months) in the patients in group II (P < 0.05). Serum testosterone levels during therapy were similar in both groups (18.4 ± 2.6 vs. 23.9 ± 4.2 nmol/L). At the time of final evaluation 2 patients in group II still had open epiphyses, with bone ages of 16 and 17 yr.

**Cortical bone density**

**Initial determinations.** The initial cortical bone density was significantly below that of age- and sex-matched controls both in group I with fused epiphyses (0.71 ± 0.02 compared with 0.86 ± 0.01 g/cm²; P < 0.0001) (4) and in group II with open epiphyses (0.62 ± 0.01 compared with 0.79 ± 0.02 g/cm²; P < 0.001) (4). When the patients were initially evaluated, cortical bone density was significantly higher in group I than in group II (P < 0.003; Fig. 1).

**Response to androgen replacement.** After serum testosterone levels were normalized for at least 1 yr, cortical bone density increased in 14 of 15 patients in group I, with mean bone density levels increasing from 0.71 ± 0.02 to 0.74 ± 0.01 g/cm² (P < 0.01; Fig. 1). Cortical bone density increased in all 6 patients in group II, with mean bone density levels increasing from 0.62 ± 0.01 to 0.70 ± 0.03 g/cm² (P < 0.01; Fig. 1). Cortical bone density increased more in group II than in group I patients (0.08 ± 0.02 vs. 0.03 ± 0.01 g/cm²; P < 0.05; Fig. 1). After treatment, mean cortical bone density remained lower than that in controls in both groups (P < 0.001). Cortical bone density was still higher in group I than in group II after treatment, but this difference was no longer statistically significant (P = 0.13). The change in cortical bone density was roughly proportional to the initial alkaline phosphatase level (r = 0.52; P < 0.02). There was no significant relationship between the change in cortical bone density and the patients' chronological age, age that treatment was begun, duration of therapy, or dietary
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0.5 0.6 0.7 0.8 0.9
Cortical Bone Density (g/cm²)

GROUP I

GROUP II

Initial Final

Initial Final

* p<0.01

0

200

180

160

140

120

100

80

60

40

Fig. 1. Cortical bone density before and after treatment of men with isolated GnRH deficiency who initially had fused epiphyses (group I) or who initially had open epiphyses (group II). The solid lines represent the mean cortical bone density, which increased significantly after treatment in both groups I and II (P < 0.01). Cortical bone density increased more in group II than in group I (P < 0.05).

calcium intake. There was no significant difference in the amount of change in cortical bone density between the patients who were treated with HCG and those who were treated with pulsatile GnRH.

Trabecular bone density

Initial determinations. Initial and follow-up trabecular bone density measurements in the patients in groups I and II are shown in Fig. 2. The initial trabecular bone density for all patients was significantly less than that in controls (110 ± 8 compared with 177 ± 4 mg/cm³; P < 0.0001) (4), and there was no significant difference in initial trabecular bone densities between the two groups (116 ± 9 vs. 96 ± 13 mg/cm³; P = 0.28).

Response to androgen replacement. After serum testosterone levels had been normal for at least 1 yr, mean trabecular bone density did not change in group I with fused epiphyses (116 ± 9 vs. 119 ± 7 mg/cm³; P = 0.60), although several patients had dramatic increases (Fig. 2). Trabecular bone density increased in all six patients in group II, with mean levels increasing from 96 ± 13 to 109 ± 12 mg/cm³ (P < 0.01; Fig. 2). After treatment, trabecular bone density for all patients remained below that in controls (116 ± 6 vs. 177 ± 4 mg/cm³; P < 0.0001) and was similar in groups I and II, (119 ± 7 vs. 109 ± 12 mg/cm³; P = 0.43). There was no significant relationship between the change in trabecular bone density and the patients’ chronological age, age that treatment was begun, duration of therapy, dietary calcium intake, or initial serum alkaline phosphatase level. There was no significant difference in the amount of change in trabecular bone density between the patients treated with hCG and those treated with pulsatile GnRH. Furthermore, there was no significant relationship between the change in trabecular bone density and the change in cortical bone density.

Serum studies and dietary calcium intake

Mean serum alkaline phosphatase levels were higher in the patients with open epiphyses (group II) than in the patients with fused epiphyses (group I) at the time of the initial studies (41 ± 4 vs. 27 ± 2 U/L; P < 0.005) (4) and at the time of the follow-up evaluation (37 ± 6 vs. 25 ± 2 U/L; P < 0.05). Mean serum alkaline phosphatase levels did not change significantly in either group during the study. Initial serum PTH (15 ± 1 ng/L), 25-hydroxyvitamin D₃ (46 ± 4 nmol/L), and 1,25-dihydroxyvitamin D₃ (95 ± 6 pmol/L) levels were normal in all patients and did not change significantly during therapy (16 ± 1 ng/L, 51 ± 5 nmol/L, and 93 ± 8 pmol/L, respectively). Dietary calcium intake was also similar in the two groups of patients, at the time of both the initial (807 ± 116 vs. 2016 ± 736 mg/day) and follow-up bone density studies (1008 ± 101 vs. 1205 ± 317 mg/day).
Bone histomorphometry

Table 1 shows the results of quantitative histomorphometry in nine patients. Two distinct histological pictures were seen (Fig. 3). Seven patients had low turnover osteoporosis, with decreases in bone resorption surfaces and indices of bone formation (percent osteoid surfaces, percent osteoid area, and tissue-based bone formation), and their mineralization lag time was prolonged (Table 1 and Fig. 3). In two of these seven men the daily rate of bone formation was so low that no bone surfaces took up both tetracycline labels. The other two patients had normal to high turnover osteoporosis with high normal percent resorption surfaces and osteoid surfaces, elevated percent osteoblastic surfaces, and a normal rate of bone formation (Table 1 and Fig. 3). Both groups of patients had wide osteoid seams.

Discussion

In this study we have demonstrated that gonadal steroid replacement is associated with increases in bone density in men with hypogonadism due to isolated GnRH deficiency and that the effect of testosterone replacement on bone density is related to the initial degree of bone maturation. In men who initially had open epiphyses, both cortical and trabecular bone density increased. During androgen replacement in men who initially had fused epiphyses, only cortical bone density increased, and this increase was less pronounced than that in the men with open epiphyses. Because increases in bone density were more apparent in the hypogonadotropinemic men with immature bone ages, these results suggest that most of the increase in bone density that occurs during treatment of pubertal hypogonadotropic men reflects the normal process of bone accretion that occurs during sexual maturation (17, 32–34). The failure of trabecular bone density to increase in hypogonadotropic men with mature bones suggests that once trabecular osteoporosis is established in skeletally mature hypogonadotropinemic men, the defect may not be reversible by androgen replacement over the short term. In addition, it is likely that prior androgen therapy limited the increases in bone density in these men.

Several studies have investigated the effects of normalization of gonadal steroids on osteopenia. Restoration of normal gonadal function increases cortical bone mass in both men and women with hyperprolactinemic hypogonadism (5, 35). In women with hypogonadism and bone loss due to the biochemical castration accompanying GnRH analog administration, trabecular bone density returns to normal once ovarian function is rapidly restored (36, 37). Finally, although most studies have demonstrated that estrogen replacement can only arrest further bone loss in postmenopausal women (38), some investigators have demonstrated small increases in bone density during estrogen replacement therapy (39–42).

The reasons why cortical bone density may show a greater response to gonadal steroid replacement than trabecular bone are unclear. Trabecular bone is more sensitive than cortical bone to estrogen deficiency in women (37, 43–46). It is possible that the differential responses of cortical and trabecular bone to androgen replacement in men with fused epiphyses reflect a difference in the time that peak bone mass is reached; peak trabecular bone density normally occurs by age 16–18 yr (17), whereas peak cortical bone density is not achieved until early adulthood (4, 16, 47). Our inability to detect changes in trabecular bone density in men with fused epiphyses may also reflect differences in the precision of bone density measurements, because our trabecular bone density technique is less precise than our technique for measuring cortical bone density. Further studies are needed to distinguish among these possible explanations.

Prior studies have produced conflicting data concern-
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FIG. 3. Light micrographs stained with Toluidine blue (left) and tetracycline fluorescence studies (right) of bone biopsies in a GnRH-deficient man with low turnover osteoporosis (A and B) and a GnRH-deficient man with the less common normal to high turnover osteoporosis (C and D). The arrows in A indicate the inactive bone surface. No tetracycline uptake is visible in B. Active bone turnover is indicated in C by the presence of two osteoclasts within a Howship's lacunae and a row of osteoblasts making osteoid. Tetracycline labels in D are indicated by the arrows. OS, Osteoid; OB, osteoblasts; OCL, osteoclasts; HL, Howship's lacunae; Tr, trabecular bone; BM, normal bone marrow.

...ing the effects of androgen administration on bone histomorphometry in hypogonadal men. Some investigators have suggested that testosterone replacement is associated with an increase in bone formation (11, 12), while others have suggested that testosterone replacement decreases the rate of bone formation (13). Most of our patients had low turnover osteoporosis at a time when they had been eugonadal for at least 1 yr, although bone turnover was normal or increased in two men. The prolonged mineralization lag time and increased osteoid seam width both suggest a concomitant mineralization defect. Our data suggest that the osteoporosis of men with IHH can result from a variety of defects in bone metabolism, although, as suggested previously (4), a defect in bone formation appears to be the most common abnormality. Because the bone biopsies were performed when the patients were eugonadal, it is possible that the bone histomorphometry was altered by androgen replacement. The reason for the mineralization defect and the different histological types of osteoporosis in these men is unclear and warrants further study.

Although bone density increased during gonadal steroid replacement, it failed to reach normal adult levels in these men over 1–3 yr of treatment. This finding may be due to the defect in bone formation in treated patients demonstrated by the bone histomorphometry. The failure of bone density to reach normal adult levels may also indicate that normal bone development requires an interplay among several different factors, only one of which has been replaced by our therapy; that puberty must occur at the appropriate time in order to achieve a normal adult bone mass; or that a more prolonged period of androgen replacement is needed.

Other investigators have also demonstrated that bone density is diminished in patients who undergo abnormal puberty. For example, cortical bone mineral content is decreased in boys with delayed puberty (32), and scoliosis and stress fractures are common in ballet dancers with delayed menarche (48). Similarly, cortical bone density is decreased in men with Klinefelter's syndrome (7, 8) and in women with Turner's syndrome, even when comparing the patients with bone age-matched controls (49). These findings are all consistent with the hypothesis that adolescent gonadal steroid deficiency causes a defect in bone development. However, because IHH, Klinefelter's syndrome, and Turner's syndrome are genetic or congenital disorders that can be associated with other somatic defects, we cannot exclude the possibility that such patients have an independent predisposition for osteoporosis.

A limitation of the present study deserves mention. Because treatment is indicated in young men with hypogonadism to stimulate pubertal development and maintain normal sexual function, an untreated control group was not included for comparison. In a cross-sectional analysis of normal adult men, cortical bone density increased slightly until age 25 yr (4, 16, 47). However, since osteopenia occurs in men who acquired hypogonadism in adult life (1, 5), bone density would be expected to decrease in adult men with untreated hypogonadism. Therefore, we feel that the increase in cortical bone density observed in our men with mature bones is related to their androgen therapy. In a cross-sectional analysis of normal adolescent boys, cortical bone density in-
increased dramatically between the ages of 16 and 18 yr (16), as it did in our patients with open epiphyses whose bone age before therapy averaged 16.1 ± 0.4 yr. This observation suggests that the increase in bone density in our men with immature bones may well reflect the completion of the normal process of pubertal bone accretion.

We conclude that bone density increases during gonadal steroid replacement in men with GnRH deficiency, although cortical and trabecular bone may have different responses to androgen replacement. Cortical bone density increases regardless of the degree of bone maturation, while trabecular bone density increases only in men who have open epiphyses. Histomorphometric analyses of bone during therapy suggest that the osteopenia of hypogonadotropic men is usually due to a persistent defect in bone formation, although some men have normal or increased bone turnover. These data underscore the importance of early diagnosis and consistent replacement with gonadal steroids in hypogonadal men to maximize their peak bone density and thereby decrease their risk of future fractures. Further studies are required to determine whether cortical bone density can be normalized by more prolonged therapy and if the osteoporosis of hypogonadotropic men can be entirely prevented if treatment is begun early.

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