Original Article

Effect of various drug treatments on bone density in hypogonadal men

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ABSTRACT

***Objective*:** To evaluate bone mass in hypogonadal men who received testosterone, alendronate, calcium and vitamin D for one year.

Methodology: In this clinical trial 44 hypogonadal men were evaluated. For diagnosing of hypogonadism, serum LH, FSH, and testosterone levels of the patients were assessed using RIA method. Bone mineral density (BMD) was measured using dual energy x-ray absorptiometery (DXA) in lumbar spine (L2-L4) and femoral neck before treatment. All patients received 250 mg IM testosterone enanthate every 15-20 days. Patients with T score<-1.5 received 70 mg oral Alendronate weekly, testosterone, 1gr elemental calcium and 400 U vitamin D daily. Patients with -1.5<T score<-1 received calcium and vitamin D supplementation and testosterone. After one year of treatment Bone mineral density was measured again. Results were compared with pretreatment BMD and the healthy age and sex matched control group. Serum testosterone level was measured again during the treatment.

Results: Forty four patients aged 18-57 years were included in this study. 25 of them completed the course of study after one year. The mean serum testosterone level was 0.5±0.5 ng/ml before the treatment. After one year, it increased to 5.5±3 ng/ml (PV=0.01). The mean bone mineral density in lumbar spine was 0.97±0.22 g/cm^2 which differed significantly from the control group at baseline (1.017±0.12g/cm^2) (PV=0.006). After one year, the mean BMD increased to 1.09±0.22g/cm^2 (PV= 0.02), which showed no statistical significant difference with the control group (PV=0.13). The mean baseline BMD in femoral neck was 0.88±0.12 g/cm^2, which showed no significant difference with the control group (0.92±0.10 g/cm^2) (PV=0.45), the mean T score before treatment showed significant difference with the control group (PV=0.00). Bone mineral density in femoral neck increased to 0.97±0.13 g/cm^2 after one year (PV=0.01). The mean annual change of BMD in lumbar spine and femoral neck was 12±8.4% and 10±7.2% respectively during one year treatment. Annual change of BMD showed no significant difference in all types of hypogonadism after one year (PV=0.34). There was no significant correlation between age and BMD level before treatment, BMD increment was higher in younger patients after treatment (PV=0.04).

Conclusion: The results show that one year administrating testosterone, alendronate, calcium and vitamin D in hypogonadal men can increase BMD significantly in lumbar spine and femoral neck.

KEY WORDS: Hypogonadism, Bone mineral density, Testosterone, Osteopenia, Alendronate.

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INTRODUCTION

Hypogonadism is one of the major risk factors for male osteopenia and osteoporosis. Few studies have evaluated the long term effect of testosterone on bone mineral density and their

results are difficult to interpret.[1] Anabolic effects of testosterone are essential to protect bone mineral density in men.[2] One of the major complications of hypogonadism is the decrease of bone mass. Even trivial hypogonadism resulting from suboptimal testosterone substitution may cause decreased bone mineralization and consequently bone fractures.[3-5]

Testosterone affects many organs. Some of these effects such as sexual determination is time-dependent and irrevocable, but other effects including effect on bones, muscular mass, hematopoiesis, prostate, energy and sexual activity are reproducible. Studies have shown that men with deficiency testosterone have decreased bone mineral density.[6-8] However, administrating testosterone increases BMD.[9] Some studies have shown the advantageous effect of testosterone on bone mass.[9,10] Still, some other does not consider IM injection of testosterone effective in the treatment of hypogonadal men because it does not copy the physiologic secretion of testosterone; instead, they suggest skin administration (Trans scrotal) as a more appropriate treatment.[2] Today, administrating alendronate is common in the treatment of osteopenia and osteoporosis.[9]

Alendronate is used as first line therapy of osteoporosis in hypogonadal or eugonadal men. Alendronate increase bone density and reduces vertebral fracture measured using a semiquantitive method in eugonadal or hypogonadal men with osteoporosis.[11] Shimon et al showed that adding alendronate to testosterone in osteoprotic hypogonadal men can increase BMD more than testosterone alone.[12] Different treatment duration and various techniques of measuring of BMD cause different response of the effects of testosterone on bone mass.[3] Various studies have evaluated therapeutic effect of testosterone on bone mass in hypogonadal men.[9,13,14] Despite the increase of 3.4-7 percent in bone mass, some studies have claimed that testosterone substitution therapy can not increase the bone mineral density to the normal range.[15] So, in this study we evaluated the effect of treatment with testosterone, alendronate, calcium and vitamin D on bone mass in hypogonadal men.

METHODOLOGY

All men with hypogonadism (in any age range) referred to the Golestan hospital endocrinology clinic were included in the study after confirmation of hypogonadism clinically and by hormonal examinations (serum level of LH, FSH, testosterone, prolactine, free T4, TSH, cortisole were measured in fasting state. Low serum testosterone with low or normal serum LH and FSH were diagnosed as isolated hypogonadism. If other Pituitary hormone were also decreased the patient were categorized as panhypopituitarism. Low serum testosterone with high serum LH and FSH were diagnosed as primary hypogonadism.

Serum testosterone level was measured using RIA method and by Immunotec kit (made in France). Patients with previous history of diseases or consumption of drugs resulting in osteopeni were excluded from the study. Bone mineral density in lumbar spine and femoral neck was measured with LUNAR-DPX device (made in USA) using DXA method. All patients received 250mg testosterone intra-muscularly every 15-20 days. In addition, 70 mg oral Alendronate weekly, 1g elemental calcium daily and 400 IU vitamin D daily were administrated for the patients with T score<-1.5. Patients with T score between -1 and -1.5 received only calcium and vitamin D with above mentioned doses. Bone mineral density was measured after one year, and the results were compared with healthy age and sex matched control group. The control group included 25 healthy age matched men without any previous diseases or drug consumption having effect of BMD. This study was approved by Ahvaz Jundishapur University of Medical Sciences Ethics Committee. The results were analyzed using the statistical software SPSS version 13. Wilcoxon paired T test was used in this study. $P<0.05$ considered significant.

RESULTS

In this study 44 patients (age between 18-57 years) were included. Twenty five patients' completed one year treatment and fallow up. The mean age of patient and control group was 33.7±16 and 34.9±11 respectively which showed no statistical significant difference (PV=0.16). Patients were divided in to three groups according to the causes of hypogonadism: three patients with primary hypogonadism (12%), 15 patients with secondary hypogonadism (64%) and seven patients with pan-hypopituitarism) (24%).

At the base line, the mean BMD of patients in lumbar spine (L2-L4) was 0.97±0.22 g/cm² and the mean T score=-2.4, while in control group it was 1.017±0.12 g/cm² and T score=-0.7 respectively, and there was statistical significant differences between them (PV=0.006 and PV=0.00) respectively. The mean bone mineral density in femoral neck was 0.88±0.16 g/cm² and in control group was

0.92±0.10 g/cm² which showed no statistical significant difference (PV=0.45). The mean T.score in femoral neck and control group was -1.4 and -0.9 respectively that showed significant difference (PV=0.00) (Table-I) and (Fig.1).

In the different type of hypogonadism (primary, isolated secondary, and pan-hypopituitarism) the mean BMD in lumbar spine and femoral neck did not show any significant differences (PV=0.26), (P=0.37) respectively. There was no significant difference in mean serum testosterone level in different types of hypogonadism (PV=0.15). The mean BMD and T score and Z score of controls and patients in lumbar spine and femoral neck before and one year after treatment has been shown in Table-I. After treatment, the mean BMD in lumbar spine increased significantly (PV=0.02), and had no significant difference with the control group (PV=0.13). Also, the mean T score in L2-L4 increased significantly (PV=0.00) and did not differ significantly with the control group (PV=0.28).). The mean BMD in femoral neck increased significantly after one year treatment (PV=0.01). The mean BMD in femoral neck, showed no difference with the control group after one year (PV=0.4). The mean T.score in femoral neck was measured before treatment which showed significant difference with the control group (PV=0.00). Mean femoral neck T score had no significant difference with the control group at the end of the first year (PV=0.38) (Table-I). The mean annual changes of BMD in lumbar spine and femoral neck was 12±8.4 and 10±7.2 percent respectively during one year treatment. There was a reverse statistical significant correlation between the age and annual changes of BMD in lumbar spine (PV=0.02), while no statistical significant correlation was observed between the age and annual changes of BMD in femoral neck (PV=0.09). There was no significant differences in the mean annual change of BMD in lumbar spine and femoral neck in different type of hypogonadism (PV=0.46 and P=0.57 respectively).

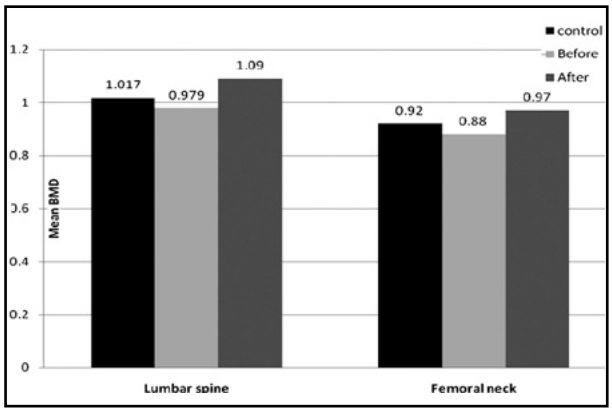

Fig.1: Comparison of the mean BMD in lumbar spine (L2-L4) and femoral neck with the control group before treatment and one year after treatment.

No significant correlation was found between the age and the mean BMD in lumbar spine and femoral neck before treatment (PV=0.22 and PV=0.05 respectively). One year after treatment, the mean BMD in lumbar spine and femoral neck showed a reverse significant correlation with the patients´ age. The increment of BMD in lumbar spine and femoral neck was higher in younger people (PV=0.03 and PV=0.01 respectively). The mean serum testosterone level was 0.5±0.5 ng/ml before treatment of hypogonadal men, and it increased to 5.5±3 ng/ml after one year treatment with testosterone enanthate (PV=0.00). There was no statistical significant correlation between different serum testosterone level (in normal range) and the mean BMD in lumbar spine and femoral neck after the treatment (PV=0.40, PV=0.21 respectively).

DISSCUSSION

The results of this study show that bone mineral density is decreased in hypogonadal men, (specially

Table-I: Comparison of the mean BMD, T score and Z score of the control group and patients before and after treatment.

Area of bone	*Spine(L2-L4)*			*Femoral neck*		
Studied group	*T score*	*Z score*	*BMD(g/cm2)*	*T score*	*Z score*	*BMD(g/cm2)*
Control	-0.72	-0.74	1.017	-0.95	-0.4	0.92
Before treatment	-2.46	-2.3	0.979	-1.42	-1.2	0.88
After one Year	-1.3	-1.1	1.09	-1	-0.50	0.97
PV*	0.00	0.00	0.006	0.00	0.00	0.45
PV**	0.00	0.00	0.02	0.00	0.00	0.01

T score: Bone mineral density in comparison with young person with the same race, and gender.
Z score: Bone mineral density in comparison with person with the same age, race, and gender.
PV*: Statistical difference between controls and patients before treatment.
PV**: Statistical difference in patients BMD before and after one year treatment.

Table-II: Comparison of annul changes percentage of BMD in different studies.

Variable Study	*No. of patients*	*Length of study(year)*	*Type of treatment*	*Treatment (year)*	*Changes % in L2-L4*	*Changes % in femoral neck*
Snyder1999	18	3	Trans scrotal Testosterone	2	7.7	4
Katznelson1996	36	1.5	IM testosterone enanthate	1.5	5	-
De rosa2001	20	6	IM testosterone enanthate	1	6.4	-
Deveogelaer1992	16	1	IM testosterone enanthate	1	5.9	-
Behre1997	72	16	IM testosterone enanthate	1	7.1	-
Shimon 2005	22	1	IM testosterone enanthate, Alendronate,	1	8.4	1.9
Present study	25	1	IM testosterone enanthate, Alendronate, calcium, Vit D	1	12.4	9.5

in lumbar spine) and administrating testosterone, alendronate, calcium and vitamin D during one year results in significant increase in serum testosterone level and BMD in the patients so that after one year treatment their BMD are comparable to healthy age matched controls. Although the mean T score in femoral neck was significantly lower than the control group, in untreated patients the bone mineral density in this area did not differ significantly with the control group (0.88±0.12 g/cm² in the patients versus 0.92±0.10 g/cm² in control group) (Table-I). In this study, the cause of hypogonadism did not affect the mean BMD in lumbar spine and femoral neck before and after treatment.

In a study by Katsnelson et al after evaluating 29 men with secondary hypogonadism, (7 men with primary hypogonadism and 44 healthy men as control group), they found that in both types of hypogonadism the lumbar spine BMD was significantly lower than control group.[9] However, De Rosa et al by studying 12 patients with secondary hypogonadism and 8 with primary hypogonadism, found that in secondary hypogonadism the lumbar spine BMD was severely lower than the control group, but femoral neck BMD was the same as control group. In another study in primary hypogonadism, the lumbar spine and femoral neck BMD showed no difference with the control group.[15] In a study by Schubert et al, men with secondary hypogonadism showed lower bone mass in comparison with the primary hypogonadism.[16] These differences may results from the difference in the number of samples, patients' age, race and the different techniques for measuring BMD.

Serum testosterone level is low in different types of hypogonadism and there was no significant difference between serum testosterone levels in various types of hypogonadism. Also, in this study, no significant correlation was observed between patients age at the time of diagnosing hypogonadism and BMD in lumbar spine and femoral neck (PV=0.28). Behre and Katznelson in their study confirmed these results.[14,15] Serum testosterone level increases significantly with the testosterone therapy and reaches to the normal range. The present study showed that the rise of serum testosterone level to normal range is enough to attain therapeutic results of BMD and higher testosterone level (in normal range) have not any significant beneficial effect on BMD. Besides, more increase in serum testosterone level may increase treatment side-effects.

This study showed that the BMD in hypogonadal men is low in lumbar spine. With testosterone substitution therapy and if necessary Alendronate, calcium and vitamin D for one year, the BMD increased and was comparable with control group (PV=0.13). So, treatment for one year seems to be enough to increase patients' BMD to the normal range.

The present study shows that the BMD in femoral neck of hypogonadal men had no significant difference with the young healthy controls (PV=0.45).[16] This is confirmed in other studies too and may be due to the lower effect of hypogonadism in men on the BMD of femoral neck.[9,14] The mean T score in femoral neck was significantly lower than the control group (-1.4 versus -0.9) (PV=0.00). The bone BMD in femoral neck increased significantly after one year treatment[10] (PV=0.01) and it showed no difference with control group.

De Rosa et al. studied 20 hypogonadal patients and, reported that the BMD in the spine was severely lower than control group, and after replacement therapy with muscular injection of 250 mg testosterone enanthate every 3 weeks for 76 months the BMD increases significantly and after one year it reached to the bone mass of control group. Femoral neck is not evaluated in this study.[15] In the study by Katznelson et al, the bone mass in

the spine was lower than control group, and after replacement therapy with 100 mg testosterone enanthate every week for 18 months, the bone mass in the spine increased 5% and was comparable to the bone mass of control group.[9]

Behre et al in a study found that after substitution therapy with 250 mg muscular testosterone every 4 weeks for 16 years, the bone mineral density in the spine rises and was comparable to control group after one year.[14] In other studies with injective testosterone for 18 months the bone mineral density in lumbar spine and femoral neck increased 3.4-7 percent (Table-II).[2,9,13,15,17] With comparison of different studies in Table-II, we conclude that bone mineral density in lumbar spine can reach to the normal range by muscular injection of 250 mg testosterone enanthate with or without Alendronate, calcium and vitamin D. However, in the present study adding Alendronate, calcium and vitamin D to the testosterone resulted in more increase of BMD in this area (3.4-7 percent in other studies versus 12.4 percent in this study).

Shimon et al compared Alendronate with placebo in osteoporosis hypogonadal men treated with testosterone they found 8.4% increment of lumbar spine BMD in alendronate (3.3% in placebo group P<0.005). Rise of BMD in femoral neck was 1.9% versus 1.4% in Alendronate and placebo group (P<0.005).[12] According to Shimon et al and our study it seems that the treatment of hypogonadal patients with testosterone and adding Alendronate, calcium and vitamin D can improve the annual rise of BMD. Nevertheless, to prove this effect it is necessary to do a long term prospective study in hypogonadal men treated with testosterone with or without Alendronate and Calcium and Vitamin D comparing them with normal population.

CONCLUSION

The results of this study show that one year administrating testosterone, Alendronate, calcium and vitamin D in hypogonadal men can increase BMD significantly in lumbar spine and femoral neck and they are comparable with healthy controls after one year treatment. The response to treatment in all types of hypogonadism is similar. Younger patients show more rise of BMD after treatment.

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