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Idiopathic Male Osteoporosis and Growth Hormone Deficiency

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Growth hormone is essential in normal bone growth and maintenance of bone metabolism. In the setting of childhood onset growth hormone deficiency, osteoporosis is inevitable without replacement therapy. Growth hormone demonstrates its function over bone in direct and indirect ways. Osteoporosis is usually overlooked in men, and many cases are defined as idiopathic after clinical examinations and laboratory tests. We aimed to demonstrate whether some cases of idiopathic male osteoporosis might actually be the result of adult onset growth hormone deficiency and we used L-dopa stimulation for growth hormone as this test is a safe and simple one to perform.

Age matched (51.2 ± 5.64 vs 54.71 ± 6.55) 17 osteoporotic and 25 healthy control subjects were enrolled in the study. Bone mineral density measurements were done at both lumbar vertebrae and femoral hip. Each subject passed through a series of clinical examinations and full laboratory study. Those subjects having no metabolic bone disease or diseases known to affect bone metabolism were included in the study.

After the basal growth hormone measurements, stimulation test with L-dopa was performed for each subject and patient. Although basal levels were not different, the difference between stimulated hormone levels was statistically significant (2.85 ± 0.5 vs 5.68 ± 1.1, $p<0.05$).

Our results imply that some cases of idiopathic male osteoporosis could actually be a result of adult onset growth hormone deficiency and L-dopa stimulation of growth hormone is a safe alternative to insulin stimulation test for this purpose.

Key words: Male osteoporosis, growth hormone deficiency, L-dopa stimulation

Introduction

Bone and mineral metabolism is regulated by intricate interplay between systemic hormones and locally produced factors such as growth factors, cytokines and prostaglandins exerting autocrine and paracrine actions on the bone cells or their precursors. Fine tuning of this complex system ensures normal bone growth and preservation of functional integrity of the adult skeleton. Growth hormone plays a major role in postnatal longitudinal bone growth due to its ability to stimulate precursor cells in the epiphyseal cartilage (1, 2). The hormone, however, also affects bone remodeling in adults (3). Despite its clear effects on bone resorption, no studies have yet demonstrated direct effects of GH on osteoclast in vitro. In animals as well as humans GH stimulates hepatic synthesis of IGF-1. Several studies have, however, also demonstrated that GH stimulates osteoblastic synthesis of IGFs. In human osteoblastic cultures, under GH stimulation, bone cells seem only to produce IGF-2 (4). Both IGF-1 and IGF-2 stimulate osteoblastic proliferation and differentiation (5). GH thus seems to exert both direct and indirect IGF mediated actions on human osteoblasts. In studies concerning osteoporosis of elderly patients, it was shown that growth hormone

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deficiency might be responsible for the pathology (6). Adults with childhood-onset growth hormone deficiency (GHD) and younger adults with adult-onset GHD have a reduced bone mineral content (BMC) (7) and men with vertebral fractures may be more deficient in growth hormone and insulin-like growth factor-I (8).

Male osteoporosis is mostly neglected by physicians as a public health problem. The lifetime risk of any fracture of the hip, spine or distal forearm in men aged 50 years has been estimated to be 13%, compared with 40% in women (9). Epidemiologic studies, also, revealed that about 30% of all hip fractures (10) and 20% of vertebral fractures (11) occur in men. Although the overall incidence of osteoporosis is less in men than in women, the disease still represents an important public health problem. In particular, hip fractures are associated with substantial mortality and morbidity, even more so than in women (12).

In male patients presenting with osteoporotic fractures, major causes of skeletal fragility, such as hypogonadism, glucocorticoid excess, primary hyperparathyroidism and alcohol abuse, can often be identified. In as many as 50% of osteoporotic men, however, no etiologic factor can be found: these men suffer from a syndrome commonly referred to as idiopathic osteoporosis, which is presumably related to some type of osteoblast dysfunction. In western countries, a third of osteoporotic men have idiopathic disease (13). Recent evidence indicates that the loss of skeletal integrity in men may be partially related to endocrine deficiencies, including vitamin D, androgen and/or oestrogen deficiency and growth hormone deficiency.

The aim of our study was to test the hypothesis that osteoporosis of the adult males may be related to deficiencies in skeletal mechanisms that are mediated by growth hormone and to diagnose the growth hormone deficiency and whether we might be able to lower the number of the cases accepted as idiopathic.

Patients and Methods

Age matched (46.2 ± 4.64 vs 48.71 ± 5,65; p: 0.48) seventeen osteoporotic and 25 healthy adult men, as control subjects, were allocated in to the study. As the criteria of osteoporosis, a T score less than -2.5 SD was accepted. To diminish the effect of ageing on the bone density, patients and subjects were chosen from the middle age groups. There was no statistically significant difference concerning body mass index (25.3 ± 0.54 vs 26.35 ± 0.75; p: 0.26). No patient had a history of thyroid dysfunction, glucocorticoid and anticonvulsant use, diabetes mellitus, Cushing's disease, Paget's disease, gastrointestinal disease, gastrointestinal surgery, malignancy, or any other known metabolic bone disease. Subjects were not consuming alcohol or cigarettes. There was no history of childhood GH deficiency, delayed puberty, pituitary disease or deficiency. Also 24-hour urine calcium and phosphorus excretion, serum calcium, phosphorus, bone alkaline phosphatase, total protein and albumin, liver function tests, parathyroid hormone, 25-hydroxyvitamin D, free and total testosterone and LH, FSH and thyroid function tests were performed in the Biochemistry and Endocrinology laboratories of the Medical faculty of Ege University. All of these laboratory results were within normal ranges. Bone mineral densities of the lumbar spine and femoral neck were measured by dual energy X ray absorpsiometry (Hologic QDR 4500 A). Growth hormone measurements were performed in blood samples, both basal and stimulated by L-Dopa. Five hundred mg L-dopa was given to each subject per oral after an overnight fast and blood samples were drawn at 0, 60, 120 and 180 minutes and the highest peak during this time perod was regarded as the maximum response (14). The only side effect encountered during the test was nausea. Growth hormone was measured by the chemiluminescence method (DPC Diagnostic Products Corporation Inc, Los Angeles, CA 90034, USA.).

Statistics

Independent-Samples T test was used for the analysis of the difference between groups. Results are reported as the mean ± SEM.

Results

There was significant statistical difference between the two groups regarding mean lumbar vertebral bone densities (Table 1).

Growth hormone levels were measured at 0., 1st, 2nd and 3rd hours after stimulation with L-Dopa.

There was no difference at basal levels, but statistically significant differences were obtained after the stimulation (Table 2).

Two patients in the osteoporotic group (2/17; 11.7%) had values of stimulated growth hormone level below 0.05 µg/L, meanwhile this number in the normal density group was 2/25 (8%). In the osteoporotic group five subjects responded to stimulus with a growth hormone level below 5 µg/L; and in the normal density group four subjects responded below this value.

Table 1. Statistical differences between bone mineral densities of control and osteoporotic patients.

Area of measurement	MeanBone Mineral Densities g/cm		P
	Osteoporotic group	Control group	
L1	0.765 ± 0.035	0.945 ± 0.026	p< 0.05
L2	0.820 ± 0.039	0.999 ± 0.028	p< 0.01
L3	0.801 ± 0.032	1.014 ± 0.026	p< 0.01
L4	0.827 ± 0.021	1.013 ± 0.026	p< 0.01
Femoral hip	0.708 ± 0.023	0.830 ± 0.024	p< 0.05
Trochanter	0.647 ± 0.025	0.749 ± 0.020	p< 0.01
Ward's triangle	0.505 ± 0.024	0.687 ± 0.030	p< 0.01

Table 2. Statistical analysis of mean differences of basal and maximally stimulated growth hormone values.

	Number	Basal GH µg/L	Stimulated GH µg/l
Osteoporotic group	17	0.40 ± 0.21	2.85 + 0.5
Control group	25	0.48 ± 0.14	5.68 ± 1.1
p value		0.88	< 0.05

Discussion

Several hormones are needed for normal bone growth but GH is the only hormone that in a dose dependent way stimulates longitudinal bone growth. Hypophysectomy has marked effects on longitudinal bone growth and the histological features of the growth plate, and these effects can be reversed by GH substitution therapy (15). From experience in patients with acromegaly, it is known that cortical bone mass is increased and trabecular bone mass is normal. However, bone mineral content and bone area are increased leading to a higher biomechanical competence of bone as shown in rats (16).

Growth hormone replacement therapy has found a place in cases of osteoporosis where deficiency is demonstrated (7, 17). However as the symptoms of growth hormone deficiency are subtle, many cases remain undiagnosed. No universally accepted criteria have yet been adopted for the diagnosis of growth hormone deficiency in adults. Most of the time, growth hormone levels are not detectable without stimulation. A range of stimulation tests have been developed over the past decades, primarily for the evaluation of growth hormone secretion in short statured children. A group of these tests are named "screening" tests such as, L-dopa stimulation test and exercise test. Other tests such as insuline-induced hypoglycemia and arginine test are called "definitive" tests. Similar tests are performed to diagnose growth hormone deficiency in adults. The diagnostic value of a more recently developed procedure, measurement of IGF-1, was found to be limited by the large overlap in values between normal and GH deficient subjects even after age stratification (19). Although the insulin tolerance test to induce hypoglycemia is preferred as the gold standard test for detecting growth hormone deficiency, this test needs multiple blood samples, and is potentially dangerous, requiring regular monitoring of patients in a specialized investigation unit. For these reasons we preferred to use L- dopa test as it is simpler and safer to perform as a first line test.

GH responsiveness declines with age so that the diagnostic criteria used to define GH deficiency differ between adults and children. The accuracy of a single test in positively predicting growth hormone deficiency at a cut-off level of 6 ng/ml is 81% (20). The published studies, in the aggregate, favor 5 ng/ml as a responsible value for a stimulated criterion in men less than 50 years old (14). In this study, we chose a cut-off value of 5 ng/ml of growth hormone.

Kurland et al. reported normal growth hormone secretory reserve in 14 men with idiopathic osteoporosis but reduced IGF–1 levels (20). In their study, GH secretion was stimulated by intravenous arginine infusion over 30 minutes followed 1 hour later by oral L-dopa. All their patients responded to at least one stimulus with the majority responding to both, but 5 patients (35%) responded either to

arginine or to L-dopa but not to both. They suggested other regulators that control IGF-1 production such as gonadal steroids, dehydroepiandrostenedion, IL-1 or platelet-derived growth factor for the IGF-1 deficiency in idiopathic osteoporotic men.

On the contrary to Kurland's study, we have demonstrated that osteoporotic men have less provoked levels of growth hormone compared to non-osteoporotic subjects. We carefully evaluated each patient for possible etiologies of osteoporosis, and could not establish any of these. Thus these men would be diagnosed to have idiopathic osteoporosis. However this study clearly demonstrates that fewer patients than control subjects respond to the stimulation test with levels of growth hormone more than 5 μg/L, and the statistical difference is significant when patient and control groups' results are compared. We also checked those subjects with a low response for other pituitary disorders, but there was none.

Our findings correlate well with the literature showing that in the setting of growth hormone deficiency osteoporosis develops. The results demonstrate that previously unrecognized cases of growth hormone deficiency may be the etiologic factor of idiopathic male osteoporosis. Depending upon our findings, we may suggest that stimulation tests for growth hormone be included amongst the routine tests for diagnosis of idiopathic male osteoporosis. For this purpose L-dopa stimulation is a safe and practical first line test not requiring frequent blood sampling. If the deficiency of the growth hormone is suggested by L-Dopa stimulation, other tests such as IGF-1 measurement and insulin tolerance test, could be performed to support the diagnosis.

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