HYPERPROLACTINEMIA IN ELDERLY PATIENTS WITH OSTEOPOROSIS

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ABSTRACT

INTRODUCTION: Reduced bone mineral density is a universal problem of modern society. Hyperprolactinemia was found to be associated with reduced bone mineral density and hence the interest developed to determine this hormone in elderly.

AIMS AND OBJECTIVE: To study the levels of serum prolactin and other bone markers in elderly patients with osteoporosis.

MATERIALS AND METHODS: Elderly male and female patients who were screened for osteoporosis were selected for the study. They were grouped into two groups. Apparently normal elderly subjects without osteoporosis were grouped as controls. Elderly patients who were diagnosed with osteoporosis were grouped as cases. A value for BMD > 2.5 SD lower than the young adult mean was diagnosed as osteoporosis based on ultrasound of os calcis. Blood samples were collected from them and serum calcium, serum phosphorus, serum alkaline phosphatase and serum prolactin were estimated.

STATISTICAL ANALYSIS: The statistical significance of the study parameters were obtained from the corresponding p-value, which was arrived at using the student's t test. The correlation of serum prolactin with the other parameters of the study was arrived at using the Karl Pearson correlation coefficient.

RESULTS: The samples were analyzed and their mean values determined. The mean levels of the analysed biochemical parameters were 10.08 ± 6.82 ng/ml for serum prolactin, 9.71 ± 0.731 mg/dl for serum calcium, 3.91 ± 0.459 mg/dl for serum phosphorus, 10.17 ± 14.69 IU/L for serum alkaline phosphatase and -0.2 ± 0.77 for bone mineral density from apparently healthy elderly individuals and were considered as reference range for the study. It was found that serum prolactin levels were elevated above the reference range in patients with osteoporosis. (p value .001) Serum calcium and serum phosphorus were reduced below the reference range. Serum alkaline phosphatase was increased above the reference range.

CONCLUSION: Serum prolactin levels were elevated above the reference range in elderly patients with osteoporosis (p value < .001).

KEYWORDS: Osteoporosis, Serum prolactin, Hyperprolactinemia, Bone mineral density.

INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural increase in bone fragility that renders bone more susceptible to fracture. It is a major healthcare problem in India with an estimated 50% of healthy females and 30% of men over 50 years having low bone mass. It is preventable and treatable and there are no warning signs until fracture occurs. Osteoporosis is defined as 'bone mineral density less than 2.5 standard deviations below mean peak value in young adults'.

Approximately 99% of the body's calcium is contained in bone. The concentration of calcium, phosphate and magnesium in plasma are dependent on the net effect of bone mineral deposition and resorption, intestinal absorption and renal excretion. Parathyroid hormone

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(PTH) and calcitriol are the principle factors regulating these processes.\(^1\)

Bone Mineral Density (BMD) is the amount of mineralised bone tissue in a given area, usually calculated as gms/cm^2. It is a measure of bone density which is the amount of bone tissue in a certain volume of bone and it reflects the amount of calcium in bones. Bone mass is increased by physical exercise, intake of calcium during childhood and puberty. Bone mass is reduced by late menarche, early menopause, nulliparity, caffeine ingestion, cigarette smoking, alcohol use, immobilisation and insufficient dietary intake of calcium, phosphate and Vitamin D\(^2\). BMD decrease with age when the fracture risk raises rapidly.\(^3\-^4\) There is a decrease in mineral to matrix ratio in osteoporotic tissue.\(^5\) When BMD is reduced, depending upon the degree of reduction it is either known as osteopenia or osteoporosis.

Over a 10 year period 18% of 65 year old women with osteoporosis will experience a fracture, increasing to 33% among those with BMD more than four standard deviations below the peak mean. The life time hip fracture risk for 50 year old women is nearly 15%.\(^6\)

The hallmark of osteoporosis is reduction in skeletal mass caused by an imbalance between bone resorption and bone formation. Loss of gonadal function and aging are the important factors that contribute to the development of osteoporosis. Several hypotheses regarding the pathogenesis of osteoporosis are available but the basic multi cellular unit theory put forward by Holick MF, kvane SM, Frost HM has been gaining wide acceptance\(^7\).

Systemic hormones that influence the skeleton, including estrogen and parathyroid hormone which alter the production of local factors e.g. cytokines, prostaglandins and growth factors. Gonadal hormone deficiency is the cause for highest incidence of osteoporosis in post menopausal women, young women with low estrogen level and in hypogonadal men.\(^8\-^10\)

Low estrogen levels are associated with vertebral fractures in men.\(^11\) Similarly androgen deficiency may be important in women. Increase in PTH levels which increases with age, is found to accelerate bone loss.\(^12\-^13\) The increase of the hormone is probably due to decreased dietary intake of and impaired intestinal absorption of calcium, often associated with vitamin D deficiency.\(^14\) Estrogen deficiency may also play a role in the increase of PTH.\(^15\) Production of IL-1, TNF-α and IL-6 may be increased in estrogen deficient and osteoporotic patients.\(^16\-^18\)

The National Osteoporosis Foundation has recommended prevention of osteoporosis by evaluation for osteoporosis on all postmenopausal women who present with fracture, recommend BMD testing to all women younger than 65 years.\(^19\)

Serum prolactin levels have been found to be increased in patients with osteoporosis.\(^20\) Prolactin is a protein hormone of the anterior pituitary gland that was originally named for its ability to promote lactation in response to the suckling stimulus of hungry young mammals. It is not only synthesized in the pituitary gland but also within in the central nervous system, the immune system, the uterus, and its associated tissues of conception and the mammary gland. Its biological role is not only in reproduction but it also controls a variety of behaviours and even plays a role in homeostasis. Prolactin releasing stimuli are nursing stimulus, light, audition, olfaction and stress. Dopamine of hypothalamic origin provides inhibitory control over the secretion of prolactin.\(^21\)

Hyperprolactinemia may be due to hypoestrogenism, calcium mobilization from bone, prolactin receptors in the bone and prolactin dependent increase in parathyroid hormone related peptide level. Bone markers like serum calcium, serum phosphorus, serum alkaline phosphatase and serum prolactin were estimated in patients who were at high risk for developing fracture. Hyperprolactinemia is associated with reduced BMD.\(^22\) It is the most common hypothalamic pituitary disorder encountered in clinical endocrinology. The precise means by which estrogen deficiency causes increase bone turnover is not known, possible mechanism includes a direct effect on osteoblasts via estrogen receptors. Estrogen reduces calcium and phosphorus excretion. Estrogen deficiency accelerates the bone turnover. Deficiency during puberty can impair the attainment of normal peak bone density there by making women vulnerable to skeletal fracture.
BMD was studied in hyperprolactinemic women and compared with normal subjects. The mean BMD in gm/cm² in hyperprolactinemic women was 9% less than is normal subjects. Negative correlation was found between BMD and the duration of hyperprolactinemia.

AIMS AND OBJECTIVES
1. To estimate the levels of serum calcium, serum phosphorus, serum alkaline phosphatase, serum prolactin in cases and controls.

2. To get a reference range for the above blood parameters for the study and find if they correlate with the bone density.

MATERIALS AND METHODS
Elderly individuals both male and females who were apparently healthy were selected for the study. Patients who were diagnosed with diabetes mellitus, chronic renal failure, liver disease or those who were on drugs for other ailments were excluded from the study. Patients who were screened for osteoporosis were grouped into two groups. Apparently normal elderly subjects without osteoporosis were grouped as controls. Elderly patients who were diagnosed with osteoporosis were grouped as cases.

Blood samples were collected from 120 elderly patients after obtaining informed consent from them. Diagnosis of osteoporosis was based on ultrasound of os calcis and a value for BMD > 2.5 SD lower than the young adult mean.

BMD was estimated using ultra sound of os calcis and based on T score patients were diagnosed as having osteoporosis. [Table-1]

Table-1 Diagnostic Categories Of Osteoporosis Based On Measurement

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>A value for BMD or BMC ≥ ISD of the young adult reference mean</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>A value for BMD or BMC &gt; ISD and &lt; 2.5 SD lower than the young adult mean</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>A value for BMD or BMC &gt; 2.5 SD lower than the young adult mean</td>
</tr>
<tr>
<td>Severe Osteoporosis</td>
<td>A value for BMD or BMC &gt; 2.5 SD lower than theyoung adult mean in the presence of one or more fragility fractures</td>
</tr>
</tbody>
</table>

A short burst of ultrasound is passed through the heel, the frequency varying from 200 to 1000 KHz. The amplitude spectrum is compared with that from water alone to give a plot of attenuation in the os calcis against frequency, and the slope of the linear portion of this graph is taken to characterise the bone. This is advantageous when compared to dual energy x-ray absorptiometry and quantitative computed tomography examinations which require more space and investment.

The calcaneum has many advantages for the assessment of osteoporosis. First of all it is very easy to access. It is a weight bearing bone like the neck of the femur and the vertebral bodies. It is approximately 90% trabecular bone. The posterior half of the bone has parallel surfaces on the medial and lateral aspects and hence the passage of ultrasound waves is most unhindered and best suitable for BMD measurements.

T SCORE:
It measures, the deviation of the subjects BMD value from the mean BMD for young adult population, in units of the population standard deviation (SD). Blood samples were analysed for serum calcium, serum phosphorus, serum alkaline phosphatase and serum prolactin. Serum prolactin was estimated by enzyme linked immunosorbant assay method using pathozone prolactin of OD 427 of omega diagnostics. Serum calcium was estimated by Arsenazo method. Serum phosphorus and serum alkaline phosphatase were estimated by commercially available Erba kits.

STATISTICAL ANALYSIS:
The statistical analysis was performed for the present study using 'statistical package for social science (SPSS). Significance of the study parameters were obtained from the corresponding p-value, which was arrived at using the student's -t test. p values of < 0.05 were considered statistically significant. The correlation of serum prolactin with the other parameters of the study namely s.calcium, s.phosphorus, s.alkaline phosphatase were arrived at using the Karl Pearson correlation coefficient.[Table-2]
Table - 2 Karl Pearson's Correlation Coefficient

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>Correlation of S.Prolactin with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S.Calcium mg/dL</td>
</tr>
<tr>
<td>Overall</td>
<td>r value</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>r value</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>r value</td>
</tr>
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<td></td>
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</tr>
</tbody>
</table>

r value interpretation

0.0-0.2 poor correlation
0.4-0.6 moderate correlation
0.2-0.4 fair correlation
0.6-0.8 substantial correlation
0.8-1.0 very good correlation

RESULTS

The results obtained from the above study were analyzed. Table - 3 shows the mean and standard deviation of the biochemical parameters namely serum prolactin, serum calcium, serum phosphorus, serum alkaline phosphatase and BMD in the two groups of study. Comparison of mean and SD of controls and osteoporotic group shows a highly significant p value (0.001) for s.alkaline phosphatase, s.prolactin and BMD.

Table 3. Comparison Of Mean And SD Of Control Vs Osteoporosis

<table>
<thead>
<tr>
<th>Group</th>
<th>S.Calcium (mg/dL)</th>
<th>S.Phosphorus (mg/dL)</th>
<th>S.Alkaline phosphatase (IU/L)</th>
<th>S.Prolactin (mg/ml)</th>
<th>BMD (gm/cm^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Mean 9.71</td>
<td>3.91</td>
<td>101.71</td>
<td>10.08</td>
<td>-0.20</td>
</tr>
<tr>
<td></td>
<td>SD + 0.731</td>
<td>0.459</td>
<td>14.69</td>
<td>6.82</td>
<td>0.77</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Mean 9.10</td>
<td>3.80</td>
<td>115.73</td>
<td>20.75</td>
<td>-2.71</td>
</tr>
<tr>
<td></td>
<td>SD + 0.559</td>
<td>0.415</td>
<td>14.49</td>
<td>7.00</td>
<td>0.19</td>
</tr>
<tr>
<td>p value</td>
<td>0.09</td>
<td>0.23</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>NS</td>
<td>HS</td>
<td>HS</td>
<td>NS</td>
</tr>
</tbody>
</table>

DISCUSSION

Reduced bone mineral density is a universal problem of modern society. Osteopenia and osteoporosis are the two different grades of the condition with the density being much more reduced in osteoporosis. Osteoporosis is now considered as a major health care problem in India and is a silent risk factor for fracture just as hypertension is for ‘stroke’. By the year 2050, osteoporosis is likely to be a major demographic factor due to changes in the life style and the increase in the survival rate of the elderly.

Hyperprolactinemia was found to be commonly associated with reduced bone mineral density. Bone mass determination is done only with the help of DEXA Scan (Dual Energy X-ray Absorptiometry). As hyperprolactinemia was found to be associated with osteoporosis, determination of serum prolactin, a hormone of the anterior pituitary gland, can be a useful assessment in the determination of reduced BMD. Hence the interest developed to determine this hormone in the elderly who are ‘high risk’ individuals prone to develop osteopenia and osteoporosis and the ensuring complication ‘fracture’.

Analysis of the results showed the reference range 10.08 ± 6.82ng/ml for serum prolactin, 9.71 ± 0.731mg/dl for serum calcium, 3.91 ± 0.459mg/dl for serum phosphorus, 101.71 ± 14.69IU/L for serum alkaline phosphatase and -0.2 ± 0.77 for BMD from apparently normal elderly individuals and were considered as valid reference range.

When the levels of biochemical parameters in osteoporosis were compared with controls highly significant increase of serum alkaline phosphatase (p value: 0.001) and serum prolactin (p value 0.001) were observed against a highly significant decrease in BMD (p value 0.001). BMD with T score of -2.7 SD obtained in the study of osteoporotic group satisfies the T’ score norms.

The significant decrease of serum calcium observed in the osteoporotic elders is due to impairment in calcium absorption and reduced renal conservation. Lowering of serum calcium level will trigger the parathyroid to secrete more parathormone where by the level of calcium will be restored. The effect of PTH on bone to maintain calcium homeostasis by resorption of bone calcium leads to a decrease in BMD leading to osteoporosis. In the elderly it has been reviewed that there is a rise in serum prolactin at the rate of 5.3% per year due to loss of hypothalamic pituitary regulatory function that occurs with aging. The increase in prolactin level has been ascribed to an age-related decline in dopamine, the neurotransmitter responsible for inhibition of prolactin secretion. [24] [Figure -1]
Increase in osteoclastic activity is the cause for increase in serum alkaline phosphatase, decline in dopamine in the elders is the cause for hyperprolactinemia. Hyperprolactinemia in osteoporosis correlates with the finding of Anne Kilbanski, & Neer, R that the metabolic manifestations of hyperprolactinemia is reduced BMD. As per Kilbanski & Rosenthal DL prolactin causes calcium mobilisation through calcium receptors which is responsible for osteoporosis.

CONCLUSION
From the above study reference range for the biochemical parameters were established. The cut off level of serum prolactin to determine osteoporosis is 11g/ml. Serum prolactin level was increased above the reference range in osteoporosis significantly (p value: 0.001).

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