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Determination of Serum Procollagen I N-Terminal Peptide in Iraqi Postmenopausal Women with Osteoporotic Vertebral Fractures

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Abstract: *This study measures serum Procollagen I N-Terminal Peptide (PINP) levels in normal weight, overweight and obese postmenopausal women with osteoporotic vertebral fractures and compare these levels with body mass index matched controls. Eighty (80) postmenopausal women were included in this study with age range (50-77 years). Subjects were divided into two groups: Group A: forty four (44) women with osteoporotic vertebral fractures (Patients), and group B: thirty six (36) women without osteoporosis and without vertebral fractures (serve as controls). patients and controls also divided into three subgroups according to their body mass index(BMI) (normal weight, overweight and obese women). There are significant increase in mean value of serum PINP levels in normal weight, overweight and obese patients as compared with BMI matched controls (P=0.0001) with no significant differences between subgroups for both patients (P=0.401) and controls (P=0.814). In conclusion serum PINP levels highly increased in patients as compared with controls independently of BMI of both patients and controls, thus elevating serum PINP levels can be regarded as a risk factor for rapid bone loss.*

Keywords - *Body mass index, Primary osteoporosis, Procollagen I N- Terminal Peptide, Vertebral fracture.*

I. Introduction

Osteoporosis (OP) is a major health problem worldwide. It is defined as a chronic disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk [1].

Vertebral Fracture (VF) is very common and is the most frequent osteoporotic fracture [2]. Its consequences can be grouped into three categories: pain, physical changes and impairment and psychosocial declines [3]. VF are often asymptomatic and the correct diagnosis requires lateral radiographs of both the thoracic and lumbar spine. The most commonly vertebral fractures site involves the mid thoracic region (T7–T8) and the thoracolumbar junction (T12–L1) these locations correspond to the most mechanically compromised regions of the spine [4,5].

Collagens are quantitatively the most abundant protein in mammals, representing 25% of the total. Type I collagen is the main protein of bone matrix (>90% matrix content). It is synthesized in osteoblast as a precursor of Procollagen I that contains N- and C-terminal extended domains, these are cleared from the rest of the molecule by specific extracellular tissue protease before its incorporation into the collagen fibrils [6]. Byproducts of type I collagen synthesis are the amino- and carboxy-terminal Procollagen I extension peptides (PINP and PICP) [7].

Both extension peptide cleared by liver and incorporated in to bone matrix [8]. PINP concentration in the serum is proportional to the bone mineralization process and synthesis of bone matrix [9] and measurement of PINP appear to be more sensitive marker of bone formation rate in osteoporosis [10], the PINP concentration is directly proportional to the amount of new collagen laid down during bone formation [11].

II. Subject And Methods

Eighty (80) postmenopausal women were included in this study with age range (50-77 years). All women were attended to Osteoporosis outpatient clinic in Al- Yarmouk Teaching Hospital. Subjects were divided into two groups: Group A: forty four (44) women with osteoporotic vertebral fractures (Patients), patients also divided into three subgroups according to their body mass index (BMI) (1) Fifteen (15) normal weight women (2) seventeen (17) overweight women (3) twelve (12) obese women and group B: thirty six (36) women without primary osteoporosis and without vertebral fractures (serve as controls). Controls also divided into three subgroup (1) Eight (8) normal weight women (2) Twelve (12) overweight women (3) Sixteen (16) obese women. BMI was calculated as weight in kilograms per square meter [weight/ (height)^2], women were considered normal weight at BMI (18.5-24.9 kg/m^2), overweight women (25-29.9 kg/m^2) and obese women at (BMI >30kg/m^2) [12].

Complete case history was taken from each women and lateral X- ray of the thoracic and lumbar spine were taken for all women of both groups which scored according to kleerkoper method for diagnosis of vertebral fracture [13]. Also Patients diagnosed as primary osteoporosis and controls as normal by measuring bone mineral density (BMD) by Dual energy X-ray absorptiometry (DXA) according to World Health Organization (WHO) diagnostic guidelines:

- T-score -1.0 or greater is "normal".
- T-score between -1.0 and -2.5 is "osteopenia".
- T-score -2.5 or below is "osteoporosis" [14].

Serum investigations included calcium, phosphorous and alkaline phosphatase measured by spectrophotometer, all these parameters were normal in controls and patients with primary osteoporosis to distinguish osteoporosis from other metabolic bone disease such as (Osteomalacia and Paget disease). In addition PINP measured by enzyme linked immuno sorbent assay (ELISA).

All women were not drink alcohol, nonsmoker, had no diseases known to affect bone metabolism such as (endocrine disorders including hyperparathyroidism, thyrotoxicosis and diabetes mellitus, gastrointestinal tract diseases including ulcerative colitis, celiac disease and inflammatory bowel disease, liver diseases, renal disease, hematologic disorders including multiple myeloma, mastocytosis, lymphoma and leukemia, inherited disorders including osteogenesis imperfecta, Marfan´s syndrome, hemochromatosis, rheumatoid arthritis and ankylosing spondylitis. Also they were not taking any drug known to affect bone turnover such as (Steroid therapy, thyroxine, heparin, barbiturates, phenytoin and Thiazolidinediones).

III. Statistical Analysis

Data were analyzed using computer facility of SPSS-18 (Statistical Package for Social Science – version 18). The results were expressed as numbers, percentage, range and mean ± SD (standard deviation). Significance of difference was assessed using Student-t test for two independent means or ANOVA (Analysis of variance) for more than two independent means.

IV. Results

There is significant increase in mean value of age in patients as compared with controls, while no significant change in mean value of serum calcium, phosphorus and alkaline phosphatase between patients and controls as shown in **Table 1**. Also there is no significant difference in mean value of BMI between patients and controls **Table 2**. In addition there is significant increase in mean value of serum Procollagen I N-Terminal Peptide levels in patients as compared with BMI matched controls with no significant differences between subgroups for both patients and controls as shown in **Table 3** and **Fig. (1)**.

Table (1): Mean value of age, serum calcium, phosphorus and alkaline phosphatase for patients and controls.

Parameters	Patients n=44		Controls n=44		P value
	Mean±SD	Range	Mean±SD	Range	
Age (years)	62.77±7.40	(50-77)	58.92±4.84	(50-67)	0.009*(S)
Serum Calcium Normal (2.1-2.6 mmol/L)	2.15±0.13	(2.0-2.4)	2.21±0.15	(2.0-2.5)	0.109 (NS)
Serum Phosphorus Normal (0.8-1.6 mmol/L)	1.13±0.17	(0.9-1.4)	1.16±0.17	(0.9-1.5)	0.526 (NS)
Serum Alkaline phosphatase Normal (21-92 U/L)	66.55±13.79	(40.0-88.0)	65.56±14.01	(38.0-88.0)	0.752 (NS)

S= significant, NS= non-significant.

Table (2): Classification of patients and controls according to body mass index.

BMI (Kg/m²)	Patients		Controls		P value
	No	%	No	%	
Normal (18.5-24.9)	15	34.1	8	22.2	0.388(NS)
Overweight (25-29.9)	17	38.6	12	33.3	
Obese (=>30)	12	27.3	16	44.4	
Mean±SD (Range)	27.48±5.23	(20.0-40.2)	29.00±4.70	(20.3-40.4)	0.179 (NS)

NS= non-significant.

Table (3): Mean value of Serum Procollagen I -N-Terminal Peptide according to body mass index.

BMI (Kg/m^2)	Serum Procollagen I -N-Terminal Peptide (PINP) (ng/ml)		
	Patients (Mean±SD)	Controls (Mean±SD)	P value
Normal (18.5-24.9)	53.91±4.43	42.80±4.65	0.0001*(S)
Overweight (25-29.9)	55.06±4.47	43.81±2.90	0.0001*(S)
Obese (=>30)	56.94±4.58	44.39±3.84	0.0001*(S)
P value using ANOVA	0.401(NS)	0.814 (NS)	

S= significant, NS= non-significant.

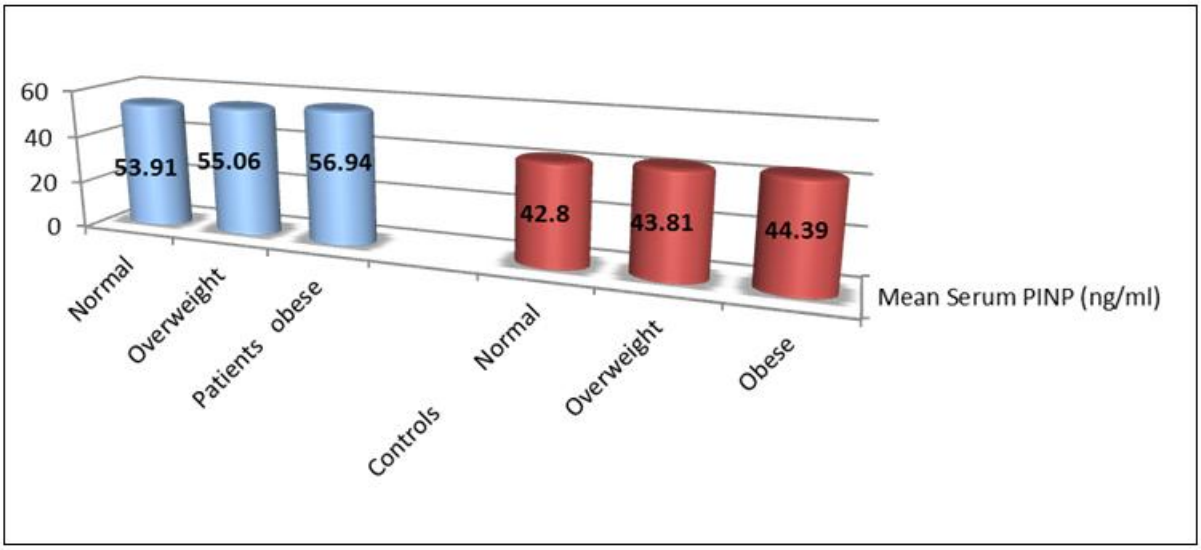

Fig. (1): Serum Procollagen I -N-Terminal Peptide levels of patients and controls according to body mass index.

V. Discussion

Human aging is associated with a progressive decline in bone mass and an increased susceptibility for fracture. Age-related bone loss is consequence of changes in hormones as well as bone cell number and function [15]. Moreover, with aging there is cellular changes in the bone microenvironment include changes in the mobility and differentiation of mesenchymal stem cells, with subsequent alterations in bone cellularity [16].

In addition, Prevalence of osteoporotic vertebral compression fractures increases with age. In older women with vertebral fractures the cortical shell of a vertebral body contributes only about 10% of the resistance to compressive loads. Thinning and microcracks in trabecular bone occur with age, excess accumulation of microcracks results in critical weakening which in turn leads to vertebral compression and to fracture [17].

Biochemical markers represent the molecules directly connected to both the structure and function of bone tissue. PINP is a marker of early bone formation, generally appearing during osteoblast proliferation and produced during the formation of type I collagen. It representing an indicator of mineralization process and bone matrix formation [9].

The data of this study demonstrated that serum Procollagen I N-Terminal Peptide (PINP) levels were significantly higher in normal weight, over weight and obese postmenopausal women with vertebral osteoporotic fractures as compared with that BMI matched controls. Several studies support these results which found that high bone turnover and low bone mass in women with postmenopausal osteoporosis reflect an increase in the number of active bone remodeling units, with elevated osteoclast activity within each unit [18]. As a result, products of osteoblast and osteoclast measured as biochemical markers in serum and urine were elevated [19, 20].

Martinez et al. found that PINP levels in postmenopausal women with OP were significantly higher than controls [21].

In OFELY study (prospective cohort study) found a significant association between increased baseline levels of serum PINP, Osteocalcin (OC) and bone alkaline phosphatase (B-ALP) and the risk of fractures [22].

In addition **Garnero P et al** suggested that high levels of bone formation markers are associated with a greater bone loss [11]. **Stepan JJ** noted that markers of bone metabolism reflect the whole-body rates of bone formation and resorption and may therefore reliably predict the imbalance in bone turnover and the rate of bone loss [23].

Ingle BM and coworkers concluded that bone turnover can change after a fracture because of immobilization, callus formation and/or frequent regional activation of bone turnover [24].

VI. Conclusion

There are significant increase in serum PINP levels of normal weight, overweight and obese postmenopausal women with osteoporotic VF as compared with BMI matched controls independently of BMI of both patients and controls, thus elevating serum PINP levels can be regarded as a risk factor for rapid bone loss.

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