Journal of Advances in Medicine and Medical Research

32(11): 72-79, 2020; Article no.JAMMR.59148
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Comparison of Serum Level of Bone Resorption Markers with Bone Densitometry in Elderly Individuals in Port Harcourt, Rivers State

Kiyesi Adekemi[1*], Ehimen Phyllis Odum[2] and Victor Chukwuma Wakwe[2]

[1]Department of Chemical Pathology, Faculty of Basic Clinical Sciences, College of Medicine, Afe Babalola University, Ado-Ekiti, Ekiti State, Nigeria.
[2]Department of Chemical Pathology, Faculty of Basic Clinical Sciences, College of Health Sciences, University of Port Harcourt, Rivers State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. Author KA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors EPO and VCW assisted in designing and supervising the work, made inputs in the manuscript and modification of the study. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2020/v32i1130535
Editor(s):
(1) Dr. Anthony Olasinde, Federal Medical Centre Owo, Nigeria.
Reviewers:
(1) Deepti Gupta, India.
(2) Hisaya Tanioka, Japan.
Complete Peer review History: http://www.sdiarticle4.com/review-history/59148

Original Research Article

Received 10 May 2020
Accepted 15 July 2020
Published 27 July 2020

ABSTRACT

Introduction: This study concentrated on serum bone markers, N and C- telopeptide and tartrate resistant acid phosphatase (TRAP), and their concentrations were evaluated in the serum of elderly participants and compared with that of the young of the same gender. Markers for bone resorption are proteins, and they are mainly measured in the urine and serum, where they serve to assess bone turnover.
Methodology: A cross-sectional prospective study conducted at the orthopaedic and Family Medicine Departments of the University of Port Harcourt Teaching Hospital, a public tertiary healthcare facility located in Choba and Alakahia communities of Obio/Akpor Local Government Areas of Rivers state, Nigeria, among elderly patients aged 60 years and above.
Results: Considering the age of the test population, all the females were post-menopausal and no statistical difference was observed in relation to the results for gender in the study. Also, the

**Corresponding author: E-mail: kiyesiadekemi@gmail.com;*

plasma creatinine, calcium and albumin results of both controls and participants were within normal reference range. The study was necessitated by the fact that, in the environment of the study (Port Harcourt), elderly individuals frequently complain of bone pain, thus, the serum levels of the aforementioned bone resorption markers (N and C telopeptide and tartrate resistant acid phosphatase) was estimated among these elderly individuals, with the view that its outcome can help physicians to initiate protocols that will prevent the consequences of increased bone resorption, intervenes before bone becomes fragile and aid the prediction of osteoporosis.
Conclusion: This study was able to establish that the serum levels of NTX, CTX and TRAP were increased in elderly participants above the age of sixty years than controls.

Keywords: Bone markers; plasma creatinine; bone densitometry; metabolism.

1. INTRODUCTION

With increasing ageing population in both developed and developing countries, bone and mineral metabolism disorders are becoming relevant to everyday medical practice [1,2]. The process of ageing is peculiar to every clime, both developing and developed [3] and occurs when a country's median age rises and shifts the distribution of its population towards older age [4]. International anthropological studies conducted in the 1970's and published in the 1980's have clearly defined the basis for defining old age, which puts it into chronological, changes in social role and changes in capabilities respectively, with change in social role being the predominant characteristic and beginning at the age of 60 years, and this cut off adopted by most developing countries [5].

Some discrepancies have however ensued regarding this definition for elderly individuals, with most developed countries pegging theirs at 65 years [4,6], and the United Nations having no standard numerical criterion but for the adoption of the 60 years benchmark [7], though not in African, where old age is associated with retirement from active service. Thus, there is no consensus, at the moment, regarding the global standard for defining old age [8].

Clinically, several methods are employed to assess bone age, such as Tanner White house, Bone Xpert, Greulich, Pyle and X-ray [9,10]. However, it is worthy to note that these methods have their distinctive characteristics, ranging from assessment of skeletal maturity to prediction of adult height. Broadly, assessment of bone age can be used to diagnose growth disorders or failures, rule out congenital adrenal hyperplasia, primary amenorrhea and hypothyroidism [9,10].

It has been observed that bone mass decreases earlier in females than males [11]. In males, a greater propensity of the rate of decrease commences between forty-five and fifty years. James [11] also reported that the percentage of skeletal mass loss is about 1% per year in males, as compared to 2% per year in females. In females, there is also variable loss of bone mass as their age progresses, especially, after menopause, while the fraction of bone mass loss in males is consistent. For instance, from menopause to five years after menopause, the rate is between 2%-3% and 1% afterwards and cumulatively, about 53% of bone mass is lost by the age of 80 years, as compared to the cumulative loss of about 18% in males at that same age [11].

According to Hienz [12], bone resorption is a process in which osteoclasts breakdown bone tissues and release minerals, such as calcium, from the bone tissue to the circulation (blood). These minerals are detected at increased levels in the urine and serum of elderly people, signifying an increase in bone resorption in this age category. This is contrary to what occurs in adolescents (10-19 years), in which the net bone formation exceeds rate of resorption, thus, an increase in the total bone mass, with the peak attained between 15-25 year and equilibrium bone formation and resorption remaining constant for about ten years [13,14]. The constant loss of bone minerals as one grows old, make the bone less dense and more fragile and susceptible to osteoporosis [15]. It is also reported that, in addition to old age, some other factors, which are both intrinsic and extrinsic, contribute to expose bones to a higher likelihood of being fractured [16]. The intrinsic factors have been listed to include genetics, alterations in cellular composition of the bone, hormonal changes, vascular status and biochemical status of the individual [17], while those listed as extrinsic factors include physical activity, nutrition, drugs and co-morbid medical conditions [18]. According to Feng and McDonald [19] and Seibel [2], the hormones that play vital roles in

the remodelling of bones are vitamin D, parathyroid hormone, steroid hormones, growth factors (growth hormone and insulin- like factors) and cytokines (interleukin- 6, interleukin- 1 and tumor necrosis factor). Studies have also shown that pro-inflammatory cytokines are the main cytokines implicated in bone remodelling [20], with hyperproduction observed to aid demineralization of bones [21].

Markers for bone resorption are proteins, and they are mainly measured in the urine and serum, where they serve to assess bone turnover. These markers include N-telopeptide (type-1 collagen), C- telopeptide (type- 1 collagen), pyridinoline cross links, hydroxyproline, bone sialoprotein and tartrate resistant acid phosphatase- 5b [22]. The proteins found in bones include type- 1 collagen, sulphated proteoglycans, acidic glycoproteins and osteocalcin [23]. Studies have shown that there are two kinds of tartrate resistant acid phosphatase (TRAP) in serum, 5a and 5b, but 5b is specific bones while the 5a may have originated from other sources such as activated macrophages and dendritic cells [24]. Also, the 5a subcomponent has been reported to be a sialic acid, while its 5b counterpart is not [25].

In the most recent half decade, the understanding that there is a close relationship between the pathogenesis of osteoporosis and ageing, has elicited the interest of scientists to study the process of bone loss occasioned by ageing [26]. The pathogenesis of bone resorption, which can be observed on the surface of the bone [15], involves the attachment of osteoclasts to the osteon [27,15], which then leads to an infolding of the cell membrane of the osteoclast to produce collagenase and other enzymes [28] and further excavation into the bone and subsequent release of minerals, such as calcium, magnesium, phosphate and collagen into the extracellular fluid [29]. Other than the osteoclasts (bone resorption), other cells found in bone are osteoblasts (bone formation), osteocytes (bone maintenance) and stromal cells [23,15] and each of these have their characteristic functions. Collectively, they undertake the remodelling of bone.

Human bones are composed of 33% organic and 67% inorganic matter. The organic matter comprises of mainly collagen (28%) and non-collagen protein (5%), while the inorganic matter comprises of 57% hydroxyapatite crystals and 10% calcium carbonate [30]. Similarly, the collagen component of bones has mainly type- 1 (95%) and type- V (5%) and the non-collagenous component comprising of osteocalcin, osteopontin, saloprotein and osteonectin.

This study concentrated on serum bone markers, N and C- telopeptide and tartrate resistant acid phosphatatse (TRAP), and their concentrations were evaluated in the serum of elderly participants and compared with that of the young of the same gender. This is based on the fact that bone matrix is mainly composed of collagen, which is responsible for its integrity and strength, and these markers are mostly composed of type-1 collagen. The study was necessitated by the fact that, in the environment of the study (Port Harcourt), elderly individuals frequently complain of bone pain, thus, the serum levels of the aforementioned bone resorption markers (N and C telopeptide and tartrate resistant acid phosphatase) was estimated among these elderly individuals, with the view that its outcome can help physicians to initiate protocols that will prevent the consequences of increased bone resorption, intervenes before bone becomes fragile and aid the prediction of osteoporosis.

2. METHODOLOGY

This cross-sectional prospective study was conducted at the orthopaedic and Family Medicine Departments of the University of Port Harcourt Teaching Hospital, a public tertiary healthcare facility located in Choba and Alakahia communities of Obio/Akpor Local Government Areas of Rivers state, Nigeria. The facility undertakes management of patients, training of health professionals and medical and allied research, while serving as referral medical facility for health facilities within the state and other neighbouring states such as Bayelsa, Imo, Abia and Akwa-Ibom. The participants were healthy elderly individuals of both gender that are 60 years old or above, and presented at the recruitment points in the departments earlier mentioned, while a second group served as controls and were aged 15-25 years old, taking into cognizance the fact that that is when peak bone mass is achieved in individuals and a second group of controls aged 30-45 years old, when bone mass begins to decline in humans [13,14]. A total number of 220 individuals participated (110 test and controls each). Descriptive statistics was employed determine frequencies and mean, while inferential statistics

was used to correlate the parameters, such as ANOVA and Chi-square.

The reagents that were used for the study are human cross-linked N- telopeptide type- 1 collagen, human cross-linked C- telopeptide type- 1 collagen, human tartaric resistant acid phosphatase 5b ELISA and Randox creatinine assay kit for calcium and albumin. Other materials that were used include assay microplate, adhesive strips, microplate reader, water bath, automated microplate washer, absorbent paper towels, deionized/distilled water, pipette and pipette tips, test tubes and cuvettes, graduated cylinders, calibrated micropipettes, centrifuge, spectrophotometer, timer, laboratory coats, sterile gloves, glass pipette filter, waste disposal bin and the instruction manuals from the manufactures of the various reagents. Laboratory methods for conducting the assays, as prescribed by the manufacturers were also strictly adhered to, and when in doubt, the manufacturers were contacted to clarify concerns arising.

3. RESULTS

As previously mentioned, 110 participants and controls were recruited each for the study. The participants age ranged 60-85 years (mean age was 66.6 + 6.6 years). There were 44(40.0%) males and 66(60.05) females. 46(50.6%) had history of hypertension, while 13(14.3%) had co-morbidities of hypertension and diabetes mellitus, but none had history of only diabetes mellitus. Similarly, 78(80.0%) had bone pain but 32(20.0%) did not have.

Considering the age of the test population, all the females were post-menopausal and no statistical difference was observed in relation to the results for gender in the study. Also, the plasma creatinine, calcium and albumin results of both controls and participants were within normal reference range. The serum N- telopeptide was observed to be higher in the participants than control (p= 0.00) and is the same for serum C- telopeptide in participants and controls (p= 0.01).

Table 1. Table of numbers

	Age group (years)		Frequency (n)	Percentage (%)
Controls	1	15 - 25	50	45.5
	2	30 – 45	60	54.5
Participants	60 and above		110	100

Table 2. Serum N–telopeptide in participants and controls

Group	N Tel(ng/L)
Participants	162.1 ± 36.2
Controls (15 – 25 years)	139.6 ± 23.6
Controls (30 – 45 years)	140.6 ± 30.1
Total number of controls	141.5 ± 51.4
p- value of participants and total controls	0.00

Table 3. Serum C- telopeptide in participants and controls

Group	C Tel (ng/L)
Participants	38.1 ± 12.1
Controls (15 – 25 years)	23.4 ± 9.5
Controls (30 – 45 years)	23.9 ± 8.2
Total number of controls	24.1 ± 10.1
p- value of participants and total controls	0.01

Table 4. Comparison between serum levels of TRAP in participants and controls

Group	TRAP (ng/L)
Participants	45.8 ± 19.5
Controls (15 – 25 years)	32.4 ± 12.5
Controls (30 – 45 years)	34.9 ± 18.2
Total number of controls	34.6 ± 11.2
p- value of participants and total controls	0.00

Table 5. Comparison of bone densitometry and serum bone resorption markers using range

T Score	N- telopeptide (ng/L)	C- telopeptide (ng/L)	TRAP (ng/L)
Normal (>-1.0)	117.5 – 139.7	22.9 – 43.3	24.9 – 47.3
Osteopaenia (-1.0 - - 2.5)	139.8 – 142.7	43.4 – 48.2	25.7 – 44.7
Osteoporosis (< -2.5)	>143	>49	>45

61.8% had osteopaenia while 18.2% had osteoporosis

Table 6. Correlation of BMD, C- telopeptide, N -telopeptide and TRAP

Parameters	Subjects (r)	Control (r)
C –telopeptide	0.06	0.02
N –telopeptide	0.02	0.07
Tartrate resistant acid phosphate	0.03	0.05

4. DISCUSSION

This study was conducted among 220 participants, 110 each for test and control respectively, with the test group being between 60-85 years of age while the control were sub-grouped into two, those aged between 15-25 years in group I and corresponding to the peak bone mass attainment, and the others aged between 30-45 years in group II and corresponding to when bone mass begins to decrease [13,14].

The study shows that serum creatinine, calcium and albumin in the test group were within the reference range considered to be normal. This finding is, however, slightly different from what should be, since the average elderly person is envisaged to have a negative calcium balance [31]. The negative calcium balance in the elderly is attributed to severe chronic illnesses, malabsorption syndrome and poor nutritional status that usually accompany ageing [32]. The slight variation can be attributed environment and nature of prevalent foods within different climes.

This study also observed that the comparison of serum N- telopeptide in the participants and controls was higher in the elderly test group than the younger control group. This finding is similar with other previous reports of high levels of N Telopeptide (NTX) in elderly [33,34]. This points to bone resorption, as higher values of NTX in the elderly participants suggest higher loss of bone mineral density.

The serum C Telopeptide (CTX) in this study was found to follow the same pattern between the test and controls, as the levels were also higher in the elderly test group than controls, with the same explanation as for the serum N Telopeptide. Elevated levels of CTX in serum of the elderly participants are a predictor of risk of osteopaenia or osteoporosis, since it indicates depreciation in the BMD. This finding is similar to the study done by Ivaska [35] and the authors predicted that participants with high biomarkers had increased risk of pathological fractures. The finding disagrees with that of Nguyen [36] which showed that CTX was not sufficiently sensitive to predict the rate of change in BMD, but our results revealed that CTX is a sensitive predictor. The difference in the findings between this and that of Nguyen [36] may be due to difference in study regions, as this was conducted in Africa while that of Nguyen was done in Asia.

In the same vein, this study observed that the serum levels of TRAP were higher in the elderly participants than controls. This means that TRAP like NTX and CTX can be used as a good bone marker. Irie [37] in their study done on elderly individuals (294 men and 213 women, aged 73.4± 6.5 years) showed that elevated serum level of TRAP – 5b is independently correlated with decreased BMD in women but not in men. This differs from the result of our study, as our study observed no difference in the level of serum concentration of TRAP -5b in both sexes. Also, several studies have suggested that low bone mineral density is an important determinant of increased bone resorption and can be evaluated using bone markers like NTX, CTX and TRAP [38,39,40]. The finding in this study further agrees with that of Ross and Knowlton [40] in which osteoporotic fracture was monitored elderly post-menopausal women for four years and opined that markers of bone resorption were significant predictors of bone loss rate.

In this study, bone densitometry was done using dual X- ray absorptiometry and the T–score as a reference guide to interpret the bone densitometry. A T- Score of > -1.0 means that

BMD is normal, between -1.0 and -2.5 indicates osteopaenia (mild to moderate bone resorption) and <-2.5 is osteoporosis (severe form of bone resorption that leads to pathological fracture). On this premise, this study observed that 68(61.8%) of the elderly participants were osteopaenic, 20(18.2%) had osteoporosis and 22(20.0%) had normal bone mineral density. Studies of BMD using bone densitometry on proximal femur and proximal radius in a population of elderly individuals showed that BMD was significantly related to age in both gender [41]. This observation agrees with the finding in this study, which showed that highest percentage of the elderly subjects recruited had osteopaenia. A combination of bone densitometry and indices of bone resorption improved fracture risk prediction in elderly individuals [42,43]. In the environment of this study most hospitals do not have equipment to perform dual X–ray absorptiometry, however, they may be able to afford reagents to estimate bone resorption markers.

It has been shown from the results of this study, that reference ranges of the serum markers of bone resorption could be used to estimate BMD. For example, an elderly individual with serum NTX of 120 ng/L will be said to have a normal T –score of > -1.0. A normal T –score means the individual has a normal BMD. On the other hand, an elderly individual with a serum NTX of 145 ng/L will be estimated to have a T -score of < -2.5. Such individual will be said to have osteoporosis. Without having the dual X–ray absorptiometry equipment, the markers could be used to estimate the BMD of elderly individuals. It is however, noteworthy, that combination of resorption markers will improve the diagnostic ability of the bone markers.

Similarly, the correlation of serum NTX and CTX between the test and control participants were statistically significant, 0.00 and 0.01 respectively and is similar for serum levels of NTX and CTX and TRAP, which was also significant at 0.00.

5. CONCLUSION

This study was able to establish that the serum levels of NTX, CTX and TRAP were increased in elderly participants above the age of sixty years than controls. Dual X-ray absorptiometry readings corresponds with suggested values of the serum markers of bone resorption and may be useful for diagnosing BMD of normal, osteopaenia and osteoporosis. The serum markers can also be used to monitor patients on treatment.

6. RECOMMENDATIONS

Findings from this study have public importance owing to the fact that bone pain is a common complaint among the elderly, thus, the study helped to understand that at this age majority have osteopaenia and some already have osteoporosis. Therefore, it is recommended that elderly patients who are likely to have resorption be enlightened on markers of bone resorption, that they can be used to diagnose osteoporosis.

CONSENT

Written and informed consent was obtained from the participants.

ETHICAL APPROVAL

Ethical approval for the study was obtained from the Ethical Committee of the orthopaedic and Family Medicine Departments of the University of Port Harcourt Teaching Hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Lunenfeld B, Stratton P. The clinical consequences of an ageing world and preventive strategies. Best Practice and Research Clinical Obstetrics & Gynaecology. 2013;27(5):643-659.
2. Seibel MJ. Biochemical markers of bone turnover part I: Biochemistry and variability. The clinical biochemist. Reviews of Australian Association of Clinical Biochemists. 2005;26(4):97-122.
3. Cadmus EO, Owoaje ET, Akinyemi OO. Older persons' views and experience of elder abuse in South Western Nigeria: A community-based qualitative survey. Journal of Aging and Health. 2014;27(4):711-729.
4. Juni MH. Ageing population: A public health implication. International Journal of Public Health and Clinical Sciences. 2015;2(3).
5. Glascock AP, Feinmen SL. A holocultural analysis of old age. Comparative Social Research. 1980;3:311-332.

6. Krueger K, Botermann L, Schorr SG, Griese-Mammen N, Laufs U, Schulz M. Age-related medication adherence in patients with chronic heart failure: A systematic literature review. International Journal of Cardiology. 2015;184:728-735.
7. Gesinde AM, Adekeye OA. Counselling services for remediating the biopsychosocial challenges of the aged in Nigeria. Journal of Functional Management. 2011;3(1):89-98.
8. Freitas MC, Queiroz TA, Sousa JA. The meaning of old age and the aging experience in the elderly. Revista da Escola de Enfermagem da USP. 2010;44(2):407-412.
9. Ewa P, Arkaduz G, Sylvia P, Huang HK, Vicente G, Fei C. Computer assisted bone age assessment: Image preprocessing and epiphyseal/metaphyseal ROI extraction. IEEE Transactions on Medical Imaging. 2001;20(8):715-729.
10. Bull RK, Edwards PD, Kempe PM, Fry S, Hughes IA. Bone age assessment: A large scale comparison of Greulich and Pyles and Tanner and Whitehouse methods. Archives of Disease in Childhood. 1999;81(2):172-173.
11. James W. Structure and function of the musculoskeletal system, Second Edition: Physical activity helps reduce bone loss– Human Kinetics; 2011.
Available:www.human kinetics.com
12. Hienz SA, Paliwal S, Ivanovski S. Mechanisms of bone resorption in periodontitis. Journal of Immunology Research. 2015;1-10.
13. Kloss FR, Gassner R. Bone and aging: Effects on the maxillofacial skeleton. Experimental Gerontology. 2006;41:123-129.
14. Teegarden D, Proulx WR, Martin BR, Zhao J, Mc Cabe GP, Lyle KM. Peak bone mass in young women. Journal of Bone Mineral Resources. 1995;10:711-715.
15. Clark B. Normal bone anatomy and physiology. Clinical Journal of the American Society of Nephrology. 2008;3(3):131–139.
16. Ferruci L, Baroni M, Ranchelli A, Laureteni F, Maggio M, Mecocci P, Ruggiero C. Interaction between bone and muscle in older persons with mobility limitations. Current Pharmaceutical Design. 2014;20(19):3178–3179.
17. Demontiero O, Vidal C, Duque G. Aging and bone loss; new insights for the clinician. Therapeutic Advances in Musculoskeletal Diseases. 2012;4(2):61-76.
18. Pereira CL, Vogelaere P, Baptista F. Role of physical activity in the prevention of falls and their consequences in the elderly. European Review of Aging and Physical Activity. 2008;5(1):51-58.
19. Feng X, McDonald JM. Disorders of bone remodeling. Annual Review of Pathology. 2011;6:121-125.
20. Ginaldi L, Di Benedetto MC, De Martinis M. Osteoporosis, inflammation and ageing. Immunity and Ageing. 2005;2(1):1-14.
21. De Martinis M, Franceschi C, Monti D, Ginaldi L. Inflamm-ageing and lifelong antigenic load as major determinants of ageing rate and longevity. FEBS Letters. 2005;579(10):2035-2039.
22. Swaminathan R. Biochemical markers of bone turnover. Clin Chim Acta. 2001;313(1-2):95-105.
23. Florencio-Silva R, Sasso GR, Sasso-Cerri E, Simões MJ, Cerri PS. Biology of bone tissue: Structure, function and factors that influence bone cells. BioMedical Research International. 2015;1-17.
24. Halleen JM, Tiitinen SL, Ylipahkala H, Fagerlund KM, Vaananen HK. Tartrate-resistant acid phosphatase 5b (TRACP 5b) as a marker of bone resorption. Clinical Laboratory. 2006;52(9-10):499-510.
25. Halleen JM, Alatalo SL, Suominen H, Cheng S, Janckila AJ, Väänänen HK. Tartrate-resistant acid phosphatase 5b: A novel serum marker of bone resorption. Journal of Bone and Mineral Research. 2000;15(7):1337-1345.
26. Boskey AL, Coleman R. Ageing and bone. Journal of Dental Research. 2010;89(12):1333- 1348.
27. Van Oers RF, Klein-Nulend J, Bacabac RG. The osteocyte as an orchestrator of bone remodelling: An engineer's perspective. Clinical Reviews in Bone and Mineral Metabolism. 2014;12(1):2-13.
28. Suda T, Takahashi N. Contributions to osteoclast biology from Japan. Proceedings of the Japan Academy. Series B, Physical and Biological Sciences. 2008;84(10):419-438.
29. Moe SM. Disorders involving calcium, phosphorus and magnesium. Primary Care: Clinics in Office Practice. 2008;35(2):215-237.
30. Palacios S, Neyro JL, Ferrer J, Villero J, Redondo E, Caloto MT. N- telopeptide

Study Group. Reduction of urinary levels of N-telopeptide correlates with treatment compliance in women with postmenopausal osteoporosis receiving alendronate. Menopause. 2012;19(1):67-74.
31. Heanery RP, Gallagher J, Johnson C, Neer CC, Parfitt AM, Whedon GD. Calcium nutrition and bone health in the elderly. American Journal of Clinical Nutrition. 1982;36(5):986-1013.
32. Bonjour JP, Kranzelin M, Levasseur R, Warren M. Dairy in adulthood, from foods to nutrient interactions on bone and skeletal muscle health. Journal of Annual College of Nutrition. 2013;32:251–263.
33. Baxter I, Rogers A, Eastell R, Peel N. Evaluation of urinary N- telopeptide of type-1 collagen measurement in the management of osteoporosis in clinical practice. Osteoporosis International. 2012;2:1-2.
34. Scariano JK, Garry PJ, Montoya GD, Duran–Valdez E, Baumgartner RN. Diagnostic efficacy of serum cross linked N-telopeptide and amino terminal procollagen extension propeptide measurements for identifying elderly women with decreased BMD. 2009;237–243.
35. Ivaska KK, Gerdhem P, Väänänen HK, Åkesson K, Obrant KJ. Bone turnover markers and prediction of fracture: A prospective follow-up study of 1040 elderly women for a mean of 9 years. Journal of Bone and Mineral Research. 2010;25(2):393-403.
36. Nguyen TV, Meier C, Jacqueline R, Eismen JA, Seibel MJ. Bone turnover in elderly men, relationships to change in bone mineral density. BMC Musculoskelet Disorder. 2007;8:13.
37. Irie S, Hayashida N, Shikanwa T, Taira Y, Sekitani Y, Seitan T. Suitability of tartrate resistant acid phosphatase type– 5b as a screening marker for bone mineral density in community dwelling elderly individuals. Tohoku Journal of Experimental Medicine. 2011;224:105-110.
38. Mc Clung MR. The relationship between bone mineral density and fracture risk. Current Osteoporosis Rep. 2005;3(2):57-63.
39. Sarka S, Reginster JY, Crans GG, Diez-Perz A, Pinette KV, Delmas PD. Relationship between changes in biochemical markers of bone turnover and BMD to predict vertebral fracture risk. Journal of Bone Mineral Resources. 2004;19(3):394–401.
40. Ross PD, Knowlton W. Rapid bone loss is associated with increased levels of biochemical markers. Journal of Bone Mineral Resources. 1998;13(2):297–302.
41. Hannan MT, Felson DT, Anderson JJ. Bone mineral density in elderly men and women; Results from the Framigham osteoporosis study. Journal of Bone Mineral Resources. 1992;7(5):547-553.
42. Sornay–Rendu E, Munoz F, Granero P, Duboeuf F, Delmas PD. Identification of oteopaenic women at high risk of fracture; The OFELY study. Journal of Bone Mineral Resources. 2005;20(10):1813–1819.
43. Granero P, Hausher E, Chapuy MC, Marcellic A, Grandjean H, Muller C. Markers of bone resorption predict hip fracture in elderly women. The EPIDOS prospective study. Journal of Bone Mineral Resources. 1996;11:1531-1538.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/59148