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Urinary N-telopeptide - A diagnostic Test or A Screening Test?

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ABSTRACT

Dual-energy X-ray absorptiometry (DEXA) scan is the gold standard investigation for diagnosing osteoporosis. The limitations of "gold standard" Dual-energy X-ray absorptiometry scan were many. The aim of this study is to find whether urinary n telopeptide can be used to diagnose osteoporosis — prospective cohort study done at Sri Ramachandra Medical University between August 2014 to December 2018. The study was done amongst the postmenopausal females and older males who came to the University hospital as an inpatient or an outpatient with suspected osteoporosis. We had 110 persons participated in the study. The patients were divided into two groups. Group I was cases whose Dexa scan was osteoporosis/ osteopenia, and Group II was a control that had standard Dexa. The results from Dexa Scan are taken as the gold standard against urinary n telopeptide and a 2x2 table formed. Sensitivity, specificity, positive predictive value, likelihood ratio, area under ROC curve will be calculated. The mean value of urinary N Telopeptide in the case group was 182.5 and in control group was 49.8. The ROC curve was formed and cut off was calculated to be 71. Urinary N telopeptide can very well be considered as a diagnostic test and can't be considered as a gold standard diagnostic test as there is some limitation as it is a bone resorption biomarker having some pre-analytical and biochemical variability which can alter the results. It can be used as an adjuvant and as a screening test along with gold standard Dexa in diagnosing osteoporosis.

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INTRODUCTION

Osteoporosis is one of the preventable health care burdens of our society. It is an asymptomatic disorder unless complicated by fracture. The aetiology of osteoporosis is multifactorial, and the diagnosis is usually delayed. Dual-energy X-ray absorptiometry (DEXA) scan is the gold standard investigation for diagnosing osteoporosis. Advantages of Dexa scan were minimal radiation, wider availability, better precision and its fracture prediction is almost accurate (Cummings *et al.,* 2002). But there are certain limitations like it cannot account for the ongoing bone resorption and it is only a static measurement at a given point of time. Non-assessment of bone geometry and its composition are its major disadvantage. Measurement of depth can't be done using a Dexa scan. Hence skeletal size can't be measured accurately (William *et al.,* 2012). Dexa scan reports can vary on different scan machinery, a location change of machine and between technicians. Direct observation of Dexa scan can give a better result, but it can't always be done. All these factors make Dexa scan a gold standard investigation questionable. The new bone biomarker N-Telopeptide (NTx) is a specific marker of bone resorption and is being used for osteoporosis treatment monitoring (Bettica *et al.,* 92, Bonde *et al.,* 95). The aim of this study is to find whether

urinary n telopeptide can be used to diagnose osteoporosis.

MATERIALS AND METHODS

A prospective cohort study was done at Sri Ramachandra Medical University from August 2014 to December 2018. The study was done amongst the postmenopausal females and older males who came to the University hospital as an inpatient or an outpatient with suspected osteoporosis. The institutional ethics committee approval was obtained prior to the case collection. The Inclusion criteria were a female person age 65 and above, female person age 60 or less with risk factors, postmenopausal young female with one or more risk factors, Male person age 70 and above, Males younger than 50 with risk factors and patients who come within 24 hours following trivial fall fractures. The risk factors were patients having body mass index less than twenty, Asian, sedentary life Style, osteoporosis or fragility fracture history in family members, sustained previous fracture or a recent fragility fracture, prolonged steroid use, more than two to three alcohol drinks per day, early menopause below forty-five years, vitamin D deficiency, depletion of testosterone hormones in male and neurological illness like dementia which makes person prone to fall. The exclusion criteria were persons having any pathological fracture, chronic or acute kidney disease, liver failure, tumour and malignancy, hyperthyroidism or hyperparathyroidism and any drug intact which can affect bone metabolism.

All patients who participated in the study underwent Dexa scan, urinary n telopeptide. Based on the results of DEXA scan patients were divided into cases and control. The sample size was fixed at 43 in each group after consulting statistician. Dexa scan was done using GE healthcare Prodigy pro DEXA machine. Dexa scan for right hip was done for all patients. If the patient is having any fracture or operation done in the right hip, Dexa scan will be done in the left hip or spine [5,6]. The nocturnal and daytime variability and daily variability were the significant factors that can affect the bone biomarkers. The level of bone resorption markers will be elevated during dawn and will be low in the dusk. Hence for our entire patients' Urinary sample was collected for 24 hours from 6 am to next day 6 am in a sterile plastic container. A urine sample was analysed by Elisa technique for urinary n telopeptide level.

We had 110 persons of two groups who took part in the study. Group, I was cases whose Dexa scan was osteoporosis/ osteopenia, and Group II was a control that had normal Dexa. The results from Dexa Scan were taken as the gold standard against urinary n telopeptide and a 2x2 table formed. Sensitivity, specificity, positive predictive value, likelihood ratio, area under ROC curve will be calculated. The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To find the significant difference between the bivariate samples in Independent groups the Unpaired sample t-test was used. In both the above statistical tools the probability value .05 is considered as significant level.

RESULTS

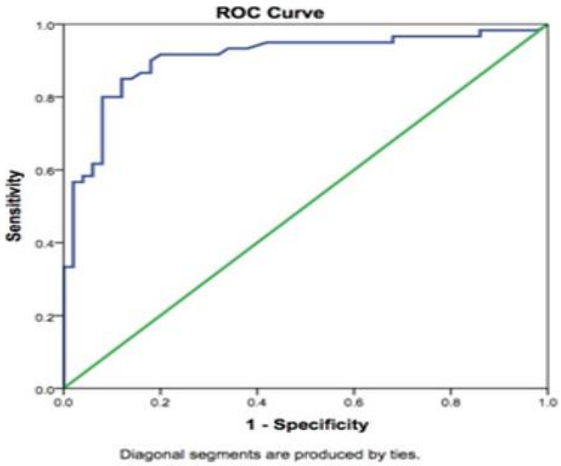

Figure 1: Receiver operating Characteristic curve

We had sixty people who had Dexa scan report either as osteoporosis or osteopenia forming the cases and fifty people who had Dexa scan normal as controls. The mean value of urinary N telopeptide in the cases was 182.5 and in control were 49.8. The receiver operating characteristic curve was formed and cut off was calculated to be 71 as elicited in figure 1. Taking 71 as cutoff the true positive, true negative, false positive and false negative were calculated, and sensitivity of urinary n telopeptide was found to be 85%, specificity 86%, Positive predictive value of 87.93 and negative predictive value of 82.69 and accuracy of 85.50.

DISCUSSIONS

Osteoporosis is a silent killer, which drastically increases the risk of fracture if not detected early and managed appropriately. Dual-energy X-ray absorptiometry (DEXA) scan is the gold standard investigation for diagnosing osteoporosis. However, the limitations of "gold standard" Dual-energy X-ray absorptiometry scan were many. There were many non-invasive investigations like quantitative ultrasound, quantitative CT scan, FRAX questionnaire, serum and urinary biochemical bone turnover markers. Out of all these investigation bone biomarkers were considered superior as it measures ongoing bone resorption that bone was occurring during that

period. Increased bone turnover means increased bone loss, which in turn increases the fracture risk. Bone biochemical resorption markers were the newer investigation, which was highly sensitive, and it is easy for the clinical purpose (Kanis *et al.,* 2001, Kanis 2002). It is imperative that the elderly population needs an unsurpassed tool for the prediction of fracture risk and osteoporosis prevention.

Table 1: Sensitivity and Specificity for 71

Cases	Control	
51	7	58
True Positive	False Positive	Test Positive
9	43	52
False Negative	True Negative	Test Negative
60	50	110

There were certain controllable sources and uncontrollable source of variability associated with biochemical bone markers. The analytical and preanalytical variability should be lower or nill to make a biochemical bone marker superior to other investigations (Biver 2012). Out of all bone turnover markers, urinary n telopeptide had ideal above-set characters making it as one of the important markers that can predict fracture. From Figure 1, the ROC curve the cut of the value of urinary n telopeptide was calculated as 71. Taking 71 as cut off from table 1 urinary n telopeptide sensitivity and specificity were calculated as 85% and 86% respectively. From our study, we can easily delineate normal and osteopenic/osteoporotic patients, as our cut off is 71. Any value more than 71 means osteoporosis/osteopenia while markedly elevated levels (>1.5-2) may indicate the co-existence of alternative bone conditions like osteomalacia.

Osteoporosis detection using Dexa scan alone will be a stumbling block. The bone resorption marker can independently predict the fracture risk. If we consider both Dexa scan and biomarker, then the fracture risk will have increased significantly than considering them alone (Garnero 2000). Bone biomarkers can't be considered as a replacement for Dexa scan instead can be used as an additional tool. If we suspect osteoporosis, it is better to go for urinary n telopeptide, and those who test positive, i.e. more than 71 alone can go for current gold standard DEXA scan. For the betterment of the patient, the amalgamation of these two diagnostic tests Dexa scan and urinary N Telopeptide will identify the person at high risk for fracture. Urinary n telopeptide assessment is being cheaper than DEXA. The cost of a single region DEXA scan is around 2500 rupees while urinary n telopeptide Elisa kit is around 25000 for 100 patients. If urinary n telopeptide test were done more frequently and more in number, the kit could be purchased at a much cheaper rate. Since the test is cheap, it can very well be used as a diagnostic test also.

CONCLUSION

Urinary N telopeptide can very well be considered as a diagnostic test and can't be considered as a gold standard diagnostic test as there is some limitation as it is a bone biomarker having some pre-analytical and biochemical variability which can alter the results. It can be used as an adjuvant and as a screening test along with gold standard Dexa in diagnosing osteoporosis.

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