ORIGINAL ARTICLE

ALKALINE PHOSPHATASE AS A SCREENING TEST FOR OSTEOMALACIA

Muhammad Amin Chinoy, Muhammad Imran Javed*, Alamzeb Khan, Nooruddin Sadruddin*****

Department of Trauma and Orthopaedics, The Indus Hospital, *Baqi Medical University, Karachi, **Ayub Medical College, Abbottabad, ***Imam Clinic, Karachi, Pakistan

Background: Vitamin D deficiency remains common in children and adults in Pakistan despite adequate sunlight exposure. Diagnosis in adults is usually delayed and is made following pathological fractures that result in significant morbidity. The objective of this study was to see whether Serum Alkaline Phosphatase levels could be used as a screening test for osteomalacia. **Methods:** The Study was conducted at Fatima Hospital, Baqai Medical University, Gadap, Karachi, between July 2002 and June 2005. Serum calcium levels are commonly used to screen patients suspected of osteomalacia, and raised serum alkaline phosphatase (SALP) is considered a diagnostic finding. We used SALP to screen patients who presented with back or non-specific aches and pain of more than six months duration. **Results:** Three hundred thirty-four (334) patients were screened of which 116 (35%) had raised SALP. Osteomalacia was diagnosed in 92 (79.3%) of these 116 either by plain radiographs, bone biopsy or isotope bone scan. Fifty-four (53.4%) of the 101 cases had a normal level of serum calcium. **Conclusions:** Osteomalacia is likely to be missed if only serum calcium is used to screen patients. Serum Alkaline Phosphate should be used as the preferred method for screening these patients.

Keywords: Osteomalacia, Metabolic bone disease, Serum Alkaline Phosphatase (SALP), Screening

INTRODUCTION

Osteomalacia (a deficiency of vitamin D or its active metabolite 1,25 Hydroxy Vitamin D_3 in serum) is a common disorder seen in orthopaedic and rheumatology practices in South East Asian region, despite adequate sunshine.[1,2] Vitamin D deficiency and the secondary increase in parathyroid hormone levels result in inadequate mineralization of the osteoid seam. The diagnosis is often delayed, with the majority of patients diagnosed when they present with Looser's zones or pathological fractures. The diagnosis of osteomalacia should be based on a combination of serum levels of calcium, alkaline phosphatase, vitamin D and parathyroid hormone, along with radiological evidence of Looser's zone or pathological fractures.

Most of these patients present with a combination of symptoms including muscular pain, and chest pain, lower back pain and difficulty in getting up and walking. In extreme cases, patients develop a waddling gait. Female patients are frequently anaemic with a history of multiple pregnancies. Many patients live in over-crowded homes that are typically in buildings with no access to fresh air or sunlight. If vitamin D deficiency is suspected in a general physician practice, usually only a serum calcium level is checked. With basic knowledge of physiology, it is quite clear that levels of serum calcium will either be normal or in the lower range of normal in patients with osteomalacia, and these patients will be missed if only serum calcium is used to screen patients.

The vitamin D assay though specific and diagnostic, is expensive and not universally available as is the serum parathyroid test. These are appropriately considered diagnostic tests but are not appropriate for screening purposes. There is ambiguity about the role of Serum Alkaline Phosphatase (SALP) levels and their specificity and sensitivity in the diagnosis of osteomalacia. SALP may be raised in other disorders of bone metabolism as well as in diseases of the liver and biliary tree. This study was done to determine the suitability of SALP as a screening tool for osteomalacia.

MATERIAL AND METHODS

This was a prospective study carried out between July 2002 and June 2005 at Fatima Hospital, Baqai Medical University. We enrolled females 14 years of age or above presenting with back pain[3] or muscular aches and pains of six months or greater duration as well as those with multiple pregnancies with the same symptomatology, who were clinically suspected of osteomalacia. Serum Calcium levels and Serum Alkaline Phosphatase levels were done as well as SGPT and Gamma GT to rule out any Hepatobiliary cause. Radiographs of the pelvis (anterior-posterior view) were also obtained. They are essential for proper diagnosis and we prospectively looked into it at the same time to evaluate if SALP was useful as a screening tool or not, in addition to its established role as a diagnostic modality

All patients were seen by one of the authors and enrolled in the study. Patients who had proven Connective tissue disorders (Including RA, SLE and Ankylosing Spondylitis), patients with Hepato-biliary disorders or those with Hypertension and on medicines were excluded from the study.

Patients who had raised levels of SALP with normal radiographs and normal LFTs were offered trephine bone biopsy[4] from the posterior iliac crest under local anaesthesia which was done by one of the authors. Patients who refused bone biopsies were offered an isotope bone scan.[5] This was done at the Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN). They were given 2 doses of injectable vitamin D_3, to see if there was an improvement in their symptoms, if they refused to have Isotope Bone Scan as well. Data was analysed using SPSS-10.

RESULTS

From July 1999 to June 2002, SALP was checked in 334 female patients. One hundred and sixteen (35%) patients had raised SALP levels. The age distribution of the patients was 14 to 60 years, with mean of 24 years. Duration of the osteomalacia symptoms ranged from 24 weeks to 312 weeks (6 years), with a mean of 87 weeks.

Of the 116 patients with raised SALP levels, 71 (61%) had radiographic evidence of Looser's zone or pathological fracture. Remaining 45 (39%) patients who did not have any radiological evidence of osteomalacia, bone biopsy from the posterior iliac crest was done in 18 and isotope bone scan was done in 8 patients. The remaining 19 patients who refused all sorts of investigations were given 2 doses of injection Vitamin D_3, 600,000 IU.

Fifteen bone biopsies and 5 Isotope bone scans were positive for osteomalacia. Among those who were given Vitamin D_3 injections, 10 patients had marked improvement in their symptoms, 1 patient did not show any improvement in their symptoms, and 8 were lost to follow up. Serum Calcium was found to be normal in 54 (53.4%) in which a confirmed diagnosis of osteomalacia was made.

The Positive Predictive value of a raised Serum Alkaline Phosphatase level was 97.5%. One patient who had a negative bone scan, but with a very high level of SALP (over 9 times the normal), a subsequent biopsy confirmed osteomalacia. Five patients with radiological evidence of osteomalacia had normal or upper limit of normal level of alkaline phosphatase. There were only 5 false negative results, giving a negative predictive value of 4.31% for this investigation.

DISCUSSION

Osteomalacia is a common disorder found in our community. This is despite the fact that we have adequate amount of sunlight, and hence its occurrence should be minimum. However various studies from countries such as India, Saudi Arabia[6], Kuwait[7] and Turkey[8] have shown that even in those countries with similar climatic conditions, osteomalacia seems to be quite common. In some of these studies, the cultural and clothing patterns[9] as well as the use of veil have been implicated in the causation of osteomalacia. Similarly, it is common among the Immigrant population from countries of South-East Asia to countries like UK[10] and Norway and Denmark.

This is especially common in females of child bearing age.[11,12] Previous studies have documented its occurrence in females, who have repeated pregnancies, and those who are living in crowded and congested areas, in multi story buildings with very little exposure to sunlight. Various studies have looked into the amount of body surface area exposed to sunlight, its variants Ultraviolet B and its relationship to skin pigmentation.[13] Turnbull[14] and colleagues showed that pre-Vitamin D_3 effective UV wavelengths in the shade were most significant for tree shade and a shade umbrella, and they also studied conditions of shades in a north facing covered veranda and in a car with windows closed. Studies have also looked into the role of betel and betel nuts as well as the amount of lime on the betel leaves and their subsequent role in osteomalacia and osteoporosis by inactivation of 25 hydroxylase.[15] Through standard fortification of various food stuffs including milk and its products and margarine, osteomalacia has largely been eradicated in developed countries. Ghee and oils are the only foods fortified with vitamin D in Pakistan and their fortification level may not be sufficient to fulfil the vitamin D requirement of the population. All these play an important part as causative agents in the pathogenesis of osteomalacia and its rampant occurrence in our society.

Unfortunately, despite its very common occurrence, diagnosis is often delayed. This is usually due to poor socioeconomic factors initially, when patients present quite late to a physician. These are usually young to middle aged females who have to look after the household, do the cleaning and washing, home shopping, caring for the many children that each of them have, as well as caring for the aged in the family. Sometimes they are also working as housemaids in addition to their other duties, which leave them with very little time to look after themselves or to seek medical advice at an early stage.

When they do finally seek medical advice, initially most of them are treated symptomatically. If any investigation is ordered, it is the Serum Calcium Level, which we have shown in our study to be Normal or low normal in most of the patients. Thus an early diagnostic window is missed, and these patients continue with their aches and pains and muscle weaknesses until they develop pathological fractures and a waddling gait. This hypovitaminosis D myopathy has also been shown in the Danish study comparing veiled Arab women with Danish controls.[16] Most subjects present at this stage with waddling gait. The radiographs become positive at this stage (Looser's zone), though spontaneous bilateral displaced femoral neck fractures have also been

reported.[17] At this stage, biochemical changes are now established.[18]

In this study, we evaluated the role of SALP as a screening marker for osteomalacia, instead of serum calcium level. The non-invasive gold standard test for diagnosis of osteomalacia is the serum levels of 25-hydroxy Vitamin D, but these were not available anywhere in the country at the time of this investigation. Our premise was that, that if there is an early rise in the SALP level, then this could be used as a screening investigation in the very poor and vulnerable segment of the society.

We did have adequate follow-up for most patients in the study, with only 10 patients lost to follow-up, all of whom belonged to the therapeutic arm of the study, i.e., those who had refused to both bone biopsy or bone scan, and were given Injections of Vitamin D. Presumably all of them had improved with therapy and did not bother or have the time and resource for a follow up visit. Even in the worst case scenario, where we presume them to have another diagnosis or disease, this is a small number and compares well with other studies internationally, where the drop out rate is less than 10%.

The major limitation in this study was the minimum amount of biochemical tests that were done. 25-hydroxy Vitamin D levels were not available anywhere in Pakistan when this study was initiated, and even now when they have become available, they are expensive and still only few selected centres are doing it. Similarly serum PTH, serum phosphorus, and urinary calcium and phosphorus levels again were not done in this very poor segment of the society because of lack of resources. Haemoglobin does not have a direct causative effect on osteomalacia, but accompanies it most of the time because of nutritional deficiencies. We did not do Haemoglobin levels, but its association has been demonstrated in various local and international papers.

For a test to be of value as a screening tool, it should fulfil certain criteria. It should be cheap, readily available, non-invasive, have a high sensitivity and specificity and have a high Positive Predictive value and low Negative Predictive value. Serum Alkaline Phosphates levels, as shown in our study fulfils almost all these criteria.

CONCLUSION

Raised Serum Alkaline Phosphates (SALP) is a sensitive screening tool for diagnosis of osteomalacia. We have concluded that this marker be routinely checked in female population at high risk.

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Address for Correspondence:

Dr. Muhammad Amin Chinoy, Professor & Head, Department of Trauma & Orthopaedics, The Indus Hospital, Korangi Crossing, Korangi, Karachi. **Tel:** +92-21-35112711, **Fax:** +92-21-35112717, **Cell:** +92-300-8246750.
Email: dr-chinoy@cyber.net.pk