CARBOXY TERMINAL TELOPEPTIDE – A BONE BIOMARKER

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RESEARCH ARTICLE

CARBOXY TERMINAL TELOPEPTIDE – A BONE BIOMARKER

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ARTICLE INFO

ABSTRACT

Advances in bone cell biology over the past few decades have resulted in several new biochemical markers for the assessment of bone homeostasis. Since traditional diagnostic tools are inherently limited as they assess only the history and not the current status of disease, there arises a need for the development of new diagnostic tests that can detect the presence or the current status of disease, predict the future of disease progression & evaluate the response to therapy thereby improving the clinical management of the patients. CTx is a bone resorption marker produced during osteoclastic bone resorption and detected in urine or serum using ELISA. Serum CTx is a highly specific and sensitive marker of bone resorption that can rapidly indicate a patients response to bisphos phonate therapy.

INTRODUCTION

Biological markers commonly called as biomarkers are objectively measurable biological characteristics that represent the biological state. Biomarkers are defined as " A characteristic that is objectively measured and evaluated as an indicator of normal biological process, pathogenic process or pharmacological responses to a therapeutic intervention". (1998, National Institutes of Health Biomarkers Definitions Working group) (13). These biomarkers play an important role in diagnosis, monitoring and therapy outcomes and drug discovery. Bone biomarkers are enzymes or proteins released during bone remodeling that measure the rate of bone metabolism. Bone biomarkers can be bone formation or resorption markers. Though they cannot establish specific diagnosis, they reflect metabolic abnormalities and help in assessing bone remodeling and monitoring the treatment response in metabolic bone diseases.

Bone Biomarkers

The bone turnover markers can be either formative or resorptive markers(8)

Types of bone biomarkers

Table 1

Bone Formation Markers	Also Known As	Specimen
Alkaline phosphatase (total)	ALP	Serum/Plasma
Alkaline phosphatase (bone specific)	B-ALP	Serum/Plasma
Procollagen type1N propeptide Osteocalcin	P1NP	Serum/Plasma Serum
Bone resorption markers	**Also known as**	**Specimen**
C-Terminal telopeptide of type 1 collagen	CTX Crosslaps	Serum or plasma
N-Terminal telopeptide of type 1 collagen	NTX	Urine , serum
Pyridinium crosslinks: deoxypyridinoline, pyridinoline	DPD, PYD	Urine

CTX Bone Turnover Marker

The Carboxy-terminal telopeptide of type1 collagen commonly referred to as CTX is a specific resorptive bone marker that highly correlates to bone turnover rate. It is readily available for laboratory testing and It measures the presence and concentration of the cross linking peptide sequence of type1 collagen of bone, that is cleaved by osteoclasts during resorption. So its serum levels will be proportional to the osteoclastic activity (9). CTXis measured from serum as sCTX and from urine as uCTX. Compared to NTX serum CTX concentrations are more useful in monitoring osteoporosis and

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other bone diseases. A raised concentration is highly correlated with increased risk of fractures independent of bone mineral density. CTX measurements are also helpful in monitoring the treatment response to drugs like bisphosphonates which are administered as antiresorptive agents in osteoporosis.

More than 90% of the organic matrix of bone comprises of type 1 collagen and osteoclast mediated degradation of this type 1 collagen results in release of CTX. (1)(3). Alpha1 chain C-telopeptide of type 1 collagen releases s CTX that has undergone aging associated peptide chain rearrangement (beta isomerisation) (1). ELISA's is the current s CTX assay that uses antibodies that recognize the aminoacid sequence Glu-Lys-Ala-His-Asp-bGly-Gly-Arg, that is referred as Crosslaps sequence.(1)

Variability of CTX

CTX similar to all bone turn over markers tend to show both biological and analytical variability. Biological variability is an inter & intra individual variation and it follows circadian rhythm. Factors like age, gender, ethnicity, menopausal status, and osteoporotic stage, administration of anti-resorptive agents or calcium supplements influence to attenuate the biological variability (12) but the disparity is diminished with fasting. Similarly CTX is cleared by liver & kidney and thus influenced by diseases affecting these systems (For example a decrease in GFR will decrease the urinary excretion of CTX and therefore increase in serum levels). Similarly inter individual variation show higher metabolic rates in infant's upto 3yrs and are relatively stable throughout adolescence. The major disadvantage of CTX is its large Circadian variation is the major disadvantage of CTX that necessitates a morning fasting sample for accurate interpretation (10) (5).

Analytical variability is the technical variation that shows within & between batches. Hence precision, accuracy and standardization remains problematic. It is postulated that these markers should be measured by standardization assays to minimize immunochemical heterogeneity & also it is recommended for the manufacturers to adopt standards of international reference and minimize batch to batch variability.

Risk Stratification

Though it is said that the normal laboratory values ranges between 50pg/ml, actual normal values is well over 300pg/ml and is most commonly 400-550pg/ml (8).Marx stratified patients into minimal, moderate and high risk categories with CTX values for predicting the risk of osteonecrosis of jaw.

Table 2 Risk Stratification

CTX value in pg/ml	Assigned risk
<100	High
100-150	Moderate
>150	Minimal

Controversies of CTX

CTX is highly sensitive for predictive purposes, but it also has certain limitations like inter-patient variability, non-standardization laboratory reference ranges, variation in terms of both fasting and non-fasting sampling and low interpretability of CTX values for oral and IV bisphosphonates. CTX is used as a predictive test in a number of studies, where as the others concluded that CTX was not an adequate marker. CTX studies is recommended as an absolute indicator for risk assessment as said by Marx but also proposed a categorization for patients with values of CTX less than 150pg/ml as generalized "risk zone"(6).

Sample stability

Successful biomarker measurement necessitates appropriate control in sample collection & preparation. The bone turn over markers like Osteocalcin & TRAP5B are highly sensitive to thermal changes and levels can be significantly reduced after a few hours storage at room temperature(2)(7). But significant reduction has not been detected in CTX levels stored at -20c or lower for up to 3 years; nevertheless it rapidly decreases in serum at both 4°c to 37°c. Though the molecular mechanism underlying is unknown, this decrease can be minimized by EDTA (11) (4).

Uses of CTX bone turnover markers

CTX helps to

- Predict bone loss.
- Identify people at risk of primary & secondary osteoporosis and fractures.
- Predict the response prior to treatment commencement
- Monitor the response to treatment
- Identify non-responders which will include those not adhering with treatment protocol (includes patients not taking the medication or not following the instructions of administration)
- Identify over suppression of bone turnover in patient on long term osteoporosis therapy
- Monitor people who have been on long term treatment or show signs of over suppression or taking a treatment holiday.

CONCLUSION

Oral bisphosphonates induced osteonecrosis of jaw is a rare clinical entity that is less frequent, less severe but more predictable, and more responsive to treatment protocols than intravenous bisphosphonate induced osteonecrosis. The morning fasting serum CTX bone suppression marker is a useful tool for the clinician to assess the risk and guide treatment decision. Though sCTX remains more reliable and less variable than NTX, bone specific alkaline phosphatase or parathyroid hormone, treatment should not be determined by the result of a single test alone.

Good clinical judgement and a thorough review of medical history remain the most effective means to determine appropriate treatment. In particular, the route and duration of administration of bisphosphonates must be essentially considered before interpreting CTX results.

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How to cite this article:

Jaishree Tukaram Kshirsagar., Yashodha, SR., Premkumar,K., Carboxy Terminal Telopeptide – A Bone Biomarker. *International Journal of Recent Scientific Research Vol. 6, Issue, 11, pp. 7491-7493, November, 2015*

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