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To study the level of sclerostin in type 2 diabetic patients and its correlation with other markers of bone turnover

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Abstract
Both osteoporosis and diabetes mellitus are the two greatest burden to the modern society and the incidence of both the diseases is increasing day by day. When present simultaneously causes their additive effect on outcome of patients morbidity and mortality [2]. By definition osteoporosis is defined as deviation of Z score beyond -2.5 of SD on DEXA. In T2DM bone quality is poor due to impaired blood glucose, poor glycemic control, decreased levels of insulin like growth factor impaired vit D and calcium metabolism, possible vascular abnormalities, associated neuropathy, acidosis, ketosis, associated abnormalities of sex harmone levels and history of repeated fall in patient of DM [3]. Previous experimental and histomorphometry observations often evidenced a condition of low bone turnover and decreased osteoblast activity in both DM1 and DM2 [4].
Several indicators are available to monitor the exent of osteogenesis and bone remodelling in both normal subjects and cases of type 2 DM and its correlation with glycemic control indices can correlate bone quality and glycemic control in cases of DM. Harmonal factors which can alter the prevalence of apoptotic activities against osteoblasts/osteocytes have potential therapeutic value for the treatment of osteoporosis. BUT breakthrough discovery of role of marker such as Sclerostin (ten Dijke *et al.* 2008; Winkler *et al.* 2003) leads to the concept that these osteoblastic regulators secreted by osteocytes highlight the importance of the presence of osteocytes in bones. Measurement of bone turnover markers (BTMs) provides a noninvasive approach to assess the bone-remodeling process [5]
Sclerostin:- Mechanism by which sclerostin inhibits bone remodeling. The biological importance is underlined by both experimental studies in knockout animals and clinical observations in subjects with sclerosteosis and van Buchem disease, two genetic disorders with impaired sclerostin production and markedly increased bone mass [5]. Circulating sclerostin levels can be measured in peripheral blood, increase progressively with age [6], and are negatively regulated by estrogens and PTH in both women and men [7]. Remarkably, a recent study also demonstrated that changes in circulating sclerostin levels reflect changes of similar magnitude in bone marrow plasma sclerostin [8]. Moreover sclerostin levels are increased in long-term immobilized patients and negatively correlate with bone formation markers [9].
Neutralizing monoclonal antibodies against sclerostin have been developed and are under investigation as potential novel anabolic therapy for osteoporosis [10].

Keywords: sclerostin, diabetic patients, bone turnover.

Introduction
Both osteoporosis and diabetes mellitus are the two greatest burden to the modern society and the incidence of both the diseases is increasing day by day. When present simultaneously causes their additive effect on outcome of patients morbidity and mortality.

Osteoporosis:- Osteoporosis is defined as decreased bone mineral density, detoriation of bone microarchitecture, amount and variety of protein in bones detoriates. WHO defines osteoporosis as detoriation in bone mineral density more than 2.5 SD than mean peak bone mass and if the detoriation is less than 2.5 it is labeled as osteopenia based on DEXA reports. If osteoporosis is present with a fragility fracture it is known as established osteoporosis.

Type 2 DM:-Localised bone lesion of foot is most common presentation of bony abnormality in type 2 DM. Type 2 DM is associated with poor quality of bone due to impaired blood glucose, poor glycemic control, decreased levels of insulin like growth factor impaired vit D and calcium metabolism, possible vascular abnormalities, associated neuropathy, acidosis, ketosis, associated abnormalities of sex harmone levels and history of repeated fall in patient of DM.

Sclerostin:- A glycoprotein coded by SOST gene located on chromosome 17 locus q11.2 with C terminal cysteine like domain with the length of 213 residue DSSP secondary structure 28% beta pleated sheets.

Function: Earlier was considered as non-classical bone morphogenic protein but recent studies reveal that it's an LRP 5/6 receptor and inhibiting WNT signaling pathways. WNT pathway has an anabolic effect on bone formation so sclerostin by inhibiting wnt pathway hinders bone formation. It also has a functional resemblance with DKK1 (involved in embryonic development by inhibiting wnt pathway) which has broader tissue distribution [1].

Regulation Of Secretion: Secreted by osteocytes. Increased by calcitonin and decreased by parathharmone, mechanical loading and cytokines. Osteo gene x is an inhibitor of sclerostin.

Abnormality: Lack of expression of gene leads to sclerostosis.
Level of sclerostin (pmol/liter) in case of type 2 DM is to be compared against various marker of bone mineral quality to prove the relation of bone mineral density with level of sclerostin.And its potential to replace the multiple markers and radiation exposure in patient to monitor proper bone growth in a patient

AIM:- To study the level of Sclerostin (a bone anti anabolic marker) in patients with type 2 DM and to observe its relationship between other bone turnover markers (creditability as a marker of bone growth).

Material & Methods:- A total of 50 male subjects were recruited in this study after having a written consent from the patient. This study is a prospective, open labelled, observational study.

Inclusion Criteria:-Patient diagnosed as a case of type 2 DM according to American diabetes association criteria and age between 40-60 yrs.

Exclusion Criteria:-Chronic disease other than DM**,** disease effecting bones eg; Paget disease, malignancy, liver dysfunction, anaemia, vit D def, renal insufficiency, any blood related malignancy etc. Any previous or current treatment with drug altering bone metabolism eg; calcium, vit D, calcitonin, thiazide steroids, anti convulsant.
S.Sclerostin levels were estimated by sandwich elisa method. A monoclonal antibody specific to sclerostin has been precoated onto a microplate. The colour development and the intensity is measured at 450 nm. and the result is obtained by comparing colour intensity with predefined values.
Conversion factor 1 pg/ml = 0.044 pmol/l (MW: 22.5 kDa). Serum values of apparently healthy Individuals-Median 24.14 pmol/l.

Vit D estimation was done using immunoassay. BSAP level was estimated by ELISA method. Serum calcium and serum phosphate by automated analyser DEXA scan and X ray D/L spine was done to quantify the level of osteopenia in the subjects.

Observation:- All the patient enrolled in the study the median age was 47.63 with SD of 6.88 yrs.

Mean distribution of different indices used in the study

PARAMETERS	Mean	Std deviation	Std mean error
SCLEROSTIN(pmol/l)	79.84	20.04	2.83
HbA1C (%)	8.93	1.73	.245
25 (OH)VIT D(pg/ml)	24.66	3.18	.45
BSAP(U/L)	28.8	9.2	0.54
BMD(gm/sqcm)	1.239	.0619	.008
S. calcium(mg/dl)	8.75	0.348	0.049
s.Phosphate(mg/dl)	3.35	0.6	0.054

On applying PEARSON'S formulae correlation coefficient was calculated between different indices of bone turnover markers and serum sclerostin. Correlation of variables with serum sclerostin.

Variables	HbA1c	Vit -D	BMD	S.Calcium	BSAP	S.phosphate
Correlation coff (r value)	0.846	-0.638	-0.701	-0.459	-0.225	-0.35
P VALUE	<0.001	<0.001	<0.001	0.01	0.004	0.685

Results
On applying Pearson formulae for correlation coefficient calculation between serum sclerostin level and bone mineral density as measured on DEXA scan the r value comes out to be 0.701 with the significant P value of less than 0.001. Implies higher values of serum sclerostin are associated with the lowered bone mineral density. Similarly there is a negative correlation between serum sclerostin and VIT D level with the value of r=-0.638 and a significant P value of less than 0.001 denotes the higher level of serum sclerostin are associated with lower values of vit D.
The correlation coefficient between serum sclerostin level and Serum calcium level comes out to be -0.459 with the insignificant P value of 0.01 denotes there is no significant correlation between serum sclerostin and serum calcium level.
The correlation coefficient i,e r value between serum sclerostin and bone specific alkaline phosphatase comes out to be -0.225 with the significant P value of 0.004 which denotes the inverse relation between the two variables i,e increased sclerostin level leads to decreased bone growth reflected in lower values of alakaline phosphatase. On calculation of correlation coefficient between serum sclerostin and serum phosphate the r value comes out to be -0.03 and the P value of 0.685 which was insignificant denotes absence of any significant correlation between serum sclerostin and serum phosphate level. Also on applying the pearson formulae on correlation between long term glycemic control and indicators of proper bone mineralisation i,e BMD and Vit D the r values comes out to be negative for both, 0.770 and 0.752 respectively and both with significant P value of less than 0.001.

Conclusion
Higher levels of serum sclerostin is associated with lower values of indicators of positive bone growth i,e VIT D and BMD. There is no significant relationship of sclerostin level with serum calcium and serum phosphate level. Serum sclerostin level is inversely related with marker of positive bone growth i,e bone specific alkaline phosphatase

Discussion
Several clinical and experimental observation suggested an increased skeletal fragility both in type 1 DM as well as type 2 DM. The pathophysiology of reduced bone strength,

decreased resistance to stress and increased bone turnover in both types of DM are multifactorial such as glycemic control, general condition, ethinicity etc.

Recent observations with monoclonal antibodies against sclerostin in animal models or postmenopausal women clearly demonstrated that an acute reduction in sclerostin levels leads to an increase in bone formation and a suppression in bone resorption as mentioned in Padhi D, Jang G, Stouch B, Fang L, Posvar E 2011 Single-dose, placebo-controlled, randomized study of ROMOSOZUMAB (AMG 785), a sclerostin monoclonal antibody and in Papapoulos SE 2011 targeting sclerostin as potential treatment of osteoporosis.

This could be particularly important not only for a better understanding of the causes of skeletal fragility in diabetes and its correlation with higher values of s.sclerostin but also for its potential therapeutic implications, providing the basis for the use of the monoclonal antibody against sclerostin. In future serum sclerostin level may be used as a marker for skeletal fragility. Avoiding unnecessary exposure to radiation and also a series of investigations to diagnose skeletal growth defect.

Limitations

1)-All patients used in the study are diabetic but lacking any other cause of decreased bone mineral density.

2)-Small sample size

3)-Unavailability of the marker for diagnostic tool in Indian clinical practices.

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