To Study the Efficacy of Teriparatide in Improving Remodeling of Foot Bones in Chronic Charcot Neuroarthropathy in Patients With Diabetes Mellitus.
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Patients and methods:

People with type 2 diabetes and inactive charcot neuroarthropathy of foot attending the diabetic foot care unit of department of endocrinology at Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh were prospectively enroled in the study. An informed and written consent was obtained from all the participants and the Institute Ethics Committee approved the study protocol. The diagnosis of inactive charcot foot was confirmed on clinical and radiological examination (Eichenholtz's classification) (16) of the foot. The inactive charcot foot was suggested by the absence of signs of activity i.e lack of temperature difference between two feet (measured using infrared thermometer) and no T2 hyperintensity on Magnetic resonance imaging (MRI) and/or the presence of deformities like pes-planus or rocker bottom foot with a prior history of active charcot neuroarthropathy (12 months prior) or scrutiny of treatment records revealed active charcot foot (total contact cast) in recent past. The patients with active charcot neuroarthropathy (within 12 months), active on inactive charcot neuroarthropathy, osteomyelitis of foot bones, concurrent peripheral vascular disease, presence of non-healing ulcer or a history of foot ulcer in the past 12 weeks, presence of vascular calcification on foot X-ray, osteoporosis at lumbar spine or hip (defined as T Score$\leq$ -2.5), renal failure (eGFR<60 ml/min), previous/prevalent bone malignancy, previous malignancy with metastasis to bone, received teriparatide or bisphosphonates earlier (within past 12 months), primary hyperparathyroidism, pregnant women were excluded from the study. Patients were randomized by computerized random program into two groups to receive Teriparatide (T group) 20 μg between 8-9 pm or placebo (P group) subcutaneous daily. The clinician in-charge, the participants, radiologist and the nuclear medicine specialists were unaware of the treatment group allocation. The adherence to teriparatide or placebo was ensured by telephonic call and collecting empty cartridges on subsequent visits

from the participants. The standard treatment for inactive charcot neuroarthropathy by advice for effective offloading with modified footwear were provided to all patients.

The affected foot was divided into three regions of interest (ROI) depending upon the site of involvement as per Sanders and Frykberg radiological grade (17). The forefoot (R1) included

the foot proximal to tarso-metatarsal (TMT) joint; mid-foot (R2) included the TMT joint and the tarsal bones; and hind foot (R3) included the talus, calcaneum, talo-calcaneal and the ankle joint. The clinical details pertaining to diabetes, glycemic status, presence of micro vascular and macrovascular complications were recorded including the local examination of the foot. Measurements of serum calcium, alkaline phosphatase, creatinine, parathyroid hormone iPTH(1–84)] and 25- hydroxy vitamin D were performed at baseline, 3 months and 12 months. Samples for bone turnover markers i.e P1NP and CTx were collected in the morning after overnight fast at 0, 3 and 12 months and measured with electrochemiluminescence immunoassay (ECLIA) on COBAS600 (Roche, Germany) [PINP, Orion Diagnostica, Espoo, Finland; interassay coefficient of variance (CV) 3.1–8.2%and CTX with Ostex, Seattle, WA USA; interassay CV 6.7–14.8% kits].

Radiological Work-up:

Weight bearing foot radiograph (antero-posterior and lateral) were obtained for the calculation of calcaneal inclination angle (CIA), talar declination angle (TDA), angle of medial longitudinal arch (ALA) and lateral talo-calcaneal angle (TCA). Calcaneal inclination angle was calculated by the angle formed at the intersection of the line drawn from the anterior inferior calcaneal border of the calcaneo-cuboid articulation and another line from the calcaneum to the 5th metatarsal. Talar declination angle formed between the line representing the talar axis and a line representing plantar surface of the calcaneum to the 5th metatarsal. Angle of medial longitudinal arch

5th metatarsal. Lateral talo-calcaneal

is drawn between the calcaneal inclination

axis and a line drawn along the inferior edge of the

was defined as the angle between the mid-talar axis and calcaneal inclination axis.

angle

Bone mineral density (BMD) measured in gm/cm^{2}of the foot as a whole and individually at the region of interest (ROI) was performed on DXA (Hologic Inc., Bedford, MA, USA) at

baseline and 12 months. The software used for the vertebral BMD was applied for the foot BMD and reproducibility was assessed by three repeated measurements.

Nuclear Imaging:

Regional ^{18}F-PET/CT images of the feet were acquired at baseline, 3 and 12 months using a dedicated PET/CT scanner (Discovery STE16 or 710, GE Healthcare, Milwaukee, WI, USA) in 3-D mode at 1, 2 and 3 hours after intravenous injection of 185MBq (5mCi) of Na^{18}F-fluoride. The CT variables for acquisition were 140kV, 40mA & pitch of 1.375:1. Reconstructed trans-axial, coronal and sagittal images were viewed on advantage workstation adw 4.6. Semi quantitative analysis for standardized uptake value (SUVmax) was done by drawing the ROIs at the fore, mid and hind foot regions and compared with the baseline ^{18}F-PET/CT for change in SUVmax. Increased tracer uptake in the fore, mid and hind foot in relation to the background normal bone was taken as abnormal. A SUVmax $\geq$ 2.5 at 2 hours was considered significant based on our prior experience [15].

Outcome Measure:

Primary outcome measure was the change in SUVmax on ^{18}F-PET/CT compared to baseline. Bone turnover markers, foot BMD (ROI) and foot inclination angles were the exploratory variables.