Anthropologist 29(2,3): 202-210 (2017)
DOI: 10.31901/24566802.2017/29.2-3.14

Human Upper Limbs (Distal Radius) Show Direct Dependency on Vitamin D as Osteogenic Factor but it is not seen for The Lower Limbs (Midshaft Tibia) - Evolutionary Insights for Human Bipedalism

Mayank Shukla*, Amrinder Singh, and Shweta Shenoy

Faculty of Sports Medicine and Physiotherapy, Guru Nanak Dev University, Amritsar, Punjab, India

KEYWORDS Bone. Bipedalism. Evolution. Vitamin D. Weight Bearing. Winter

ABSTRACT Lower limbs bear the entire body weight under the influence of gravity in various activities of daily living like walking. Upper limbs are not having any comparable weight bearing role in modern bipedal human beings. Thus, there may be evolutionary differences in limbs for their dependency on osteogenic factors like nutrition, weight bearing, and environmental aspects. The level of vitamin D may be predominantly important for the non-weight bearing upper extremity skeletal mineralization during winters as compared to lower limbs in modern bipedal humans. Vitamin D's association with quantitative ultrasound derived T and Z scores were checked and its osteogenic role explored in this study. Vitamin D level using enzyme - linked immunoassay (ELISA) and ultrasound derived T and Z scores of radius and tibia were checked during winters for a correlational study on 20 participants. Present study results show significant positive correlation (r=+0.491; p=.038) and significant positive linear regression analysis for quantitative ultrasound derived T score of distal radius (p=0.033*, R2=.241, b0= -1.51, b1=0.053) with vitamin D levels; whereas the correlation of vitamin D was not significantly positive for midshaft tibia's T score (r=+0.298; p=.229). Thus, a direct dependency of vitamin D for only the upper limb has been seen, for osteogenic function.

INTRODUCTION

Human evolution is a perpetual and essential change centered on survival and adaptation, and has been happening at a very slow pace. Bipedalism is also one aspect of it along with the evolved brain that sets us apart in the animal kingdom. The entire evolution on the earth has been directly under the Sun and till the recent past of our species; it has been largely attributed to outdoor living activities (David-Barrett and Dunbar 2016). Wrist fractures (distal radial fracture) are usually sustained in outdoors activity and are reported in winter season as the first indicator of osteoporosis (Bartl and Bartl 2017). Bone is a hard connective tissue that has two major components, collagenous matrix, and minerals. Loss of collagenous matrix and minerals leading to a low bone mineral density (↓BMD) T score of < - 2.5, is known as osteoporosis whereas loss of minerals in adults is known as osteomalacia. It has been suggested that significant overlap between the two exists with a central role of vitamin D (Nordin 2010). The living bone constantly remodels itself as per the various stimulants like weight bearing and vitamin D levels. Bone remodels in response to loading as per Wolff's law (Frost 2004). Various sites of the skeletal system are known to have different loading patterns. The calcium release or absorption, by bone, is dependent upon them. During osteoporosis, the calcium is released due to hypovitaminosis D, from the bones and same is for the case of distal radius, as discussed here.

The survival instinct has increasingly demanded skill base instrumental role from upper limbs and the weight bearing - locomotor role being primarily reserved for the lower limbs (Begun 2007; Liu et al. 2016). For modern humans, early childhood development leads to bipedal stance by 12 months of age and the reflex bipedal walking starts even before that, this adaptation being rooted in the genetic programming and the lower energy cost of locomotion being one important factor affecting successful survival (Pasqua et al. 2016). Exploration of the en-

Address for correspondence:
Mayank Shukla
Phone: 9711113097
E-mail: mshukla@amity.edu

vironment by the hands is also witnessed during early childhood and the role of socio-environmental aspect for walking has been told by Geva and Orr (2016). Gripping, pinching and other prehension like activities do not cause direct weight bearing and are evolved along with visuospatial function (Bruner and Iriki 2016) for the upper limbs and the skeletal remodeling is accordingly not attributable to a weight bearing adaptation as it is for the lower limbs from a very early phase of life. The evolution of bipedal walking in humans has taken away the weight bearing function from the upper limbs (Begun 2007). Moreover, the usage of upper limb is more and more intended and limited to skilled activity; thus for purpose of osteogenic action they may be dependent upon factors other than mechanical stress of regular weight bearing activities of daily living (ADL) like walking, standing and sitting. Modern humans are living in a technologically advanced environment that produces very little demand on the upper limb skeletal system as compared to our forefathers. Furthermore, the modern aristocracy loaded life style excludes any outdoor endeavors as part of the survival drill on a regular basis, and there is no natural sun exposure to the skin surface. It leads to nutritional bone disease.

Nutritional bone disease due to serum vitamin D and calcium deficiency has been reported to be about fifty-two percent in the Indian population (Teotia and Teotia 2008). This predisposes the affected individuals to falls, fractures, and morbidity. The economic burden of managing osteoporosis - related fractures is going to be huge for India as has been documented for the other countries like United States of America (Burge et al. 2007). Factors like sunlight exposure, serum vitamin D, loading of bones, calcium levels, and heritability can affect the mineralization leading to ↓BMD at various sites of the body. During winters, it can be low when UV Index is < 3 (Shukla et al. 2012). For the high mortality rates in United States of America population in winter, the seasonal variations of vitamin D are reported to be significant (Grant et al. 2017). Vitamin D plays a greater site-specific role at a cellular level over and above the gating of calcium through the gut (Kaiser et al. 2013). This can involve non-weight bearing bones if resistance exercises are not prescribed in the presence of hypovitaminosis D for them. Vitamin D is known to control calcium and was reported to have a major role in cardiovascular diseases. Sunlight-induced few chemical mediators like nitric oxide (NO) which are well known for and acclaimed in vascular physiology, as signaling molecules are also found to affect the bone mineralization and tissue inflammation (Liu et al. 2010; Dulla et al. 2016). Such changes have been attributed to produce change in bone volumes in a consistent way for the lower limbs but are not seen consistently for the upper limbs (Chirchir et al. 2017) and further exploration is desirable. In the sample of children from Finland, an insufficiency level of vitamin D in seventy percent of children has been reported by Soininen et al. (2016) highlighting physical activity and nutritional aspects like milk intake in them.

The various factors that are generally attributed for skeletal remodeling are diverse in nature and are: 1) Environmental factors – living arrangements indoor and outdoor living and sunlight - induced vitamin D mediated calcium absorption, 2) Activity based – weight bearing and non-weight bearing function of the upper and lower limbs, 3) Nutritional factors – like protein intake and vitamin D and calcium (Ca) intake and, 4) Genetic factors – evolutionary aspects and genetic programming for the skeletal system (Weaver et al. 2016). These other factors are mainly nutritional (vitamins and minerals), or hereditary factors subjected to evolution (Terrio and Auld 2002). Lower limbs and axial skeleton weight bear during many activities of daily living (ADLs) and they may have it as a major determinant of bone remodeling for the modern humans. These factors are also interlinked with each other and may influence each other. Notwithstanding, are there any selective preferences for any one of the factors for a specific skeletal site, is presently unknown? Like vitamin D-induced osteogenic role of upper limb? This is the primary question addressed in the present study. Here, researchers show a direct dependency on vitamin D levels of upper limbs for better bone structure and strength.

METHODOLOGY

Specifically, this study looked at correlation of two different sites (distal radius and mid-shaft tibia) using quantitative ultrasound (QU) derived T and Z scores from, speed of sound (SOS) measurements, with vitamin D; and the need of regional weight bearing exercises along with walking as primary preventive approach highlighted specially during winters in northern locations.

Variables

Serum Vitamin D concentration, (25 OH D2 and 25 OH D3) levels were analyzed in centrifuged venous blood.

Quantitative Ultrasound derived T and Z score using the speed of sound measurements at the distal radius and mid-shaft tibia were recorded.

Equipments

1. Enzyme linked immunoassay (ELISA) microplate, reader.
2. SUNLIGHT US Based bone sonometer Omnisense, Imola Italy
3. ELISA 25 OH D using DL.D kits, Germany
4. Centrifuge
5. Deep freezer

Research Design

The research design used was Correlational Study Design

Sample Size

The sample size consisted of 20 participants.

Setting

The Faculty of Sports Medicine and Physiotherapy, Guru Nanak Dev University was selected for the study.

Inclusion Criteria

The inclusion criteria was:

1. Age group – 25-70 years
2. Involved in walking for at least 30 mins per day

Exclusion Criteria

The exclusion criteria was:

1. Involved in resistance training of upper limbs
2. Taking vitamin D / Ca supplements
3. Individuals taking steroids
4. Previous/recent history of fractures

Procedure

Ethical approval was granted by the Institutional Ethical Committee of Faculty of Sports Medicine and Physiotherapy, Guru Nanak Dev University Amritsar and informed consent were taken from all the participants. Inclusion - exclusion criteria were checked. Serum vitamin D 25 OH D2 and 25 OH D3 were detected from the venous sample. The venous sample was centrifuged, and frozen serum kept in (EDTA) test tubes. Enzyme- linked immunoassay (ELISA) was done using DL.D Germany Vitamin D kits. The kit performed enzyme immunoassay for the quantitative determination of 25 (OH) D levels. Bone mineral density was tested by an ultrasound (QU) based probe from midshaft tibia and distal radius. Three measurements were recorded and the average of them was taken.

Data Analysis

Using SPSS version 12.0, descriptive statistics of the variables was found out using mean and standard deviation (SD). Pearson correlation co-efficient (r) was found out for vitamin D and two sites being the distal radius and midshaft tibia. Linear regression was determined if the correlation was significant ($p=<.05^*$). Scatter plot for linear regression is drawn between vitamin D and SOS derived T score of the distal radius.

RESULTS

Total 20 participants were involved with a mean age of 47.3 ± 10.3 yrs. The mean± SD value of all the variables is given in Table 1. The mean weight being 66.9 kg with a standard deviation of 12.5 kg. The T and Z scores are seen in which lowest mean reading is for the tibial T score -1.23 and the highest reading being the radial Z score. Vitamin D levels have the mean value of 18.06 ng/ml reflecting the deficiency range. Radial T score is -.4 and it is having association with vitamin D levels, as seen in Figure 1.

The relationship of the T scores of the distal radius and midshaft tibia with vitamin D levels is seen in Figure 1. It is seen in Figure 1 that the

Table 1: Descriptive statistics of the participants showing mean and standard deviation along with the range (max- min) of various variables

S No.	*Variable*	*Mean ± SD*	*Range (Min - Max)*
1	Age	47.3 ± 10.3 Years	26-68 Years
2	Weight	66.9 ± 12.5 Kg	45-86.2 Kg
3	Height	160.8 ± 12.3 cm	145184.2 cm
4	Body Mass Index (BMI)	25.6 ± 2.7 Kg/m^2	18.2-29Kg/m^2
5	Vitamin D levels	18.06 ± 9.06 ng/ml	1.37-36.0 ng/ml
6	SOS derived radius (T)	- 0.40 ± 1.1	-2.0- +2.2
7	SOS derived radial (Z)	-.02 ± 1.69	-4.6-+2.2
8	SOS derived tibial (T)	-1.23 ± 0.99	-1.8-+2.2
9	SOS derived tibial (Z)	-0.76 ± 1.71	-3.3- +2.2

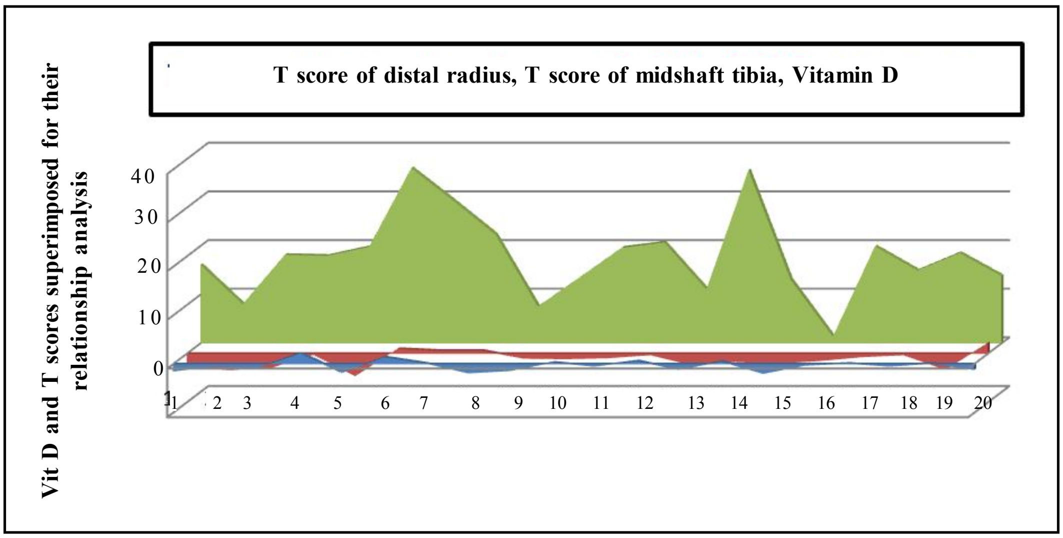

Fig. 1. Graph showing vitamin D and QU (SOS derived T score) at distal radius and mid shaft tibia in all participants. Almost mirror images are found out for radius

vitamin D levels are varying with the T scores of the distal radius in a consistent manner. This is not seen for the mid-shaft tibial T scores.

Vitamin D concentration has been found to have significant and moderately positive correlation (r= +0.491; p=0.038*) with T score at distal radius (T=- 0.4150 ±1.11), but not with mid shaft tibia (r=+0.298; p=0.229) T score (T=-1.2250 ±0.99) as seen in Table 2.

The co-efficient of determination's (R square) value is .24 as seen in Table 3, meaning twenty-four percent of variations can be explained in the quantitative ultrasound derived T score of distal radius by the vitamin D levels.

Table 2: Correlation co-efficient and level of significance of serum vitamin D concentration and QU derived T score, Age and BMI

S. No.	*Variable 1*	*Variable 2*	*Pearson correlation co-efficient*	*Significance level*
1	Vitamin D levels	Age	+0.104	.681
2	Vitamin D levels	BMI	-0.049	.848
3	Vitamin D levels	T score Distal Radius	+0.491	.038*
4	Vitamin D levels	T score Mid shaft Tibia	+0.298	.229

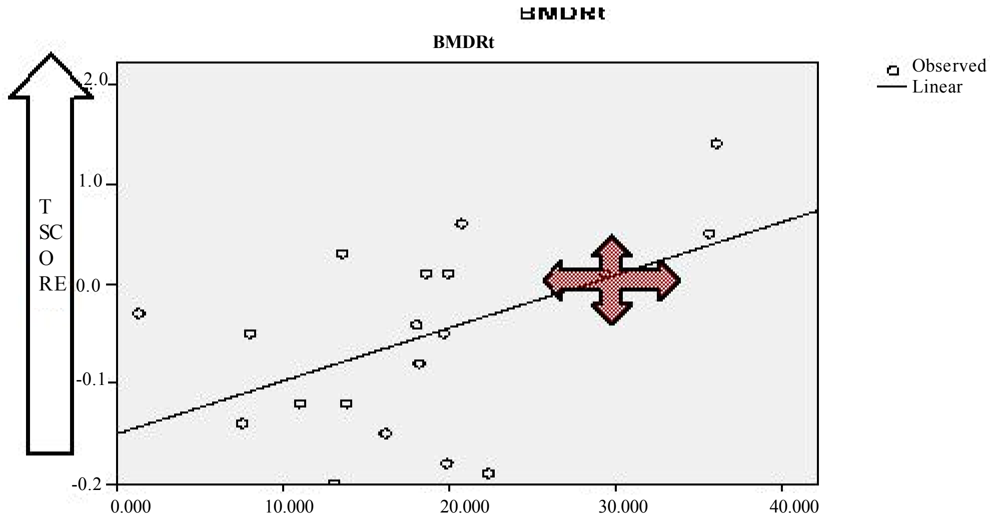

Fig. 2. Linear regression analysis of serum vitamin D concentration and QU derived T score (bone mineral density) at distal radius

Scatter diagram is plotted (Fig. 2) with this data and it is seen clearly that at 30 ng/ml is corresponding to the zero (0) level in the T score range for the distal radius. The independent variable is taken as the horizontal axis and the dependent variable is taken on the vertical axis. The co-efficients for straight line are b0 and b1 being, – 1.51 and .05 respectively (Table 3).

DISCUSSION

All participants were involved in walking at least 30 minutes per day producing weight bearing for the lower limbs; they were not involved in resistance training of upper limb. The present study was done during winters and lack of sunlight during winters may produce vitamin D deficient state (O'Neill et al. 2016) leading to secondary hyperparathyroidism further producing low bone mineral density over a period of few months. Such seasonal variations are reported as a factor for various diseases and disorders (Hartl et al. 2017) and even affecting the mortality rates (Grant et al. 2017). Low bone mineral density at radius is cited as a factor for distal radius fracture with trivial trauma (Oyen et al. 2011). For most of the world population, ultraviolet radiation B (UVR- B) part of sunlight is the primary source of vitamin D (O'Neill et al. 2016). At the time of the present study a UV Index of about 3 (during winters) is expected at the given location (Shukla et al. 2012) and is insufficient to produce optimal vitamin D levels. Such seasonal changes are informed by Pasco et al. (2004) in the Geelong Osteoporosis Study. The average value seen by the present study of vitamin D is 18.06 ±9.06 ng/ml as seen in Table 1. A plethora of diseases are associated with such deficiency values (Grant et al. 2005). It may lead to increased risk of fractures predisposing to other joint problems as well. Various other factors like weight bearing activities and physical exercises can influence it; equivocal results are reported from various studies regarding their effect (Snow-

Table 3: Model summary and co-efficients for regression analysis- linear equation

Dependent variable	*Independent variable*	*R square value*	*F value*	*Standardized co-efficients Beta*	*Un-standardized co-efficients b0*	*Un-standardized co-efficients b1*	*Sig*
QS derived R(T)	Vitamin D	.241	5.4	.491	-1.5145	.0531	0.033

Harter et al. 1992; Heinonen et al.1996; Terrio and Auld 2002). The geographical distribution and seasonal variation of sunlight where the ultraviolet index falls may lead to a variation in occurrence rates of such diseases, from summer to winter and from south to north (Maxwell 1994). The north Indian children are reported to have vitamin D deficiency (Marwaha et al. 2005).

The linear regression analysis (Table 3) also showed significant results for the distal radius (p=0.033*), thus it was found out that concentration of vitamin D may be causing decreased bone mineral density at distal radius during winter. Vitamin D supplementation or ultraviolet exposure to increase the vitamin D concentration to the levels of sufficiency (30 ng/ml) as demonstrated by histological analysis of mineralization of iliac crest are the direct implications of this (Priemel et al. 2010). The level of sufficiency is 30 ng/ml and it is not available in the population studied in the present study where only two participants reached this level. In a systematic review (Morrison et al. 2013) of falls and osteoporotic fractures distal forearm is cited by two studies to have a maximum number of site-specific fractures (SOF= 171 and Mellor 2002=496). Differences in osteocyte function with increased porosity being negatively associated with lacunar density has been reported for different sites in human skeletal system like femur, rib, and radius by Hunter and Agnew (2016). They demonstrated age dependent maximum negative association for the human radius.

Globally, it has been identified that lack of vitamin D and an increased parathyroid hormone are associated with increased bone loss. Giving supplement for it has been linked to improvement in health outcome (Lips et al. 2001). The significant correlation (+0.491 at p=.038*) is seen only for distal radius T score and vitamin D levels (Table 2). India has been reported to have a large number of vitamin D-mediated cases of osteoporosis and other diseases of the same origin have also been identified (Malhotra and Mithal 2008). In the present study, participants belonged to skin type IV and V with moderate melanin content and tanning reaction to the sun. Darkly pigmented skin and low temperature along with low UV index (winter) leading to less skin photosynthesis of vitamin D and thus hypovitaminosis D and resultant low bone mineral density (T score) of the distal radius in absence of specific weight bearing explain the significant correlation seen in Figure 2. Similar findings are reported by Arya et al. (2004) for 25(OH) D only.

Significant linear regression (p=0.033) of T score of radius only with vitamin D concentration (Table 3) is a factor that suggests the importance of weight bearing exercise interventions for the upper limbs (wrist and forearm) during winters for the susceptible population who are regularly involved in walking otherwise. Human bipedalism has produced many changes in the stress and loading muscular function of the upper limbs named musculoskeletal stress markers (Ibáñez Gimeno et al. 2013). Mechanical aspects for the bone mineralization at the distal radius during morphogenesis is also responsible for this aspect (Galtés et al. 2006). Tibial T score has a weak, non-significant correlation with vitamin D, different from distal radius (Figure 1). It may be due to weight bearing nature of tibia thus, the implication of weight bearing for upper limb as well arises. In a systematic review and meta-analysis by Nikander et al. (2010), site-specific improvement as a result of loading has been concluded.

Cochrane review could only find definitely favorable improvement for post-menopausal women in the review for vitamin D supplementation; certain adverse effects like increased nephrolithiasis and increased serum calcium levels have also been quoted (Bjelakovic et al. 2011). Recently in a review covering 29,000 participants, calcium supplementation has been related to more of stroke and myocardial infarction and this risk still remains even after adding vitamin D. They have also mentioned better prognosis for a group only receiving sunlight as a therapy (Reid et al. 2011). Interestingly, hands are most of the time still exposed for any opportunistic sun exposure.

Nutritional affluence leads to widespread obesity/overweight that loads the lower limbs. Moreover, from a physiological point of view, dietary supplements largely contain 25 OH D_2 (ergocalciferol) and not 25 OH D_3 (cholecalciferol). Their specific actions are different and may influence the benefits derived from them.

There are comparisons found for upper and lower limbs on a phylogenetic basis (Sinam et al. 2015). The hand is differentiated from the foot because – the hand is in line with the forearm while the foot is placed at 90 degrees to the leg; and most remarkably with the changed position of thumb in the hand it function changes to the more skilled and precise. There are 10 muscles only working for the human thumb, which is placed laterally and at a perpendicular axis. Thus, the carpometacarpal joint has three dimensional movements with the opposition - as the encircling of thumb and fingers, for the instrumental roles. This is distinct from the foot where the first metatarsal ball carries maximum of the body weight during normal gait. There is substantial more range of motion in the upper limb as compared to the lower limb. But the strength of bones is comparatively less. They are carrying angle advantage and the ability of the forearm to supinate and pronate for better positioning in space. Upper limbs are primarily suited for the open kinematic chain exercises whereas the lower limbs are primarily suited for the closed kinematic chain exercises. Therefore, during the process of evolution, the upper limbs gradually supinated and the thumb moved out with getting closer to the radius, leaving the weight bearing function totally.

Although, the distal radial end is an anatomically differentiated structure, by ancestral walking patterns and is used to discuss and debate whether early humans were knuckle walker or used brachiating (swinging on the branches). There are more advocates of knuckle-walking patterns, but a large number of upper limb posturing is concluded, and all types of ambulation would have produced more stress on the distal end of radius (Tallman 2012). When this is compared to the present day humans, the weight-bearing is found to be negligible, and thus, it may be producing dependence on vitamin D for QU (derived T score). The present day human evolution is also ongoing and is primarily because of the indoor living environment and can lead to the differential association with vitamin D of the two skeletal sites seen in Figure 1. In the indoor living arrangements, artificial light replaces the sunlight. The artificial light is completely non-physiological for ultraviolet radiation - induced vitamin D via photo-bio-stimulation. Similar to the way in which, plants cannot thrive in the indoor environment, and the wild animals are not able to do well indoors, humans also need natural sunlight and outdoor activities for the optimization of various health factors.

The unprecedentedly high significance ($p=0.038$) (Table 2) of radius (T score) and serum vitamin D correlation analysis (R square .241) in the broad age bracket, (26-68 yrs) brings to fore the independent osteogenic role of this ancient hormone (vitamin D) for non-weight bearing distal radius. The genetic evolution after bipedal stance has a specific mention for this. In this context and observing the not so overall favorable results of vitamin D/Calcium supplementation and need for resistance exercises along with UV exposure is highlighted by *"throwing new light on old light for light bones"*. It can also be recommended that maintenance of optimal vitamin D levels and additional resistance training for the forearms and wrist may be included along with walking during winters in a physical fitness program for primary prevention of osteoporosis.

CONCLUSION

Low vitamin D levels independently affect distal radius as osteogenic factors (reflected by the T score and vitamin D relationship), but not mid-shaft tibia in individuals undertaking regular walks. Thus, there are evolutionary implications involving bipedalism and non-weight bearing function of the upper limbs versus weight bearing locomotion role of the lower limbs.

RECOMMENDATIONS

It is recommended that the vitamin D levels should be checked in individuals who exhibit upper limb musculoskeletal symptoms, like weakness, pain, tendinitis or who have had upper limb fractures and sufficient serum levels of vitamin D (> 30 ng / ml) should be maintained for the preservation of upper limbs bone mass. Higher levels of vitamin D in the optimal range (30-60 ng / ml) are recommended for stronger upper limbs. Upper limbs need added attention for the preservation of bone mass because they lack the natural weight bearing nature of the lower limbs in bipedal modern humans. This is especially of high significance during winters in the northern locations because natural synthesis of vitamin D reaches a trough during winters. Also, specifically weight training exercises can be recommended for upper limbs in general population involved in regular walking. Thus, optimal levels of vitamin D should be maintained for the protection of bone mass of non-weight bearing upper limbs during winters.

REFERENCES

Arya V, Bhamri R, Godbole MM, Mithal A 2004. Vitamin D status and its relationship with bone mineral density in healthy Asian Indians. *Osteoporos Int,* 15: 56-61.

Bartl R, Bartl C 2017. Management of osteoporotic fractures. In: Andrea Baur-Melnyk, Tobia Geik (Eds.): *Bone Disorders*: *Biology, Diagnosis, Prevention, Therap*. Cham: Springer International Publishing, pp. 243-256.

Begun DR 2007. Comment on "Origin of bipedalism as an adaptation for locomotion on flexible branches". *Science,* 318: 1066.

Bruner E, Iriki A 2016. Extending mind, visuospatial integration, and the evolution of the parietal lobes in the human genus. *Quaternary International,* 405: 98-110.

Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M, Gluud C 2011. Vitamin D supplementation for prevention of mortality in adults (Review). *The Cochrane Library,* 6(7): 1-254.

Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A 2007. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *Journal of Bone and Mineral Research,* 22(3): 465-475.

Chirchir H, Ruff CB, Junno JA, Potts R 2017. Low trabecular bone density in recent sedentary modern humans. *American Journal of Physical Anthropology,* 162(3): 550-560.

David-Barrett T, Dunbar RI 2016. Bipedality and hair loss in human evolution revisited: The impact of altitude and activity scheduling. *Journal of Human Evolution,* 94: 72-82.

Dulla YAT, Kurauchi Y, Hisatsune A, Seki T, Shudo K, Katsuki H 2016. Regulatory mechanisms of vitamin D3 on production of nitric oxide and pro-inflammatory cytokines in microglial BV-2 cells. *Neurochemical Research,* 41(11): 2848-2858.

Frost HM 2004. A 2003 update of bone physiology and Wolff's law for clinicians. *Angle Orthod,* 74: 3-15.

Galtés I, Rodríguez Baeza A, Malgosa A 2006. Mechanical morphogenesis: A concept applied to the surface of the radius. *The Anatomical Record Part A Discoveries in Molecular, Cellular, and Evolutionary Biology,* 288(7): 794-805.

Geva R, Orr E 2016. Talk the walk: Does socio-cognitive resource reallocation facilitate the development of walking? *PloS One,* 11(6): e0156351.

Grant WB, Garland CF, Holick MF 2005. Comparison of estimated economic burdens due to insufficient solar ultraviolet irradiance and vitamin D and excess solar irradiance for United States. *Photochemistry and Photobiology,* 81(6): 1276-1286.

Grant WB, Bhattoa HP, Boucher BJ 2017. Seasonal Variations of US Mortality Rates: Roles of Solar Ultraviolet-B Doses, Vitamin D, Gene Expression, and Infections. The Journal of Steroid Biochemistry and Molecular Biology. From <http://dx.doi.org/10.1016/j.jsbmb.2017.01.003> (Retrieved on 20 March 2017).

Hartl C, Obermeier V, Gerdes LA, Brügel M, von Kries R, Kümpfel T 2017. Seasonal variations of 25-OH vitamin D serum levels are associated with clinical disease activity in multiple sclerosis patients. *Journal of the Neurological Sciences,* 375: 160-164.

Heinonen A, Kannus P, Sievanen H, Oja P, Pasanen M, Rinne M, Uusi Rasi K, Vuori I 1996. Randomized Controlled trial of effect of high impact exercise on selected risk factors for osteoporotic fractures. *Lancet,* 348: 1343-1347.

Hunter RL, Agnew AM 2016. Intra-skeletal variation in human cortical osteocyte lacunar density: Implications for bone quality assessment. *Bone Reports,* 5: 252-261.

Ibáñez Gimeno P, Galtés I, Jordana X, Fiorin E, Manyosa J, Malgosa A 2013. Entheseal changes and functional implications of the humeral medial epicondyle. *International Journal of Osteoarchaeology,* 23(2): 211-220.

Kaiser MF, Heider U, Mieth M, Zang C, von Metzler I, Sezer O 2013. The proteasome inhibitor bortezomib stimulates osteoblastic differentiation of human osteoblast precursors via upregulation of vitamin D receptor signaling. *Eur J Haematol,* 90(4): 263-272. Doi: 10.1111/ejh.12069. [Epub ahead of print].

Liu L, Yuan W, Wang J 2010. Mechanisms for osteogenic differentiation of human mesenchymal stem cells induced by fluid shear stress. Biomechanics and modeling in *Mechanobiology,* 9(6): 659-670.

Liu MJ, Xiong CH, Hu D 2016. Assessing the manipulative potentials of monkeys, apes and humans from hand proportions: Implications for hand evolution. *Proc Biol Sci,* 283(1843): 20161923.

Lips P, Duong TU, Oleksin A, Black D, Cummings S, Cox D, Nickelsen T 2001. A global study of vitamin D status and parathyroid function in post-menopausal women with osteoporosis: Baseline data from multiple outcomes of raloxifine evaluation of clinical trial. *The Journal of Clinical Endocrinology and Metabolism,* 86: 1212-1221.

Malhotra N, Mithal A 2008. Review article - Osteoporosis in Indians. *Indian Journal of Medical Research,* 127: 263-268.

Marwaha RK, Tandon N, Reddy D, Reddy HK, Aggarwal R, Singh R, Sawhney RC, Saluja B, Ganie MA, Singh S 2005. Vitamin D and bone mineral density status of healthy school children in northern India. *American Journal of Clinical Nutrition,* 82: 477-482.

Maxwell JD 1994. Seasonal variation in vitamin D. *Proceedings of the Nutrition Society,* 53: 533-543.

Morrison A, Fan T, Sen SS, Weisenfluh L 2013. Epidemiology of falls and osteoporotic fractures: A systematic review. *Clinco Economics and Outcomes Research,* 5: 9-18.

Nikander R, Sievanen H, Heinonen A, DalyRM, Uusi-Rasi K, Kannus P 2010. Targeted Exercise against Osteoporosis: A Systematic Review and Meta-Analysis for Optimizing Bone Strength throughout Life. BMC Medicine, 8: 47. From <http://www. biomedcentral. com/1741-7015/8/47> (Retrieved on 2 April 2012).

Nordin BEC 2010. Evolution of calcium paradigm: The relation between vitamin D, serum calcium and calcium absorption. *Nutrients,* 2: 997-1004. Doi: 10.3390/nu2090997.

O'Neill CM, Kazantzidis A, Ryan MJ, Barber N, Sempos CT, Durazo-Arvizu RA et al. 2016. Seasonal changes in vitamin D-effective UVB availability in Europe and associations with population Serum 25-Hydroxyvitamin D. *Nutrients,* 8(9): 533.

Oyen J, Rohde G, Hochberg M, JohnsenV, Hochberg G 2011. Low bone mineral density is a significant risk factor for low-energy distal radius fracture in middle-aged and elderly men: A case control study. *BMC Musculoskeletal Disorders,* 12: 67.

Pasco JA, Henry MJ, Kotowizx MJ, Sanders KM, Seeman E, Pasco JR, Schneider HG, Nicholson GC 2004. Seasonal periodicity of serum vitamin D and parathyroid hormone, bone resorption, and fractures: The Geelong osteoporosis study. *Journal of Bone Mineral Research,* 19(5): 752-758.

Priemel M, von Domarus C, Klatte TO, Kessler S, Schlie J Meier S, Proksch N, Pastor F, Netter C, Streichert T, Püschel K, Amling M 2010. Bone mineralization defects and vitamin D deficiency: Histomorphometric analysis of Iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. *Journal of Bone and Mineral Research,* 25(2): 305-312.

Pasqua LA, Bueno S, Matsuda M, Marquezini MV, Lima-Silva AE, Saldiva PH, Bertuzzi R 2016. The genetics of human running: ACTN3 polymorphism as an evolutionary tool improving the energy economy during locomotion. *Annals of Human Biology,* 43(3): 255-260.

Reid IR, Bolland MJ, Sambrook PN, Grey A 2011. Calcium supplementation: Balancing the cardiovascular risk. *Maturitas,* 69: 289-295.

Shukla M, Shweta S, Sandhu JS 2012. Low ultraviolet index in winter with concomitant hypovitaminosis D in northern Indian region (Amritsar) – A pilot study. *Int Journal of Life Sciences,* 1(3): 64-67.

Sinam V, Daimi T, Singh DI, Devi ND 2015. Comparison of the upper and lower limbs - A phylogenetic concept. *IOSR Journal of Dental and Medical Sciences,* 14(8): 14-16.

Snow-Harter C, Bouxsein ML, Lewis BT, Carter DR, Marcus R 1992. Effects of resistance and endurance exercise on Bone Mineral Status of young women: A randomized exercise intervention trial. *Journal Bone Mineral Research,* 7: 761-769.

Soininen S, Eloranta AM, Lindi V, Venäläinen T, Zaproudina N, Mahonen A, Lakka TA 2016. Determinants of serum 25-hydroxyvitamin D concentration in Finnish children: The physical activity and nutrition in children (PANIC) study. *British Journal of Nutrition,* 115(6): 1080-1091.

Tallman M 2012. Morphology of the distal radius in extant hominoids and fossil hominins: Implications for the evolution of bipedalism. *The Anatomical Record,* 295: 454-464.

Teotia SPS, Teotia M 2008. Nutritional bone disease in Indian population. *Ind J of Medical Res* 127(3): 219-228.

Terrio K, Auld GW 2002. Osteoporosis knowledge, calcium intake and weight bearing physical activity in three age groups of women. *Journal of Community Health,* 27(5): 307-320.

Weaver CM, Gordon CM, Janz KF, Kalkwarf HJ, Lappe JM, Lewis R, O'Karma M, Wallace TC, Zemel BS 2016. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: A systematic review and implementation recommendations. *Osteoporos Int,* 27(4): 1281-1386.

Paper received for publication on August 2016
Paper accepted for publication on April 2017