LIST OF TEN BEST PAPERS OF THE CANDIDATE

Paper 1

***Pal R**, Aggarwal A, Singh T, Sharma S, Khandelwal N, Garg A, et al. Diagnostic cut-offs, prevalence, and biochemical predictors of sarcopenia in healthy Indian adults: The Sarcopenia-Chandigarh Urban Bone Epidemiological Study (Sarco-CUBES). Eur Geriatr Med. 2020;11:725-736.*

Importance: Sarcopenia is a clinical entity characterized by low muscle strength and low muscle mass and is associated with a high risk of morbidity and mortality. Sarcopenia is not uncommon in the elderly population, nevertheless, in India, sarcopenia remains an under-diagnosed and under-reported entity. This is partly attributed to the lack of definite diagnostic criteria for identifying sarcopenia.

Published in European Geriatric Medicine in 2020 and cited 20 times till now including an editorial on it, the aforementioned manuscript presents the data of a community-based epidemiological survey (Chandigarh Urban Bone Epidemiological Study; Acronym: CUBES) conducted between December 2016 and June 2019 in the Union Territory of Chandigarh. In short, apparently healthy individuals aged 20 years and above were recruited in the study. Individuals were chosen from four sectors of Chandigarh; these sectors were in turn selected by simple random sampling. Houses within each sector were chosen by systematic random sampling, selecting every fifth house from a random starting point. Household members eligible for enrollment were selected using the 'Kish Selection Method'. Subjects with known medical comorbidities were excluded, while others underwent blood sampling. Subjects without obvious biochemical abnormalities underwent dual-energy X-ray absorptiometry (DEXA) scan for assessment of body composition (specifically muscle mass). Handgrip strength (as a measure of muscle strength) was measured in

each participant using the Jamar Plus Digital Hand Dynamometer (Jamar®, Patterson Medical). Usual gait speed (as a measure of physical performance) was measured using a 4-min walk test.

We finally included 804 participants in the study. When compared to the already established NHANES (Caucasian) Reference database, we found that Indians have lower muscle mass and muscle strength across all age decades, thereby, implying that Caucasian cut-offs cannot be used for sarcopenia in Indians. Hence, we derived indigenous sex-specific cut-offs of low muscle strength and low muscle mass to define sarcopenia amongst Indian adults. Using the herein derived cut-offs, the prevalence of sarcopenia was 3.2% in the study population, while, when the Caucasian cut-offs were applied, the prevalence was as high as 11.6%. Thus, the study highlights the importance of using indigenous cut-offs to define sarcopenia and the cut-offs have been recommended by the Research Society for the Study of Diabetes in India (RSSDI) for the diagnosis of sarcopenia and sarcopenic obesity in Indian adults in their clinical practice recommendations published in 2022.

Paper 2

***Pal R**, Bhadada SK, Aggarwal A, Singh T. The prevalence of sarcopenic obesity in community-dwelling healthy Indian adults - The Sarcopenic Obesity-Chandigarh Urban Bone Epidemiological Study (SO-CUBES). Osteoporos Sarcopenia. 2021;7:24–9.*

Importance: Sarcopenic obesity is a clinical entity characterized by the co-existence of sarcopenia and obesity. People with sarcopenic obesity are at a higher risk of metabolic complications, morbidity and mortality compared to those with sarcopenia alone. Nevertheless, just like sarcopenia, till the aforementioned publication, there

had been no literature on this entity from India and general masses and physicians alike remain unaware about this malady.

Using the database of CUBES, we found that prevalence of sarcopenic obesity in elderly (≥ 65 years) ostensibly healthy Indians was 5.4%; one-fourth of subjects with sarcopenia had concomitant sarcopenic obesity. Considering the ever-increasing elderly population of the country, sarcopenia and sarcopenic obesity is also expected to rise proportionately.

Paper 3

***Pal R**, Aggarwal A, Sachdeva N, Ram S, Garg A, Bhansali A, et al. Age- and sex-specific concentrations of bone remodeling markers in healthy Indian adults with and without vitamin D deficiency. Arch Osteoporos. 2021;16:10.*

Importance: Bone remodeling markers, also called bone turnover markers (BTMs) are a series of protein or protein derivative biomarkers released during bone remodeling by osteoblasts or osteoclasts. BTMs reflect acute changes in bone remodeling. Changes in BTMs can be observed as early as 1 month after starting anti-osteoporotic treatment as compared to DEXA scan where changes take as long as 12-18 months to get reflected; hence, several global osteoporosis guidelines recommend the use of serum type I collagen C-telopeptide (CTX) and serum procollagen type I N-propeptide (PINP) for monitoring the response and assessing the adherence to osteoporosis treatment. Nevertheless, BTMs exhibit marked inter-ethnic variation; hence, population-specific data are required. However, such population specific data had been missing from our country till date.

In the aforementioned study, we used data of 677 subjects from the CUBES study to establish age- and sex-specific concentrations of serum PINP and CTX in healthy

Indian adults with and without vitamin D deficiency. Decade-wise distribution of PINP/CTX showed that maximum values were attained in 3rd decade; subsequently, in men, levels declined with age while in women, there was a peak in the 6th decade coinciding with the early years of menopause. There was no significant difference in PINP/CTX in subjects with and without vitamin D deficiency. As of now, we are using the data at our institute to monitor response to anti-osteoporotic therapies using BTMs.

Paper 4

*Aggarwal A, **Pal R**, Bhadada SK, Ram S, Garg A, Bhansali A, et al. Bone mineral density in healthy adult Indian population: the Chandigarh Urban Bone Epidemiological Study (CUBES). Arch Osteoporos. 2021;16:17.*

Importance: Osteoporosis is a major public health problem around the globe including India, resulting in significant morbidity, mortality, and health care burden. However, the reference values used for its diagnosis are largely based on data from the western population, which may lead to over- or under-diagnosis of osteoporosis in Indians. In this study, using the CUBES database, we determined the reference range for bone mineral density for the healthy adult population of India.

According to the BMD manufacturer's data, which is based on the Western population, 70% of the Indian men (> 50 years) and 48% of the post-menopausal Indian women had osteopenia while 18% of the men and 25% of the women had osteoporosis. However, according to the re-calculated T-scores from the current study using Indian reference ranges, only 56% and 7.2% of men and 33% and 5% of women had osteopenia and osteoporosis, respectively. Thus, use of Western database, as is

usually done at all health centers and hospitals, leads to over-diagnosis of osteoporosis and osteopenia amongst Indians.

Paper 5

*Aggarwal A, Ram S, Garg A, **Pal R**, Bhansali A, Singh P, et al. Metabolic Bone Profile of Healthy Adult North Indian Population from Chandigarh Urban Bone Epidemiological Study (CUBES). Indian J Clin Biochem. 2021;36:67-73.*

Importance: Diagnosis of metabolic bone disorders (MBD) requires a battery of tests like serum calcium profile [serum calcium, phosphate, albumin, and alkaline phosphatase (ALP)], 25-hydroxyvitamin D [25(OH)D], parathyroid hormone (iPTH), skeletal survey, bone histology and molecular (genetic) workup. Out of these, serum calcium profile is the preliminary investigation and is often alone able to clinch a majority of the diagnosis related to MBD. The calcium profile and normal reference range parameters are dependent upon nutrition and vitamin D status as well as the method of measurement. In addition to this, calcium profile needs to be revised periodically with the changing nutritional and vitamin D status of the community.

The normative data of the metabolic bone profile is available for the pediatric population from India. To the best of our literature search, well-planned and dedicated studies to generate normative data for metabolic bone profile for healthy, adult Indian population are scarce. Given this scarcity of data on metabolic bone profile, this present study was planned, to estimate metabolic bone profile in a large cohort of the healthy, adult Indian population in Chandigarh to generate reference standards of serum calcium, phosphate, alkaline phosphatase (ALP), 25(OH)D and iPTH.

Herein again we used the data from the CUBES database to generate reference ranges of calcium, phosphate and ALP. The median plasma 25(OH)D in men and women

was 12.5 ng/mL and 14.3 ng/mL, respectively. Hypovitaminosis D was seen in 65.4% of individuals, suggesting that vitamin D deficiency is still highly rampant in India.

Paper 6

*Bhadada SK, Chadha M, Sriram U, **Pal R**, Paul TV, Khadgawat R, et al. The Indian Society for Bone and Mineral Research (ISBMR) position statement for the diagnosis and treatment of osteoporosis in adults. Arch Osteoporos. 2021;16:102.*

Importance: In India, osteoporosis is a major public health problem. However, in the absence of any robust regional guidelines, the screening, treatment, and follow-up of patients with osteoporosis are lagging behind in the country. Hence, the Indian Society for Bone and Mineral Research (ISBMR), which is a multidisciplinary group of physicians, researchers, dietitians, and epidemiologists and who study bone and related tissues, in their annual meeting, drafted the guidelines for the diagnosis and management of osteoporosis that would be appropriate in a resource constraint setting like India. I was a part of the committee, which was involved in formulating, drafting and publishing the guidelines.

In short, the guidelines suggest the following: Diagnosis of osteoporosis can be made in a patient with minimal trauma fracture without the aid of any other diagnostic tools. In others, bone mineral density measured by dual-energy X-ray absorptiometry remains the modality of choice. Data indicates that osteoporotic fractures occur at an earlier age in Indians than in the West; hence, screening for osteoporosis should begin at an earlier age. FRAX can be used for fracture risk estimation; however, it may underestimate the risk of future fractures in our population and still needs validation. Maintaining optimum serum 25-hydroxyvitamin D levels is essential, which, in most cases, would require regular vitamin D supplementation. Pharmacotherapy should be

guided by the presence/ absence of vertebral/hip fractures or the severity of risk based on clinical factors, although bisphosphonates remain the first choice in most cases. Regular follow-up is essential to ensure adherence and response to therapy.

Implementation of the position statement in clinical practice is expected to improve the overall care of patients with osteoporosis in India.

Paper 7

***Pal R**, Bhadada SK, Singhare A, Bhansali A, Kamalanathan S, Chadha M, et al. Tumor-induced osteomalacia: experience from three tertiary care centers in India. Endocr Connect. 2019;8:266–76.*

Importance: Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome characterized by recalcitrant hypophosphatemia. Reports from the Indian subcontinent are scarce, with most being single center experiences involving few patients. Herein, we conducted a retrospective analysis of 30 patients of TIO diagnosed at three tertiary care hospitals in India, notably, PGIMER, JIPMER, and KEM. Hitherto, to the best of our knowledge, this is the largest series of TIO from the Indian subcontinent.

The mean age at presentation was 39.6 years with female:male ratio of 3:2. Bone pain (83.3%) and proximal myopathy (70%) were the chief complaints; 40% of cases had fractures. The mean delay in diagnosis was 3.8 years. Tumors were clinically detectable in four patients (13.3%). The mean serum phosphate was 0.50 mmol/L with a median serum FGF23 level of 518 RU/mL. Lower extremities were the most common site of the tumor (72%). Tumor size was positively correlated with serum FGF23 levels. Twenty-two patients underwent tumor resection and 16 of them had phosphaturic mesenchymal tumors. Surgical excision led to cure in 72.7% of patients

whereas disease persistence and disease recurrence were seen in 18.2% and 9.1% of cases, respectively.

Paper 8

***Pal R**, Ram S, Zohmangaihi D, Biswas I, Suri V, Yaddanapudi LN, et al. High Prevalence of Hypocalcemia in Non-severe COVID-19 Patients: A Retrospective Case-Control Study. Front Med. 2021;7:590805.*

Importance: Hypocalcemia is associated with severe disease, organ failure, increased likelihood of hospitalization, admission to the intensive care unit, need for mechanical ventilation, and death in COVID-19. Nevertheless, hypocalcemia is otherwise common in critically ill patients and is associated with disease severity and increased mortality. Hence, hypocalcemia in COVID-19 patients with severe or critical disease is not unexpected. However, to date, the prevalence of hypocalcemia in non-severe COVID-19 patients has not been explored.

Hence, the present study was undertaken to compare serum total calcium and phosphate levels in patients with non-severe COVID-19 (n=72) with an equal number of age, sex, and serum 25-hydroxyvitamin D level matched healthy adult cohort. Hypovitaminosis D and hypocalcemia were seen in 97 and 67% of the patients, respectively. The patients had significantly lower serum calcium compared to healthy controls. This implies that hypocalcemia is highly prevalent even in COVID-19 patients with non-severe disease probably implying that hypocalcemia is intrinsic to the disease. Prospective studies with larger number of patients are required to prove this hypothesis and unravel the underlying pathophysiological mechanisms.

Paper 9

***Pal R**, Mukherjee S, Bhadada SK, Bhansali A, Puravoor J, Behera A. Persistence of "non-dipping" pattern in blood pressure after curative parathyroidectomy in apparently normotensive patients with symptomatic primary hyperparathyroidism. Minerva Endocrinol. 2020;45:181-188.*

Importance: Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder after diabetes and thyroid disorders. PHPT is characterized by excess production of PTH from one or more overactive parathyroid glands, resulting in hypercalcemia. The cardinal symptoms of PHPT are classically described by the pentad of "bones", "stones", "abdominal groans", "psychic moans" and "fatigue overtones". In addition, metabolic syndrome and hypertension are more common in people with PHPT. However, little is known about ambulatory monitoring of blood pressure (AMBP) in PHPT and changes in blood pressure (BP) variables post-curative parathyroidectomy. Hence, we conducted a prospective study wherein we performed AMBP in apparently normotensive patients with PHPT and reevaluated them 3 months post-curative parathyroidectomy.

AMBP was able to detect hypertension in 23.5% of the patients. There was a significant reduction in the average nighttime systolic (P=0.007) and diastolic BP (P=0.034) after parathyroidectomy. However, the average 24 hours systolic/diastolic BP, daytime systolic/diastolic BP and average 24 hours mean arterial pressure did not differ before and after surgery. Non-dipping blood pressure pattern was seen in 53% of patients at presentation and persisted in 50% of cases after successful surgery. Persistence of non-dipping pattern of BP in patients with PHPT even after successful parathyroidectomy is likely the result of permanent vascular damage induced by PHPT. This can portend an increased risk of atherosclerotic cardiovascular diseases in

patients with PHPT even after disease cure and hence all patients require regular follow-up.

Paper 10

***Pal R**, Arya AK, Aggarwal A, Singh P, Dahiya D, Sood A, et al. Weight gain after curative parathyroidectomy predicts increase in bone mineral density in patients with symptomatic primary hyperparathyroidism. Clin Endocrinol (Oxf). 2020;93:28–35.*

Importance: As mentioned above, primary hyperparathyroidism (PHPT) affects bones leading to osteoporosis and fractures. The primary aim of the study was to quantitate the change in bone mineral density as measured by dual-energy X-ray absorptiometry (DEXA) in patients with PHPT after curative parathyroidectomy and delineate its predictors.

At a median interval of 15 months, the median per cent change in BMD (ΔBMD) at lumbar spine (LS), total hip (TH), femoral neck (FN) and one-third distal radius (forearm) was 6.5%, 7.0%, 8.1% and 6.9%, respectively. Following multiple linear regression analysis, baseline BMD was found to inversely predict ΔBMD at LS, TH and forearm. Interestingly, 82.5% of the patients had a gain in body weight following curative surgery and change in body weight emerged as a significant positive predictor of ΔBMD at all sites. Thus, gain in BMD might be considered as good surrogate marker of rise in BMD after parathyroidectomy in regions where DEXA facilities are not widely available.