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RESEARCH PAPER

Diagnostic cut-offs, prevalence, and biochemical predictors of sarcopenia in healthy Indian adults: The Sarcopenia-Chandigarh Urban Bone Epidemiological Study (Sarco-CUBES)

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Key summary points

Aim To determine the diagnostic cut-offs and the prevalence of sarcopenia in India.

Findings Indians have lower muscle strength and muscle mass than Caucasians. The prevalence of 'probable sarcopenia', 'sarcopenia', and 'severe sarcopenia' is 14.6%, 3.2%, and 2.3%, respectively; corresponding values are higher using well-established Western cut-offs.

Message Indigenous and not Western cut-offs should be used to define sarcopenia in Indians.

Abstract

Purpose Comprehensive data on diagnosis and prevalence of sarcopenia in India are lacking. The present study was undertaken to determine cut-offs for low muscle strength (MS) and low muscle mass (MM), and find out the prevalence of sarcopenia in Indians.

Methods Apparently healthy individuals aged ≥ 20 years with no prior history of any co-morbidities were recruited from community by door-to-door survey. Participants eligible for study underwent blood sampling. Individuals identified as having biochemical abnormalities that could potentially affect MS and MM were excluded. Enrolled participants underwent DEXA. Muscle mass, MS, and physical performance were expressed as appendicular skeletal muscle index (ASMI), dominant handgrip strength (HGS), and usual gait speed (GS), respectively. Cut-offs for low MS and MM were defined as HGS and ASMI 2SD < mean of young reference population (20–39 years). A GS ≤ 0.8 m/s defined poor physical performance. Using them, the prevalence of sarcopenia was estimated as per EWGSOP2 recommendations.

Results After exclusion, 804 participants were enrolled (mean age = 44.4 years). Peak HGS, ASMI, and GS were achieved in the 3rd/4th decades. Muscle strength/mass was lower than Caucasians. A HGS < 27.5 kg (males)/18.0 kg (females) and an ASMI < 6.11 kg/m^2 (males)/4.61 kg/m^2 (females) defined low MS and MM, respectively. Accordingly, prevalence of 'probable sarcopenia', 'sarcopenia', and 'severe sarcopenia' was 14.6%, 3.2%, and 2.3%, respectively. Corresponding values were higher when European cut-offs were used. Only serum testosterone positively predicted HGS/ASMI/GS in males.

Conclusions Indians have low MS/MM, and hence, indigenous and not Western cut-offs should be used to define sarcopenia in Indians.

Keywords India · Sarcopenia · Muscle strength · Muscle mass · Gait speed

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Introduction

Aging is associated with a progressive loss of skeletal muscle mass and strength—a phenomenon called 'sarcopenia'. It is a "progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality" [1]. Till the dawn of the twenty-first century, sarcopenia was regarded as an age-related decline in muscle mass with little or no emphasis on muscle strength and function [2]. It was in 2010 that the European Working Group on Sarcopenia In Older People (EWGSOP) laid down a proper operational definition of sarcopenia and recommended the presence of both low muscle mass and low muscle function (strength or performance) for its diagnosis [3]. Still, low muscle mass remained the cornerstone for the diagnosis of sarcopenia. However, revised guidelines were published by the EWGSOP2 in 2018 wherein muscle strength was given the upper hand as strength is a better predictor of adverse outcomes than muscle mass [1].

The prevalence of sarcopenia in the community varies, ranging from as low as 1.6% [4] to as high as 36.6% [5] amongst healthy aging adults. The marked variation can be explained on the basis of the population being studied and the cut-offs used to define the three components of sarcopenia. EWGSOP recommends the use of normative (healthy young adult) rather than any pre-specified reference population, with cut-off points at two standard deviations (SD) below the mean reference value [3]. There is a dearth of comprehensive data on the diagnosis and prevalence of sarcopenia in India. Most of the available literature is based on Caucasian cut-offs [6]. A few available studies that have developed indigenous cut-offs have concentrated only on low muscle mass [7, 8]. One such study by Marwaha et al. has reported a prevalence of low muscle mass of 15% among healthy Indian females [7].

Hence, the present study was undertaken to determine the cut-offs for defining low muscle strength and low muscle mass, and to find out the prevalence of sarcopenia as per the latest EWGSOP2 recommendations in a group of ostensibly healthy Indian adults randomly chosen from the community.

Materials and methods

The index study was a part of the Chandigarh Urban Bone Epidemiological Study (CUBES), an observational cross-sectional study conducted in Chandigarh, wherein ostensibly healthy adult volunteers were recruited from the community by door-to-door survey over a period of two and half years (December 2016–June 2019). Chandigarh was specifically chosen for the study as its per capita income ranks fourth amongst all the states and Union Territories of India. All selected participants were duly pre-informed about the study and written informed consent was obtained from them. The study was approved by the Institute Ethical Committee, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

Details of the CUBES have been published elsewhere [9]. 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' [10]. A pre-prepared proforma comprising of questions on demography, menstrual history, co-morbidities, addictions, and drug intake was filled for the selected individual. In addition, a dietary history was obtained using the 24-h dietary recall method [11] and physical activity assessed using the Global Physical Activity Questionnaire (GPAQ) [12]. Participants eligible for the study underwent blood sampling after an overnight fast. Laboratory investigations included hemoglobin, creatinine, bilirubin, alanine transaminase, aspartate transaminase, serum albumin, total calcium, inorganic phosphorous, alkaline phosphatase, fasting blood glucose, glycated hemoglobin, testosterone, thyroid function test, 25-hydroxyvitamin D, intact parathyroid hormone, and IgA tissue transglutaminsase [IgA tTg) antibody. Volunteers without obvious biochemical abnormalities underwent dual-energy X-ray absorptiometry (DEXA) scan using the HOLOGIC Discovery A (QDR 4500; Hologic, Inc., Bedford, MA) scanner for assessment of body composition. All DEXA scans were performed by a dedicated, International Society of Clinical Densitometry (ISCD)-certified technician. Quality control procedures were carried out in accordance with the manufacturer's recommendations. A thorough physical examination and anthropometry were performed prior to DEXA scan. Height of the participant was measured three times by a standard stadiometer to the nearest centimeter and the mean of the three readings was taken as the final height. Similarly, weight was measured three times using a digital weighing machine to the nearest of 0.1 kg and the mean of the three readings was considered as the final weight. The accuracy of the weighing machine was checked every day using an ISI standardized weight of 5 kg. Finally, body mass index (BMI) was calculated using formula weight (in kg)/height (in meter)^2.

Handgrip strength was measured in each participant using the Jamar Plus Digital Hand Dynamometer (Jamar®,

Patterson Medical). Participants were asked to sit in a standard chair with the shoulder adducted and neutrally rotated, the elbow flexed at right angle, forearm being neutral, and wrist at 0º–30º of dorsiflexion. The investigator (RP) demonstrated the use of the dynamometer before handing it over to the participants. Handgrip strength was measured six times, three in each arm. The volunteers were advised to press on the handle as tightly as possible for 3–5 s each and every time; the maximum reading obtained from each arm was reported as the final result. A rest period of at least 1 min was given between two consecutive measurements on the same arm. The instrument was calibrated every year as per the manufacturer's guidelines.

Usual gait speed was measured using a 4-min walk test. A distance of 4 m was marked on the floor. The study participants were advised to walk at a comfortable speed from the start point to the stop point. The time taken to traverse the distance was measured using a stopwatch. Each participant was given two walking trials and the average of the two gait speeds (in m/s) was considered for final analysis.

Inclusion criteria comprised of all participants chosen by 'Kish Selection Method' who were willing to provide written informed consent for the study. Exclusion criteria were exhaustive and were applicable at each and every stage of the survey: (a) At the time of initial proforma filling, individuals with a history of hepatic, renal, neoplastic, respiratory, rheumatological, gastrointestinal, dermatological, endocrine (notably diabetes mellitus, hyperthyroidism, Cushing's syndrome, hyperparathyroidism), systemic infective disorders, chronic drug intake (especially steroids, statins, complementary and alternative medications, and protein supplements), addictions, total calorie intake < 2100 kcal/day (minimum required calorie level for a healthy and active life as proposed by Indian Council of Medical Research) [13], physical inactivity (defined as < 250 MET-minutes/week) [14], and contraindications to DEXA scan (pregnancy, implant placement) were excluded at the outset; (b) Following biochemical investigations, participants identified as having anemia (as per WHO definition) [15], renal dysfunction (estimated glomerular filtration rate calculated by CKD-EPI formula < 90 ml/min/1.73 m^2), low serum albumin (< 3.5 gm/dl), diabetes mellitus (as per ADA definition) [16], hyperthyroidism (subclinical or overt), overt hypothyroidism, hypercalcemia, 25-hydroxyvitamin D < 10 ng/ml, low serum testosterone in males (defined as testosterone levels below the lower limit of age-specific reference range) [17, 18], and elevated IgA tTg antibody (> 10 U/ml) were excluded prior to DEXA scan. Participants with prediabetes and subclinical hypothyroidism were, however, not excluded; (c) Following anthropometry, participants with a BMI < 18.5 kg/m^2 were excluded.

Hemoglobin was estimated using Coulter LH 780 Automated Analyzer (Beckman Coulter, Inc., Brea, CA, USA). Creatinine, liver function test, serum albumin, total calcium, inorganic phosphorous, and fasting blood glucose were measured using Modular P800 Analyzer (Roche Diagnostics, Mannheim, Germany). HbA1c was measured using Bio-Rad D10 analyzer (DCCT standardized). Serum testosterone, thyroid function test, 25-hydroxyvitamin D, and iPTH were measured by electrochemiluminescence using Elecsys 2010 Analyzer (Roche Diagnostics, Mannheim, Germany). IgA tTg antibody was measured using fluoroenzyme assay.

Statistical analysis

Sample size was calculated using the formula $n = 4pq/l^2$, where p = population proportion of low muscle mass, q = 1-p, and L = allowable error. For this study, L was presumed to be 20% of p giving a power of (1-L), i.e., 80% to study. p was taken as 15% based on the prevalence of low muscle mass in females according to the study of Marwaha et al. [7]. This yielded a value of 567. Keeping in mind the 'design effect', we had applied a correction factor of 1.2, and thus, the sample size after correction came out to be 680. The final sample size was kept as 750 to account for non-responders.

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) 23.0 software program (SPSS Inc., Chicago, IL, USA). Normality of data was checked using Kolmogorov–Smirnov test. Muscle mass was assessed using appendicular skeletal muscle mass index (ASMI) which was calculated as the sum of lean mass at arms and legs in kilograms divided by square of height in meters. Muscle strength was expressed in terms of dominant handgrip strength. All participants were divided into 10-year age groups. Appendicular skeletal muscle index, dominant handgrip, and usual gait speed in each age group were reported as mean ± standard deviation (SD). Comparisons of HGS, ASMI, and GS between males and females were made using Independent-Student T Test. HGS and ASMI of the study participants were compared with Caucasian counterpart using well-established NHANES data [19, 20]. For the purpose of generating cut-offs, individuals belonging to the 20–39 years age group were considered as the young reference population. Based on the EWGSOP recommendation, cut-off for low muscle strength was defined as dominant HGS two SD below the mean of young reference population. Similarly, low muscle mass was defined as ASMI two SD

below the mean of young reference population [3]. Cut-offs were sex-specific. Usual gait speed ≤ 0.8 m/s defined low physical performance [1, 3, 21, 22]. Based on these cut-offs, the prevalence of probable sarcopenia, sarcopenia, and severe sarcopenia was estimated [1]. Likewise, prevalence was established based on the Western (as mentioned in the EWGSOP 2010 consensus statement) [3, 23, 24], EWGSOP2 (2018) [1], International Working Group on Sarcopenia (IWGS) [25], and Asian Working Group for Sarcopenia (AWGS 2014 and 2019) guidelines [22, 26]. Finally, correlations between biochemical parameters and components of sarcopenia were made using Pearson/Spearman correlation followed by multiple linear regression analysis with backward elimination. A p value < 0.05 was considered significant.

Results

Following door-to-door survey, 1186 participants were initially enrolled. After laboratory investigations, 382 volunteers had to be excluded (286 were found to have 25-hydroxyvitamin D < 10 ng/ml, 59 had anemia, 12 were diagnosed as having diabetes mellitus, 10 had hypoalbuminemia, 5 had elevated IgA tTg antibody levels, 5 male participants had low serum testosterone, 3 had hypercalcemia, and 2 had estimated glomerular filtration rate < 90 ml/min/1.73 m^2). Amongst the 59 enrollees having anemia, 8 had a BMI < 18.5 kg/m^2. Rest of the 804 participants was deemed healthy; they underwent DEXA scan and were included in the final analysis. The group included 339 male participants (M:F = 1.13:1.55). Out of the 465 female participants, 302 were premenopausal. The mean age of the group was 44.4 ± 15.4 years (range 20–85 years). There was no significant difference in age between males and females (p = 0.548). The mean BMI of the group was 26.5 ± 2.7 kg/m^2; females had a higher BMI than males (26.8 vs. 26.0 kg/m^2, p < 0.001). The decade-wise distribution of the participants has been shown in Fig. 1. Forty-three percent of the participants belonged to the 20–39 year age group. The biochemical parameters of the participants are summarized in Table 1.

Dominant handgrip strength

The mean dominant handgrip strength (HGS) of the group was 27.7 ± 8.5 kg (males vs. females being 34.7 vs. 22.6 kg, p < 0.001). The decade-wise distribution of HGS has been depicted in Fig. 2. Peak HGS was achieved in 3rd decade and 4th decade in males and females, respectively following which there was a steady decline. HGS in the 5th decade was significantly lower compared to peak HGS in both males (p = 0.001) and females (p < 0.001).

The comparison of dominant HGS of the study participants with those of Caucasians (derived from the NHANES data) is shown in Table 2. The HGS at all age groups was lower in our participants compared to Caucasians; the difference is more marked in the 8th and 9th decades.

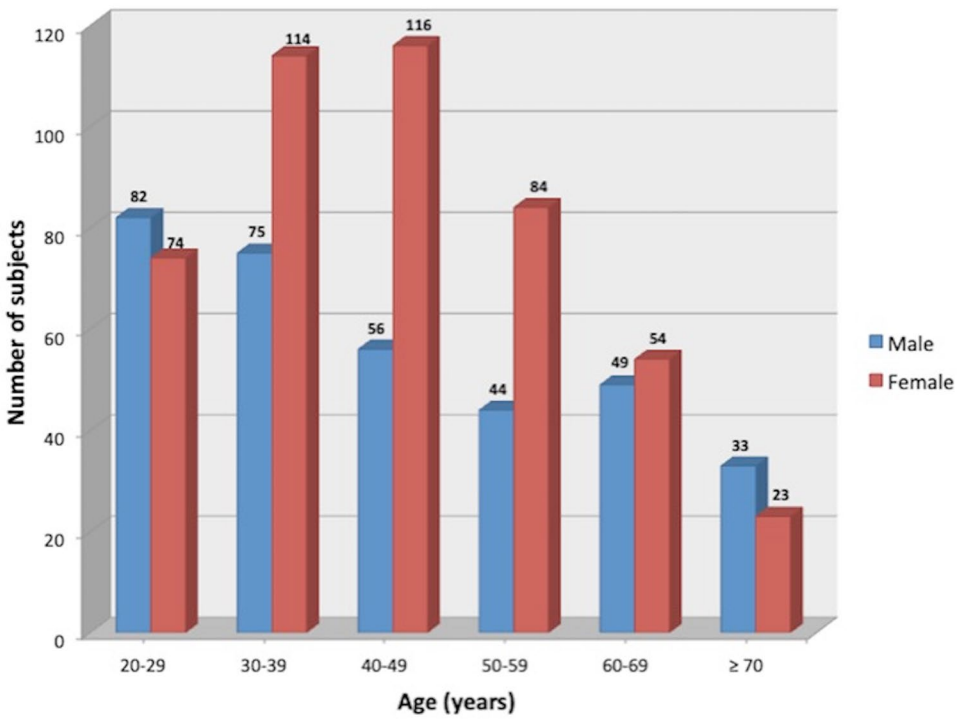

Fig. 1 Bar diagram showing decade-wise distribution of the study participants

Table 1 Biochemical parameters of the study participants ($N = 804$)

Biochemical parameter	Value
Serum albumin (mean ± SD) (gm/dl)	4.37 ± 0.21
Serum corrected calcium (mean ± SD) (mg/dl)	9.12 ± 0.16
Serum alkaline phosphatase [median (IQR)] (IU/l)	102.0 (72.0–117.0)
Serum iPTH [median (IQR)] (pg/ml)	45.98 (32.73–62.46)
Serum 25-hydroxyvitamin D [median (IQR)] (ng/ml)	16.19 (12.40–26.07)
Serum testosterone [median (IQR)] (nmol/l)	
Male	16.09 (13.40–19.47)
Female	0.87 (0.46–1.26)

SD standard deviation, *IQR* interquartile range, *iPTH* intact parathyroid hormone

Appendicular skeletal muscle index (ASMI)

The mean ASMI of the group was 6.96 ± 1.12 kg/m^2. Males had a significantly higher ASMI than females (7.62 vs. 6.49 kg/m^2, $p < 0.001$). Decade-wise distribution of ASMI has been depicted in Fig. 3. Peak ASMI was achieved in the 4th decade in both males and females. It declined thereafter, albeit less rapidly, with ASMI in the 6th and 7th decade being significantly lower than peak ASMI in males ($p = 0.012$) and females ($p = 0.017$), respectively.

The comparison of ASMI of the study participants with those of Caucasians has been shown in Table 3. The ASMI at all age groups was lower in our participants compared to Caucasians; the difference being more marked in males.

Usual gait speed

The mean usual gait speed (GS) of the participants was 1.07 ± 0.20 m/s. Males had a higher GS than females (1.13 vs. 1.02 m/s, $p < 0.001$). Peak GS was achieved in the 3rd decade in both males and females and declined thereafter with each decade (Fig. 4). The decline was more marked in males with GS in the 4th decade being significantly lower than the peak GS ($p = 0.001$), while in females, the GS in the 5th decade was significantly lower than corresponding peak GS ($p < 0.001$).

Cut-offs to define sarcopenia

For the purpose of generating cut-offs, individuals belonging to the 20–39 year age group were considered as the young reference population as peak muscle strength and mass were attained in the 3rd or 4th decades. Out of 345 participants in this group, 157 were males and the rest being females.

The mean (± SD) handgrip strength of the reference population was 39.3 ± 5.9 kg and 24.4 ± 3.2 kg for males and females, respectively. Accordingly, as per the EWGSOP recommendation [3], the cut-offs to define low muscle strength were 27.5 kg and 18.0 kg for males and females, respectively. Similarly, the mean (± SD) ASMI of the reference population was 7.83 ± 0.86 kg/m^2 for males

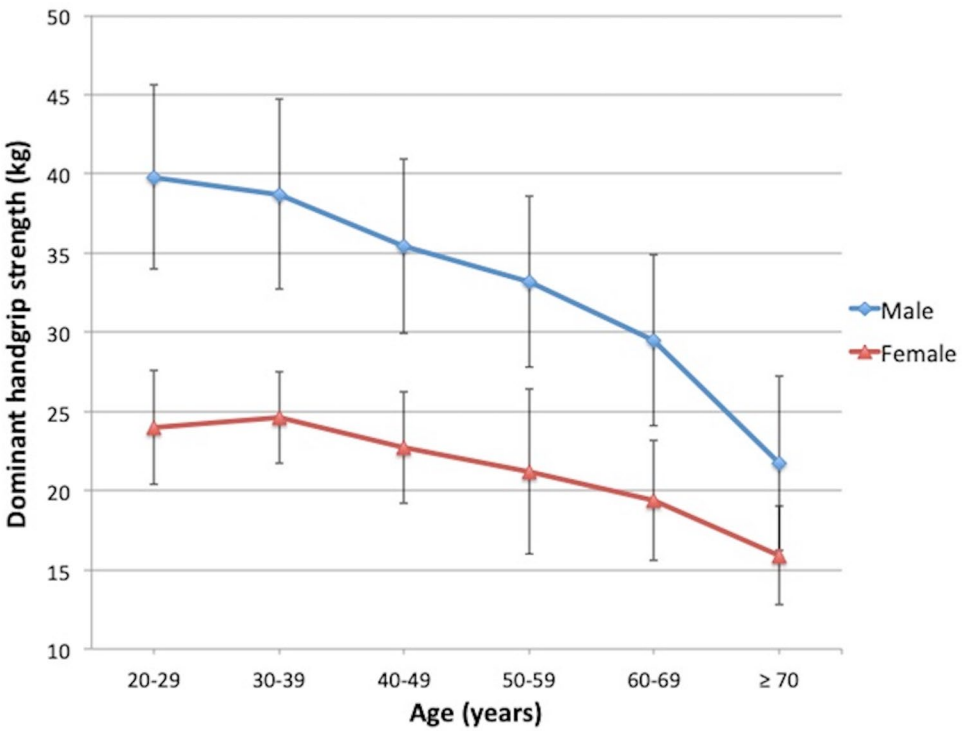

Fig. 2 Line diagram showing decade-wise distribution of dominant handgrip strength (in kg) in males and females

Table 2 Comparison of dominant handgrip strength (HGS, in kg) between Caucasians (obtained from NHANES data) and study participants

Age group	Males			Females		
	NHANES dominant HGS (kg)	Present study cohort dominant HGS (kg)	Percent difference	NHANES dominant HGS (kg)	Present study cohort dominant HGS (kg)	Percent difference
20–25	47.3	38.6	− 18.4	30.5	23.4	− 23.3
25–30	48.6	40.6	− 16.5	31.1	24.5	− 21.2
30–35	50.3	39.2	− 22.1	31.6	24.9	− 21.2
35–40	49.4	38.3	− 22.5	31.2	24.4	− 21.8
40–45	48.1	36.4	− 24.3	30.8	23.1	− 25.0
45–50	47.4	34.5	− 27.2	30.9	22.5	− 27.2
50–55	44.4	33.7	− 24.1	29.2	22.4	− 23.3
55–60	43.8	32.7	− 25.3	28.6	21.3	− 25.5
60–65	41.3	29.6	− 28.3	27.1	19.7	− 27.3
65–70	40.1	29.5	− 26.4	25.7	19.2	− 25.3
70–75	38.8	27.2	− 29.9	24.0	16.4	− 31.7
75–80	35.3	21.6	− 38.8	23.1	15.8	− 31.6
80–85	31.4	16.7	− 46.8	19.5	12.3	− 36.9

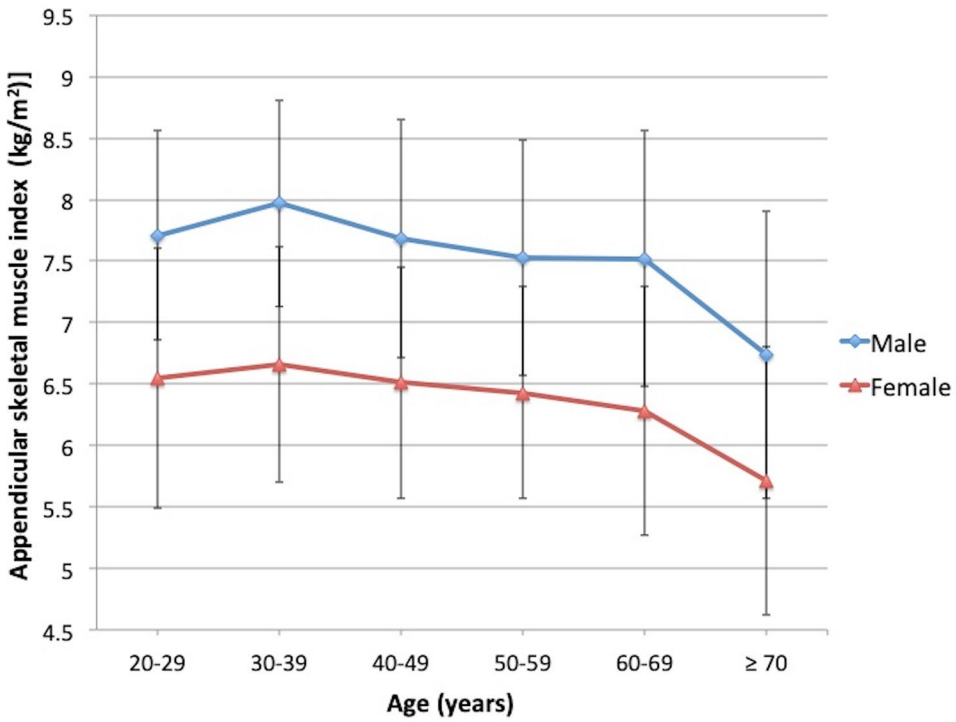

Fig. 3 Line diagram showing decade-wise distribution of appendicular skeletal muscle index (in kg/m^2) in males and females

and 6.61 ± 1.00 kg/m^2 for females. Likewise, the cut-offs to define low muscle mass in males and females were 6.11 kg/m^2 and 4.61 kg/m^2, respectively. A comparison of these cut-offs with those hitherto proposed by international organizations is shown in Table 4.

Prevalence of probable sarcopenia, sarcopenia, and severe sarcopenia

Applying these cut-offs to the entire study population ($N = 804$), we found that the prevalence of 'probable sarcopenia', 'sarcopenia', and 'severe sarcopenia', as proposed by EWGSOP2 [1] were 14.6% (males 16.8%.

Table 3 Comparison of appendicular skeletal muscle index (ASMI, in kg/m^2) between Caucasians (obtained from NHANES data) and study participants

Age group	Males			Females		
	NHANES (White) ASMI (in kg/m^2)	Present study cohort ASMI (in kg/m^2)	Percent difference	NHANES (White) ASMI (in kg/m^2)	Present study cohort ASMI (in kg/m^2)	Percent difference
20–25	8.87	7.71	– 15.0	6.81	6.49	– 4.9
25–30	8.94	7.79	– 14.8	6.86	6.58	– 4.3
30–35	9.02	8.10	– 11.4	6.90	6.68	– 3.3
35–40	9.09	7.96	– 14.2	6.93	6.62	– 4.7
40–45	9.12	7.70	– 18.4	6.95	6.53	– 6.4
45–50	9.11	7.62	– 19.6	6.93	6.46	– 7.3
50–55	9.05	7.58	– 19.4	6.90	6.44	– 7.1
55–60	8.95	7.53	– 18.9	6.84	6.38	– 7.2
60–65	8.81	7.52	– 17.2	6.76	6.31	– 7.1
65–70	8.64	7.48	– 15.5	6.67	6.16	– 8.3
70–75	8.44	7.28	– 15.9	6.57	6.02	– 9.1
75–80	8.21	6.51	– 26.1	6.45	4.57	– 41.1
80–85	7.97	4.72	– 68.9	6.33	4.72	– 34.1

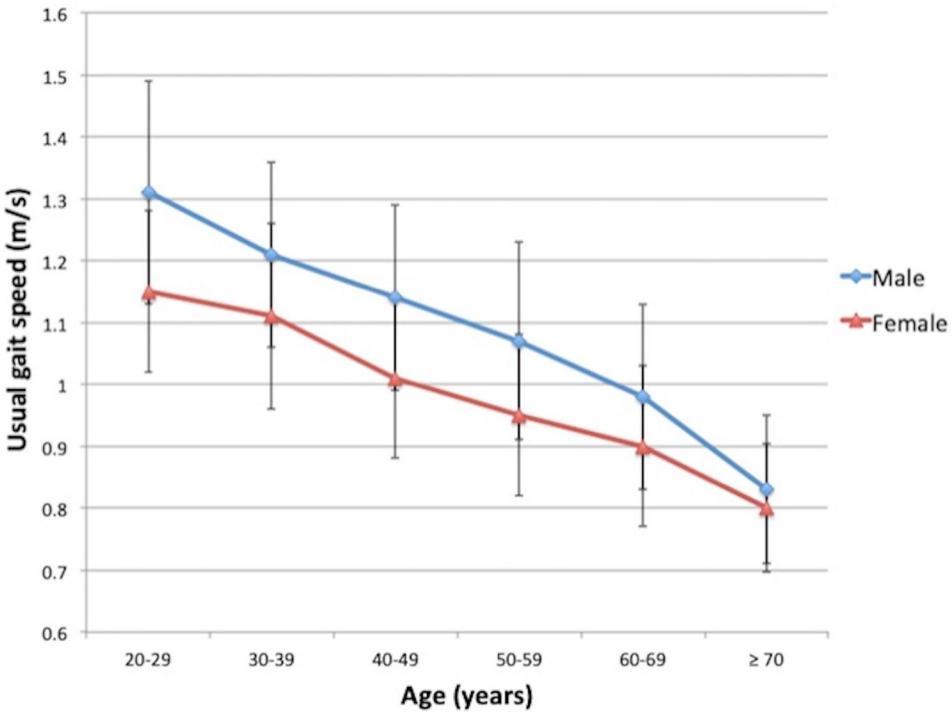

Fig. 4 Line diagram showing decade-wise distribution of usual gait speed (in m/s) in males and females

females 13.1%), 3.2% (males 4.7%, females 2.1%), and 2.3% (males 2.6%, females 1.9%), respectively. Likewise, the prevalence of sarcopenia in our study population was established as per internationally established cut-offs (Table 5).

Correlation between muscle strength, muscle mass, and physical performance with biochemical parameters

On univariate analysis (using Pearson/Spearman correlation), serum albumin was found to have significant positive correlation with HGS ($r = 0.114$, $p = 0.001$). Similarly, serum testosterone (only in males) was positively correlated with

Table 4 Comparison of cut-offs to define low muscle strength and low muscle mass derived from the present study with those proposed by international organizations

	Present study		EWGSOP (2010)		IWGS[c]		EWGSOP2 (2018)		AWGS (2014)		AWGS (2019)	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Dominant handgrip strength (in kg)	27.5	18.0	30.0[a]	20.0[a]	–	–	27.0	16.0	26.0	18.0	28.0	18.0
ASMI (in kg/m^2)	6.11	4.61	7.26[b]	5.50[b]	7.23	5.67	7.00	5.50	7.00	5.40	7.00	5.40

EWGSOP European Working Group on Sarcopenia In Older People, *IWGS* International Working Group on Sarcopenia, *AWGS* Asian Working Group for Sarcopenia, *ASMI* Appendicular skeletal muscle index

[a]Dominant handgrip strength cut-offs mentioned in the EWGSOP 2010 guidelines based on the study by Lauretani et al. [24]

[b]ASMI cut-offs mentioned in the EWGSOP 2010 guidelines based on the Rosetta study [23]

[c]IWGS does not propose cut-offs to define poor muscle strength [25]

Table 5 Prevalence of probable sarcopenia and sarcopenia as per cut-offs derived from the present study and those proposed by international organizations

	Present study	EWGSOP (2010)	EWGSOP2 (2018)	AWGS (2014)	AWGS (2019)
Probable sarcopenia					
Male	57 (16.8%)	87 (25.6%)	55 (16.2%)	42 (12.3%)	59 (17.4%)
Female	61 (13.1%)	127 (27.3%)	24 (5.2%)	61 (13.1%)	61 (13.1%)
Total	118 (14.6%)	214 (26.6%)	79 (9.8%)	103 (12.8%)	120 (14.9%)
Sarcopenia					
Male	16 (4.7%)	55 (16.2%)	35 (10.3%)	29 (8.5%)	29 (8.5%)
Female	10 (2.1%)	39 (8.4%)	07 (1.5%)	25 (5.3%)	25 (5.3%)
Total	26 (3.2%)	94 (11.6%)	42 (5.2%)	54 (6.7%)	54 (6.7%)

EWGSOP European Working Group on Sarcopenia In Older People, *AWGS* Asian Working Group for Sarcopenia

HGS ($r_s = 0.348$, $p < 0.001$), ASMI ($r_s = 0.111$, $p = 0.041$), and GS ($r_s = 0.366$, $p < 0.001$). Serum calcium, 25-hydroxy-vitamin D, and iPTH did not have any significant correlations with any of the three parameters. On multiple linear regression analyses, only serum testosterone (in males) was found to be a positive predictor of HGS, ASMI, and GS (supplementary Table 1).

Discussion

In this study, we have generated indigenous cut-offs to define low muscle strength and low muscle mass, and have estimated the prevalence of probable sarcopenia, sarcopenia, and severe sarcopenia in a population of ostensibly healthy adults randomly recruited from the community by door-to-door survey. We have demonstrated that muscle mass (expressed as appendicular skeletal muscle index) is lower in Indians compared to Caucasians across all decades, hence, applying Western cut-offs leads to an undue overestimation of sarcopenia in the Indian context. Using the cut-offs derived from the present study, we found that the prevalence of 'probable sarcopenia', 'sarcopenia', and 'severe sarcopenia' in the community were 14.6%, 3.2%, and 2.3%, respectively, figures that seem to be more realistic.

Sarcopenia is a geriatric syndrome characterized by progressive and generalized loss of muscle mass and function [3]. Sarcopenia eventually results in functional decline, physical disabilities, falls, fractures, poor quality of life, frequent hospitalizations, and mortality [27, 28]. Thus early diagnosis is critical to prevent the aforementioned adverse outcomes [29]. This entails the establishment of well-defined cut-offs to define sarcopenia. However, there exist no unanimous cut-offs that can be used to define sarcopenia for the global population. This is because of the inherent variations in muscle strength and muscle mass among populations of different ethnicities and different geographical locations. As an example, Asians have low muscle mass compared to Caucasians (even after adjustment for stature) and mean grip strength in developing countries is substantially lower than that in the developed nations [30, 31]. In addition, the rate of decline in muscle strength with aging is much more rapid in Asians compared to other ethnic populations [32]. Herein lies the need to generate region-specific cut-off values to define low muscle strength and low muscle mass as a component of sarcopenia. Indeed, the EWGSOP

(and EWGSOP2) has recommended the use of indigenous cut-offs to define and stratify sarcopenia [1, 3].

India is home to 1.37 billion people accounting for 17.7% of the world population. As is the global scenario, India's population is also aging at a rapid rate. As per the country's latest census in 2011, 104 million people were aged above 60 years; according to estimates, the number is likely to cross 230 million in 2041. Likewise, sarcopenia is expected to increase. However, hitherto, there are no compendious data on the prevalence of sarcopenia in India; neither have comprehensive indigenous cut-offs been established to define this entity. For the first time, we undertook the endeavor to determine cut-offs to define sarcopenia and find out its prevalence as per the latest EWGSOP2 recommendations [1]. We have herein shown that muscle strength (expressed as dominant handgrip strength) and muscle mass (expressed as ASMI) are lower in native Indians than Caucasians across all age decades, thereby calling for new cut-offs that are expected to be lower than the well-established European ones [1, 3, 33–36]. Such a venture was undertaken by Marwaha et al. who defined low muscle mass as ASMI < 5.11 kg/m^2 in a group of apparently healthy participants. However, the study included only females and did not include the assessment of muscle strength and physical performance [7]. Another study by Mohanty et al. found that the prevalence of sarcopenia (based on low total skeletal muscle index) was 15.3% and 20.5% in older males and females, respectively. Nonetheless, the study was conducted in a hospital setting, only 50 young participants were recruited as the reference population, and other parameters of sarcopenia were not assessed [8]. Other studies have used European cut-offs to define sarcopenia [6].

We recruited apparently healthy adults from the community by door-to-door survey. Apart from medical history, we performed an array of laboratory investigations and anthropometry and diligently excluded participants with underlying anemia, hypoalbuminemia, renal and liver disease, diabetes mellitus, hypogonadism, hyperthyroidism, hypercalcemia, celiac disease, and who were underweight (BMI < 18.5 kg/m^2), all of which can contribute to sarcopenia. These stringent measures ensured the exclusion of any 'unhealthy' individual. In addition, all the components of sarcopenia, namely muscle strength, muscle mass, and physical performance, were assessed. Decade-wise distribution of dominant handgrip strength showed that the peak was achieved in the 3rd decade in males and 4th decade in females; this is very similar to what is seen in Caucasians in whom the HGS usually peaks in the 4th decade in both males and females [19, 37]. Likewise, ASMI peaked in the 4th decades in both males and females similar to what has been reported by Marwaha et al. [7]. Data in Caucasians are inconsistent; the NHANES data showed that peak ASMI was achieved in the 5th decade in both males and females [20], and on the other hand, Imboden et al. reported that ASMI reached its peak in the 3rd decade in both the genders [38]. ASMI was lower in our study participants compared to Caucasians across all ages; however, the difference was more marked in males than in females. The decline in HGS and ASMI was stereotypical, with HGS showing a rapid decline as compared to ASMI; a phenomenon that is well described [39]. As far as physical performance was concerned, usual gait speed peaked in the 3rd decade in males and females and declined rapidly thereafter. A report by Bohannon et al. showed that usual gait speed (GS) peaked in the 4th decade among Caucasians [40]. Although the peak GS did not differ much between the present study and that reported by Bohannon et al. (1.31 vs. 1.21 m/s in males, 1.15 vs. 1.15 m/s in females), the rate of decline was much rapid in Indians as compared to Caucasians. Putting together, we can conclude than Indians have lower muscle mass and muscle strength but analogous physical performance compared to Caucasians; physical performance, however, declines at a much rapid rate.

Cut-offs to define low muscle mass and low muscle strength were derived based on the standard recommendation proposed by EWGSOP [3]. These cut-offs are much lower as compared to Caucasians [23, 24, 33–36]; however, when equated against the EWGSOP2 recommendation, the indigenous cut-offs to define low muscle strength were higher. This is because the EWGSOP2 recommendation for defining low handgrip strength is based on the data by Dodds et al. who defined weak grip strength as 2.5 standard deviations (instead of 2SD) below the gender-specific peak mean. When using 2SD, the cut-offs rose to 32 kg for males and 19 kg for females, which would surpass the cut-offs derived from the present study [37]. Similarly, the cut-points for defining low muscle strength proposed by the Asian Working Group for Sarcopenia (AWGS, initially proposed in 2014 based on data derived from South-East Asian population and revised in 2019) are very similar to those being proposed by us, although those for defining low muscle mass are still higher amongst the South-East Asians as compared to the Indians [22, 26]. On further dissection of the Asian data, we found that our cut-offs to define low ASMI are similar to those proposed by some authors [41–43], while others have reported higher thresholds [44–46]. This can only be explained on the basis of heterogeneity in the population studied by various authors. Finally, Marwaha et al. proposed a lower limit of ASMI as 5.11 kg/m^2 for defining low muscle mass in females using a cut-off of less than 20% of sex-specific normal population. When using the standard definition of 2SD below peak mean, they found a value of 4.42 kg/m^2 for defining low ASMI in females, a value very similar to what we had derived from the present study [7]. Of note, all the aforementioned studies had measured muscle mass using DEXA scan rather than by bioimpedance

analysis (BIA). Accordingly, cut-offs based on BIA are different from those based on DEXA [3]. Bahat et al. conducted a study in Turkish population wherein body composition was measured using BIA; low muscle strength was defined based on skeletal muscle mass indices (SMMI), instead of ASMI. A SMMI < 9.2 kg/m^2 in males and < 7.4 kg/m^2 in females defined low muscle mass [47]. Another very recent study from Turkey using BIA found an ASMI cut-off of 8.33 kg/m^2 in males and 5.70 kg/m^2 in females; thresholds for HGS were 28 kg for males and 14 kg for females [48]. Although HGS cut-offs are very similar to the present study, the thresholds defining low muscle mass are higher than Indians.

Using the latest EWGSOP2 recommendation and applying the indigenous cut-offs, we found that the prevalence of 'probable sarcopenia', 'sarcopenia', and 'severe sarcopenia' was 14.6% (males 16.8%. females 13.1%), 3.2% (males 4.7%, females 2.1%), and 2.3% (males 2.6%, females 1.9%), respectively. The prevalence of sarcopenia in the community is highly variable, ranging from 1.6% to 36.6% amongst healthy aging adults [4, 5]. However, most of these estimates are based on the previous EWGSOP guidelines that laid more emphasis on muscle mass than muscle strength [3]. Limited data on the prevalence of probable sarcopenia, sarcopenia, and severe sarcopenia following the paradigm shift are available [49–51]. Based on the EWGSOP2 consensus, Kim et al. found that the prevalence of probable sarcopenia (only low MS based on HGS), sarcopenia (low HGS and low ASMI), and severe sarcopenia (low HGS, low ASMI and low GS) in community-dwelling older adults were 13.7%, 9.3%, and 1.9%, respectively [49]. Our results seem to be reasonable estimates, considering the fact that the study participants were healthy and meticulously screened for the absence of any underlying disease that could have contributed to (secondary) sarcopenia.

We found a positive correlation between serum albumin and serum total testosterone (only in males) with HGS, ASMI, and GS. Multiple linear regression showed that only serum testosterone positively predicted HGS, ASMI, and GS in male. Positive correlation between serum albumin and testosterone with measures of muscle mass and strength is well documented in the literature [52–54]. The available data are also supportive of the fact that testosterone treatment has been reported to have beneficial effects on muscle mass and function, although results have been inconsistent [54]. We did not find any correlation between serum 25-hydroxyvitamin D and components of sarcopenia, even after the exclusion of participants who had been on calcium and vitamin D supplements over the past 6 months. Association between muscle mass, strength, and physical performance with serum 25-hydroxyvitamin D are highly variable; some studies have shown a positive correlation [55–57], while others have shown no significant correlation [58–61]. Moreover, the effect of vitamin D supplementation on improvement in muscle mass and strength is controversial [62].

The study did have certain limitations. First, the proportion of participants belonging to the 8th and 9th decades were relatively less; this was attributed to the scrupulous exclusion criteria that led to the elimination of a large number of older adults due to underlying co-morbidities (mostly anemia and diabetes mellitus). This ensured that the selected older participants were free from any underlying disease that could have contributed to secondary sarcopenia and falsify our findings. Second, we excluded patients with serum 25-hydroxyvitamin $D < 10$ ng/ml rather than those with a serum level < 20 ng/ml, the widely accepted definition of 'vitamin D deficiency'. This is because of the fact that vitamin D deficiency (serum 25-hydroxyvitamin $D < 20$ ng/ml) is rampant in India and setting a lower limit of 20 ng/ml would have led to exclusion of 70–80% of the recruited population [63, 64]. We believe that a cut-point of 10 ng/ml was a sensible trade-off as it identifies patients with severe vitamin D deficiency; prior studies have shown a decline in physical performance and sarcopenia in older individuals with vitamin D levels only below 10 ng/ml [65, 66]. Third, we did not derive indigenous cut-offs to define low physical performance; instead, we used a unanimously accepted value of 0.8 m/s to define low gait speed [1, 3, 21, 22]. Cut-offs to define low gait speed are based on prospective studies that predict disability and reduced overall survival [67]. Such an endeavor could not be undertaken in our observational study. Finally, we lack follow-up data on the clinical outcomes of those participants who were categorized as having probable sarcopenia, sarcopenia, and severe sarcopenia as per our study.

In conclusion, we have generated cut-offs to define low muscle strength and low muscle mass in a population of ostensibly healthy Indian adults. The cut-offs to define low muscle mass are consistently lower compared to the European cut-offs. The thresholds to define low muscle strength are similarly lower when compared to the old Western cut-offs (as proposed by EWGSOP) but higher when compared to the new ones (as proposed by EWGSOP2). Applying these indigenous cut-offs, we found that the prevalence of 'sarcopenia' was 3.2%; an estimate that is lower than when using the Caucasian cut-offs. Considering the dearth of data on sarcopenia from the Indian subcontinent, we believe that the present study will pave the way for large-scale observational and interventional studies from this part of the world.

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Compliance with ethical standards

Conflicts of interest The authors report no conflicts of interest in this work.

Ethical approval The study was approved by the Institute Ethical Committee, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

Informed consent All selected participants were duly pre-informed about the study and written informed consent was obtained from them.

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ORIGINAL ARTICLE

Bone mineral density in healthy adult Indian population: the *C*handigarh *U*rban *B*one *E*pidemiological *S*tudy (CUBES)

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Abstract

Summary Osteoporosis is a disease with a high burden of morbidity. For its accurate diagnosis, using indigenous data as reference standards is needed. However, normative data on bone density is lacking in India. Therefore, we aimed to determine the reference range for bone density for the healthy population of north India.

Introduction 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 underdiagnosis of osteoporosis in Indians. Our study aimed to determine the reference range for bone mineral density for the healthy population of India.

Methods This is a cross-sectional study of 825 subjects (men 380, women 445) (median age: 41 years, IQR 32–55 years), recruited by a house-to-house survey. The population was stratified into decade-wise groups and biochemical measurements including renal and liver function tests, glycated hemoglobin, serum calcium, 25-hydroxyvitamin D, parathyroid hormone, and bone mineral density were performed in all the subjects. The T-scores for men aged > 50 years and post-menopausal women were calculated based on the data generated from this study in young men and women aged 20–40 years.

Results 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, only 56% and 7.2% of men and 33% and 5% of women had osteopenia and osteoporosis, respectively. An age-related decline in bone mineral density, as seen in the western population, was also seen in both Indian men and women.

Conclusion We have established a reference database for BMD in healthy Indian adult population, which may have clinical implications for the diagnosis and intervention strategies for the management of osteoporosis.

Keywords Bone mineral density · Healthy population · India

Introduction

Osteoporosis is a major public health problem affecting an estimated 200 million women worldwide [1] that causes nearly 9 million fractures annually, resulting in a fracture every 3 s [2]. Of all osteoporotic fractures, hip fractures carry the greatest risk of morbidity and mortality with death rates as high as 20–24% in the first year after fracture and the risk of dying may persist for 5 years thereafter [3]. In women above 45 years of age, osteoporosis accounts for more days spent in the hospital than many other non-communicable diseases, including diabetes mellitus and breast cancer [4]. As a result, it takes a huge personal and economic toll. However, like most non-communicable diseases, osteoporosis is a treatable entity. Early prevention and treatment of osteoporosis with well-established pharmacotherapy reduces the risk of incident fractures [5] and mortality [6] and is cost-effective [7]. However, management of osteoporosis requires early diagnosis which, at present, is primarily based on bone mineral density (BMD),

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T-scores, and applying the well-accepted World Health Organization (WHO)–laid cut-offs [8]. However, these T-score cut-offs for the diagnosis of osteoporosis or osteopenia are entirely based on the western reference population, which were originally derived based on BMD measurements in 409 US white women aged 20–29 years [9]. Since then, a few other ethnic- and country-specific databases have been published but the International Society of Clinical Densitometry (ISCD) and the WHO recommend using only the western database, although it is unclear if such strategy is appropriate for other populations.

India is home to more than 1.3 billion people with approximately 230 million over 50 years of age. Data on the prevalence of osteoporosis in India is scarce with an estimated 46 million women above 50 years of age having osteoporosis [10]. This figure may be an overestimation as it is based on the western reference database [9]. Since Indians have 5–15% lower BMD at all sites compared to Caucasians [11], using BMD T-scores based on the Western reference database will definitely increase the number of Indians being diagnosed with osteoporosis and osteopenia. This can have significant clinical and therapeutic implications as many more Indians would be started on pharmacological therapy, many of whom may not require any treatment. In addition to exposing them to the potential long-term side effects of anti-fracture therapy, this will add to the great financial burden of a developing economy such as India.

Thus, it is essential to develop and use our country-specific reference data of BMD both to determine the true prevalence of osteoporosis in Indian subjects and to dictate the need for pharmacotherapy. The Indian Council of Medical Research (ICMR) has recently developed reference BMD data for healthy Indian men and women aged 20–29 years [12]. The inclusion of this specific age group implies that it was assumed that the peak BMD would be achieved in this age group. However, studies have shown that peak BMD may even be attained in the 4th decade. Normative data on BMD has also been published by Makker et al. [13], Marwaha et al. [14], and Patni [15]. However, the data by Marwaha et al. and Patni did not include men and that by Makker et al. was probably not representative of the general population. Also, the exclusion of "unhealthy" subjects was based either solely [13, 15] or largely [14] on the history provided by the subjects, with no investigations having been performed to rule out hyperthyroidism, diabetes mellitus, hypogonadism, etc. which could have adversely affected the BMD. We believe that the exclusion criteria were more robust in our study, and thus, our data was truly more representative of healthy individuals, which is an essential prerequisite for a study on normative/reference data.

Materials and methods

The study was a part of the Chandigarh Urban Bone Epidemiological Study (CUBES), an observational cross-sectional study designed to generate reference ranges for serum calcium, phosphate, alkaline phosphatase, and 25-hydroxyvitamin D in the apparently healthy population living in urban Chandigarh. All selected participants were duly pre-informed about the study and a written-informed consent was obtained from each participant. The study was approved by the Institutional Ethical Committee.

Details of the CUBES have been published elsewhere [16]. In short, apparently healthy subjects aged 20 years and above were recruited in the study. Individuals were chosen from 4 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. "Kish method" was used to select individuals from within each household, from among the members who were fulfilling the inclusion criteria [17]. Details comprising of questions on demography, medical history, menstrual history, history of fractures, history of intake of milk and milk-based products, history of medications including calcium/vitamin D supplements/anti-osteoporotic therapy, and sunlight exposure were enquired of all subjects. Subjects eligible for the study underwent blood sampling after an overnight fast. Biochemical investigations included fasting blood glucose, renal and liver function tests, serum calcium, phosphate, albumin, alkaline phosphatase (ALP), 25-hydroxyvitamin D [25(OH)D], intact parathyroid hormone (iPTH), testosterone, and thyroid profile. Individuals identified as having chronic systemic illnesses such as diabetes mellitus, renal and liver dysfunction, or endocrine disorders such as hyperthyroidism, hypercalcemia, primary hyperparathyroidism, and hypogonadism were excluded. Similarly, those with a history of "fragility" fracture or on medications likely to affect bone health (like glucocorticoids, anti-osteoporotic pharmacotherapy, oral contraceptive pill, hormone replacement therapy) were also excluded.

Serum calcium, albumin, phosphorous, and ALP levels were measured by Beckman Coulter auto-analyzer 5800. Serum calcium values were adjusted for serum albumin. Serum iPTH, 25 hydroxy vitamin D, and testosterone were measured by chemiluminescence assay using commercially available kits (Elecsys 2010 system, Roche diagnostic, Germany). HbA1c was measured using the Bio-Rad D10 analyzer (DCCT standardized).

Subjects meeting the study inclusion criteria underwent dual-energy X-ray absorptiometry (DXA) scan using the HOLOGIC Discovery A (QDR 4500; Hologic, Inc., Bedford, MA) scanner for assessment of site-specific BMD measurements. All DXA measurements were performed by a dedicated ISCD-certified technician. Quality control

procedures were carried out according to the manufacturer's recommendations.

Statistical analysis The sample size was calculated following the recommendations of the Clinical Laboratory Standards Institute (CLSI) [18], with a power of study of more than 80%. The calculated sample size was 915. GraphPadPrism-5 was used for data analyses. The Kolmogorov-Smirnov test was applied to check for normality of data. The Student *T* test was used to compare the means of two groups for parametric data and the Mann-Whitney *U* test for non-parametric data. ANOVA was used for comparing means of more than two groups for parametric data and the Kruskal-Wallis test was used for non-parametric data. The Spearman test was used to compute non-parametric correlation and the Pearson test was used to compute the parametric correlation. Subjects were classified as having normal BMD, osteopenia, or osteoporosis based on BMD T-scores generated with the in-built standard western reference database and using cut-offs established by the WHO (normal BMD T-score: ≥- 1, osteopenia T-score: - 1 to - 2.5, osteoporosis T-score: ≤ - 2.5) [8]. Also, we recalculated the T-score for each individual using the reference data generated in this study using the formula: (BMD of the subject - peak BMD)/SD_{peak}. Subsequently, subjects were reclassified as having normal BMD, osteopenia, or osteoporosis according to the new T-scores. The proportion of subjects reclassified was compared by the chi-square test.

Results

We recruited 1050 apparently healthy subjects through a door-to-door survey. Following biochemical investigations, 225 subjects were excluded because of abnormal laboratory results (184 subjects with corrected serum calcium < 8.6 mg/dl, 26 with diabetes mellitus, 7 with abnormal liver function, 4 with abnormal renal function, 3 men with low serum testosterone levels, and 1 with hypercalcemia). The remaining 825 subjects (380 men and 445 women) who underwent DXA measurements were included in the final analysis. A flow diagram explaining the process of recruitment of subjects and then subsequent BMD measurement to calculate peak BMD and T-score values has been shown in Fig. 1.

The median age of the cohort was 41 years (32–55 years), with median age being 40 years (30–55 years) for men and 42.5 years (33–55 years) for women. Of the 380 men, 149 were above 50 years of age, and of the 445 women, 160 were post-menopausal. The median height of the population was 158 cm (152.0–167.0 cm) with a median height of 168.0 cm (163.0–172.0 cm) for men and 153 cm (149.0–157.5 cm) for women. The median BMI of the population was 26.1 kg/m^2 (18.6–31.1 kg/m^2) with a median BMI of 25.8 kg/m^2 (23.6–28.5 kg/m^2) for men and 26.4 kg/m^2 (23.4–40.6 kg/m^2) for women, with no statistically significant difference between the two groups ($p = 0.07$).

The biochemical and hormonal measurements are summarized in Table 1. Vitamin D deficiency was quite prevalent, seen in 65.4% of the subjects, while vitamin D insufficiency was seen in 15% of the participants.

Decade-wise distribution of BMD in men and women are shown in Tables 2 and 3, respectively. In men, the peak BMD (in gm/cm^2) at the lumbar spine (0.990 ± 0.113) and total hip (0.958 ± 0.17) was attained in the 4th decade while that at the femoral neck (0.841 ± 0.162) and 33% radius (0.721 ± 0.052) was attained earlier in the 3rd decade. Among the women, the peak BMD (in gm/cm^2) at all the four sites were uniformly achieved in the 4th decade of life (lumbar spine 0.972 ± 0.103, femoral neck 0.787 ± 0.304, total hip 0.901 ± 0.117, 33% radius 0.650 ± 0.056 respectively) and as expected were lower than in men.

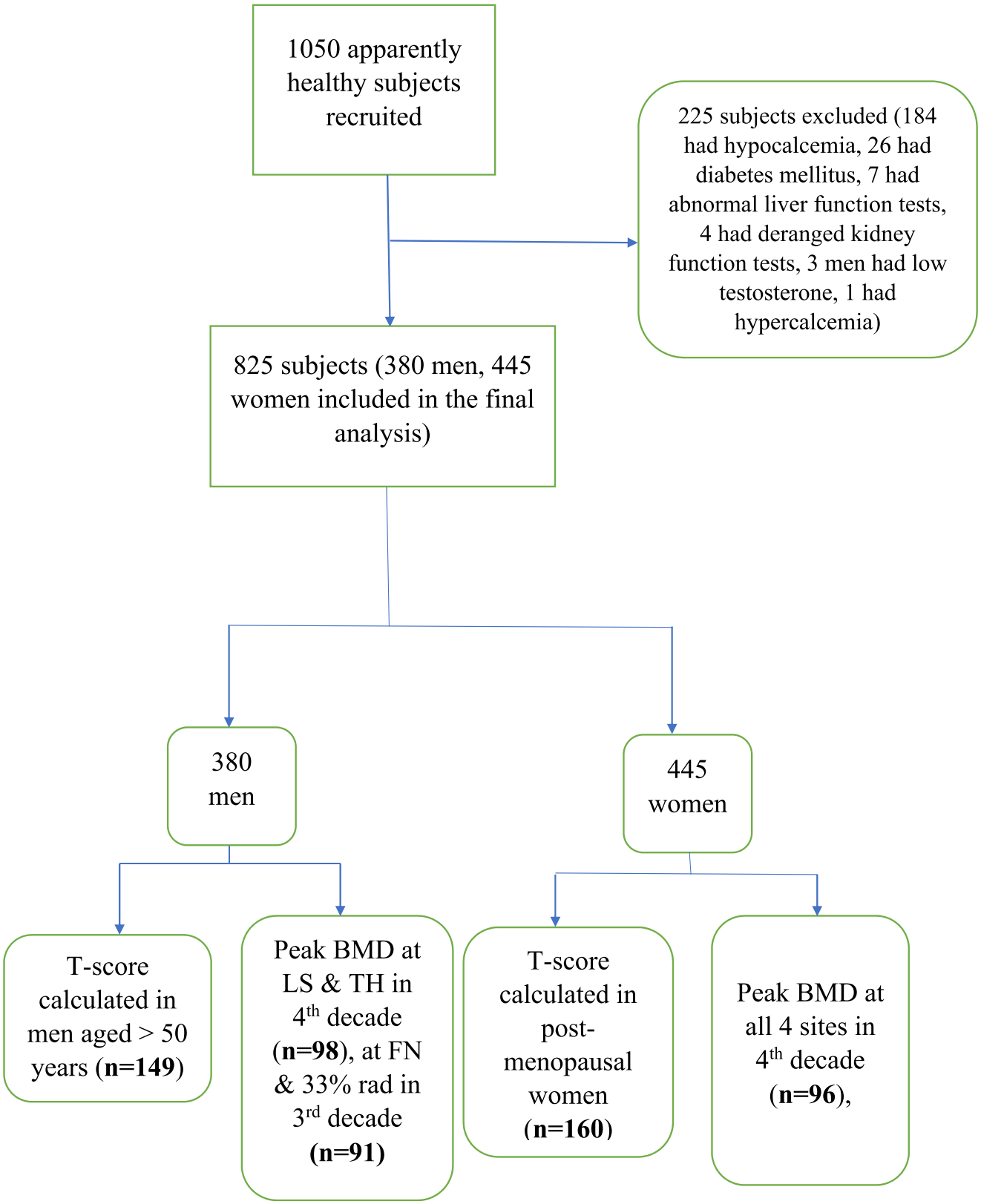
There was a negative correlation between age and BMD at all the sites (lumbar spine (r_s = - 0.13, $p = 0.02$), femoral neck (r_s = - 0.24, $p = 0.001$), total hip (r_s = - 0.13, $p = 0.02$), 33% radius (r_s = - 0.26, $p = 0.001$)). Likewise, strongly positive correlations were seen between BMD at all sites and serum testosterone, and between BMD at the hip, neck of femur, lumbar spine, and BMI. Correlations between BMD and serum calcium, iPTH, 25[OH]D, and T4 were not statistically significant.

The prevalence of osteoporosis in post-menopausal women and men aged > 50 years among our study population was calculated at various sites based on the manufacturer provided (HOLOGIC) by the western reference database. Subsequently, we recalculated the T-score for each of the aforementioned individuals using our data of peak BMD obtained among the young men and women aged 20–40 years in our study population, as explained earlier. Comparative data have been presented in Figs. 2 and 3 for the men and women, respectively. The use of our reference data reduced the prevalence of osteopenia and osteoporosis from 70.2 to 55.9% and from 17.8 to 7.2%, respectively, in men > 50 years (chi-square statistic value − 45.0, p value < 0.05) and from 48.3 to 32.9% and from 25 to 5.1%, respectively, in post-menopausal women (chi-square statistic value − 43.7, p value < 0.05). Thus, many subjects were re-classified into osteopenia or normal BMD from osteoporosis or osteopenia respectively, when we used the peak BMD from our population as a reference standard instead of the HOLOGIC reference standard.

Discussion

In this study, we have generated reference data for the BMD of healthy Indian adults. The peak BMD was achieved in either the 3rd or 4th decade in both men and women. Using these indigenous data as a reference, we reclassified them as

Figure 1: Flow diagram explaining the process of recruitment of subjects and then subsequent BMD measurement to calculate peak BMD and T-score values



◀ **Fig. 1** Flow diagram explaining the process of recruitment of subjects and then subsequent BMD measurement to calculate peak BMD and T-score values

having normal BMD, osteopenia, or osteoporosis. This led to a marked reduction in the number of subjects who would be categorized as having osteopenia or osteoporosis using the standard in-built Western reference database.

Osteoporosis is a global public health problem with major repercussions on individual morbidity and mortality as well as on the country's economy. Early treatment of osteoporosis can prevent incident major osteoporotic fractures and put an end to imminent morbidity and mortality [5, 6]. This can begin only with early and appropriate diagnosis of osteoporosis. In the present clinical scenario, areal bone mineral density, measured using DXA, is almost universally used to diagnose osteoporosis [19]. DXA has the advantage of being easy to install and operate and entails minimum radiation exposure to the patient. However, it remains operator dependent, requires perfect positioning of the patient, cannot differentiate between osteomalacia and osteoporosis, and might be fallacious in elderly subjects with vertebral osteophytes [20]. Nevertheless, a properly performed DXA scan by an ISCD-certified technician is extremely reliable and predicts incident fracture risk [21]. Accordingly, the WHO defines osteoporosis as BMD T-score ≤ - 2.5, osteopenia as - 2.5 < T-score < - 1.0, and normal BMD as T-score ≥ - 1.0 (for post-menopausal women and men > 50 years) [8].

Bone mineral density (especially peak BMD) is however not uniform and varies among different ethnic groups [22, 23]. This results from differences in skeletal size, genetic variations, and possibly prevailing nutritional status. As an example, Indians have consistently low BMD compared to Caucasians across all age groups [11]. Hence, the bone health of Indians cannot be equated to that of Caucasians and western reference BMD database should not be used to define osteopenia or osteoporosis in Indian subjects. Other factors which have implications for fracture risk, such as muscle strength and muscle mass, are also significantly different in the Indian population compared to the Caucasian population, as was shown in the sarco-CUBES study which was based on the same cohort of population as the present study [24]. Unfortunately, the DXA scanners that are commonly used to measure BMD in India (HOLOGIC, GE Lunar) have incorporated Caucasian-based reference peak BMD to calculate T-scores [25]. This will expectedly lead to overdiagnosis of osteoporosis and osteopenia and further magnify this public health problem at the country level. Subsequently, patients misclassified as osteoporosis will be treated with anti-osteoporotic pharmacotherapy, which they truly may not require. Therein arises the need for indigenous reference data on BMD that can be used to calculate T-scores and reclassify Indian postmenopausal women and men > 50 years as having normal BMD, osteopenia, or osteoporosis. Such indigenous reference data for BMD has been generated in various countries previously, which are summarized in Table 4 [12–15, 26–30].

Table 1 Biochemical and hormonal measurements of the study population (n = 825)

Biochemical and hormonal parameter	Value (median (IQR))
Albumin adjusted serum calcium	9.0 mg/dl (8.8-9.8)
Serum phosphate	3.6 mg/dl (2.8-4.3)
Serum total alkaline phosphatase	112 IU/l (52-154)
Serum 25 hydroxy vitamin D	14.5 ng/ml (7.5-37.5)
Serum iPTH	45.4 pg/ml (12-222)
Serum creatinine	0.6 mg/dl (0.4-0.9)

We recruited healthy North Indian subjects from the community by door-to-door survey following a stringent randomization technique thereby ensuring that we would encompass individuals of all socio-economic status. We made all possible attempts to rule out any underlying co-morbidity that might alter bone health. This ensured that the study population was truly healthy and ideal for generating reference data. The peak BMD was achieved either in the 3rd or 4th decades in both men and women. This is in harmony with what had been reported earlier from India where the peak BMD was attained in the 3rd/4th decade of life as well [13–15]. However, apart from Makker et al. [13] and Mukherjee et al. [12], none of the above studies had included male subjects, so data on BMD in Indian men are scarce and our study adds to it. A comparison of the aforementioned studies and the present study shows that in men, mean peak BMD at the total hip was 0.979 ± 0.131 gm/cm^2, 0.988 ± 0.131 gm/cm^2, and 0.958 ± 0.171 gm/cm^2, respectively; the corresponding values at the femoral neck were 1.019 ± 0.133 gm/cm^2, 0.894 ± 0.131 gm/cm^2, and 0.841 ± 0.162 gm/cm^2, respectively, and that at 33% radius was 0.891 ± 0.085 gm/cm^2, 0.725 ± 0.062 gm/cm^2, and 0.721 ± 0.052 gm/cm^2, respectively. Peak lumbar spine (L1-L4) BMD was comparable between the present study and that reported by Mukherjee et al. [12].

As far as women were concerned, peak lumbar spine (L1-L4) BMD was higher in the study by Marwaha et al. and comparable to ours in the other studies [12, 14, 15]. On the other hand, peak femoral neck BMD in the index study was lower compared to those reported by both Marwaha et al. [14], Makker et al. [13], and Mukherjee et al. [12] but comparable to that shown in the study by Patni et al. [15]. As far as peak 33% radial BMD is concerned, again the data presented by Makker et al. stands apart [13], being much higher than that reported by others [12, 14] and in the present study. The study by Makker et al. thus differs from most of the studies involving native Indians; although the authors state that the study

Table 2 Decade-wise distribution of bone mineral density (BMD) at various sites in the men

Age groups (n = 380)	L1-L4 BMD (g/cm^2)	Femoral neck BMD (g/cm^2)	Total hip BMD (g/cm^2)	33% radius BMD (g/cm^2)
20–29 (n = 91)	0.979 ± 0.112	0.841 ± 0.162	0.930 ± 0.141	0.721 ± 0.052
30–39 (n = 98)	0.990 ± 0.113	0.816 ± 0.124	0.958 ± 0.171	0.717 ± 0.054
40–49 (n = 68)	0.985 ± 0.141	0.767 ± 0.123	0.925 ± 0.112	0.721 ± 0.062
50–59 (n = 53)	0.927 ± 0.121	0.731 ± 0.091	0.876 ± 0.092	0.709 ± 0.082
60–69 (n = 47)	0.923 ± 0.112	0.738 ± 0.082	0.904 ± 0.095	0.703 ± 0.051
70–79 (n = 23)	1.101 ± 0.210	0.744 ± 0.121	0.926 ± 0.101	0.702 ± 0.071

had included individuals from all socioeconomic strata, no specific method of randomization was mentioned in the study [13]. This raises the question as to whether the study did include men and women from all socioeconomic strata and perhaps the inclusion of individuals of high socioeconomic class might have yielded higher BMD values. The design of our study that included door-to-door survey and robust randomization technique in household selection ensured that all sections of the society were included, making the reference data more reliable and generalizable.

In our study, BMD significantly correlated negatively with age. Similarly, BMD was positively correlated to BMI and serum testosterone levels (only in men). BMD is expected to decrease with age because bone loss increases as age advances, which is even more pronounced in females than males because of the loss of protective effect of estrogen after menopause [21]. Higher BMI is known to be protective for bone health as adipose tissue has aromatase activity that increases BMD via estrogen [31]. Serum testosterone is also protective for BMD, again via aromatization to estrogen [32]. This is the reason why hypogonadism is associated with osteoporosis, as the accrual of peak bone mass does not occur. However, contradictory data exist wherein authors have shown no correlation between BMD and serum-free/total testosterone levels [33]. In a study from South India, BMI and physical activity were shown to have a protective effect on BMD [34]. While in another study from North India by Marwaha et al., BMD was positively correlated with BMI, similar to what was seen in our study [35]. Surprising it may seem, most of the studies (including ours) do not show any correlation between BMD and serum 25-hydroxyvitamin D levels [35–37]. The prevalence of vitamin D deficiency was quite high in the study population but similar high prevalence of vitamin D deficiency (ranging from 53 to 91%) has been observed in previous Indian studies as well [34, 35].

The use of the derived reference data from this study reduced the prevalence of osteopenia and osteoporosis from 70.2 to 55.9% and from 17.8 to 7.2%, respectively, in men > 50 years and from 48.3 to 32.9% and from 25 to 5.1%, respectively, in post-menopausal women. This was seen at all sites in both men and women. This is however in contrast to what had been reported by Makker et al. and Marwaha et al. who found that the use of indigenous peak femoral neck BMD did not lead to a marked reduction in the number of osteoporotic females as when using the Caucasian database [13, 14]. This partly offsets the need for an Indian database; this is because femoral neck BMD is considered the international reference standard for defining osteoporosis and the decision to treat osteoporosis is based on FRAX score that takes into account only the femoral neck BMD. The contrasting finding of a lower peak femoral neck BMD in our population can be attributed to multiple factors. Compared to the study by Marwaha et al. [14], the BMI in our population was lower and previous

Table 3 Decade-wise distribution of bone mineral density (BMD) at various sites in the women

Age groups (n = 445)	L1-L4 BMD (g/cm^2)	Femoral neck BMD (g/cm^2)	Total hip BMD (g/cm^2)	33% radius BMD (g/cm^2)
20–29 (n = 97)	0.962 ± 0.112	0.773 ± 0.120	0.874 ± 0.133	0.642 ± 0.063
30–39 (n = 96)	0.972 ± 0.103	0.787 ± 0.304	0.901 ± 0.117	0.650 ± 0.056
40–49 (n = 73)	0.955 ± 0.144	0.749 ± 0.147	0.878 ± 0.132	0.645 ± 0.054
50–59 (n = 77)	0.902 ± 0.131	0.740 ± 0.116	0.878 ± 0.114	0.628 ± 0.073
60–69 (n = 57)	0.880 ± 0.142	0.695 ± 0.117	0.838 ± 0.109	0.582 ± 0.070
70–79 (n = 45)	0.937 ± 0.133	0.653 ± 0.104	0.784 ± 0.110	0.565 ± 0.100

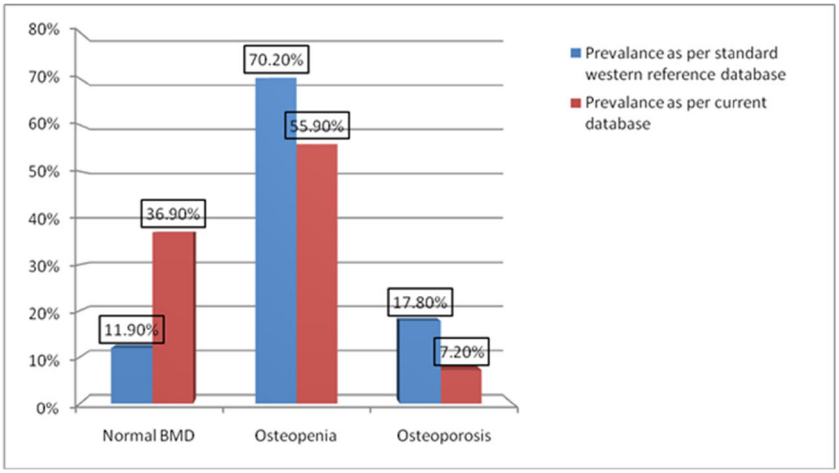


Fig. 2 Bar diagram showing the prevalence of normal BMD, osteopenia, and osteoporosis as per the western database compared to our current database as the reference (men). The difference in the percentages is significant (chi-square statistic value - 45.0, p value < 0.05)

studies [38] have conclusively shown that weight and weight change are independent predictors of femoral neck BMD. Physical activity [38], nutritional status [39], and body fat distribution [40] also have an impact on femoral BMD, which were not accounted for, in the present study. The use of DEXA fan-beam bone densitometer (Prodigy, Lunar, Madison, WI, USA) in the study by Makker et al. as opposed to HOLOGIC Discovery A (QDR 4500; Hologic, Inc., Bedford, MA) used in our study could have also lead to this finding. Overall, we would like to summarize that the differences in the BMD values in the various Indian studies could possibly be attributed to not one, but rather various factors, including but not necessarily limited to regional differences, differences in BMI, different kinds of DXA scanners used, and possible undiagnosed illnesses impacting the BMD. We believe that most of the aforementioned concerns were addressed in our study, except for the regional differences, which necessitates more such studies to be planned in different geographic locations in the country.

Limitations and strengths of the study

Our study is limited by the fact that the number of participants in the 8th decade of life was less as compared to the other age groups. This is because the life expectancy in India is 69 years. Another limitation is that we do not have a clear explanation for the reason behind our study cohort achieving the peak bone mass in the 4th decade of life. However, similar findings have been previously reported by other Indian studies.

To conclude, we have reported reference data on BMD from healthy, adult population of Chandigarh and this BMD reference range can be used to categorize subjects into osteopenia or osteoporosis in the Indian population. However, we also accept the fact that considering the wide diversity of lifestyles, eating habits, and even sunlight exposure across the length and breadth of India, it may not be ideal to extrapolate the data from the present study to the entire country, and more multi-centric studies are needed for the same.

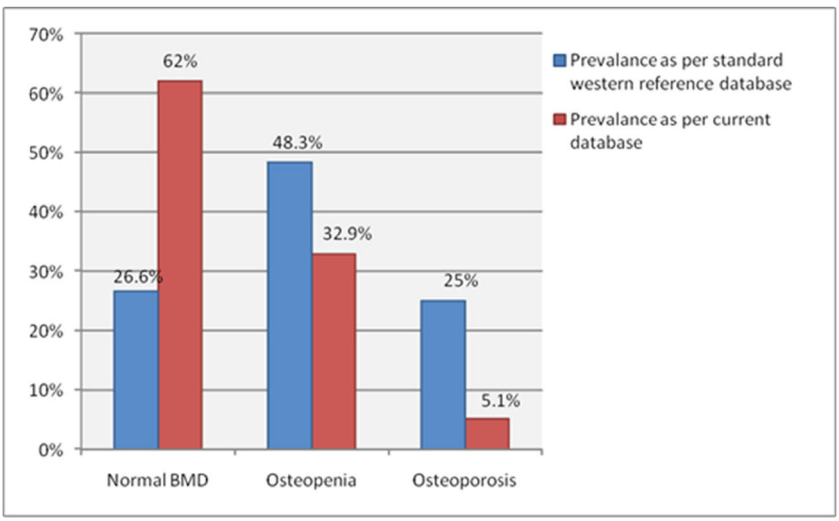


Fig. 3 Bar diagram showing the prevalence of normal BMD, osteopenia, and osteoporosis as per the western database compared to our current database as the reference (women). The difference in the percentages is significant (chi-square statistic value - 43.7, p value < 0.05)

Table 4 Indigenous reference data for BMD from various countries including India published previously

Country	Total number of subjects	Age range used to determine the peak bone mass in men (years)	Peak femoral neck BMD in men (g/cm^2)	Peak lumbar spine BMD in men (g/cm^2)	Age range used to determine the peak bone mass in women (years)	Peak femoral neck BMD in women (g/cm^2)	Peak lumbar spine BMD in women (g/cm^2)
Lebanon[25] (2000)	1023	20–29	1.033 ± 0.1	1.13 ± 0.13	20–29	0.912 ± 0.1	1.13 ± 0.13
Taiwan[26] (2004)	569	20–29	0.909	0.862	-	-	-
Iran[27] (2005)	553	30–39	1.042 ± 0.146	1.216 ± 0.141	30–39	1.022 ± 0.122	1.206 ± 0.1249
Mexico[28] (2006)	6487	20–29	1.185	1.18	20–29	1.070	1.19
Korea[29] (2010)	25043	20–29	0.919 ± 0.132	1.002 ± 0.113	20–29	0.775 ± 0.104	0.961 ± 0.109
India[12] (2010)	800	20–29	0.894 ± 0.131	0.976 ± 0.105	20–29	0.816 ± 0.115	0.954 ± 0.095
Lucknow (India)[13] 2007	1098	20–29 (femoral neck) 30–39 (lumbar spine)	1.019 ± 0.133	0.847 ± 0.136	30–39	0.967 ± 0.107	0.712 ± 0.126
New Delhi (India)[14] 2011	2034	-	-	-	30–35	0.995 ± 0.13	1.123 ± 0.14
Jaipur (India)[15] 2010	300	-	-	-	30–39	0.773 ± 0.120	0.942 ± 0.114
CUBES (current study)	825	20–29 (femoral neck) 30–39 (lumbar spine)	0.841 ± 0.162	0.990 ± 0.113	30–39	0.787 ± 0.304	0.972 ± 0.103

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Author contributions All authors contributed to the study conception and design. Material preparation and data collection and analyses were performed by Anshita Aggarwal, Rimesh Pal, Abhilasha Garg, and Sanjay Kumar Bhadada. The first and the final drafts of the manuscript were written by Anshita Aggarwal and Rimesh Pal and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability Available on request to the corresponding author.

Compliance with ethical standards

Conflicts of interest None.

Ethics approval The study was approved by the Institute Ethical Committee, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

Consent to participate Written-informed consent was obtained.

Code availability Not applicable.

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