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Comparison of bone mineral density in healthy children from many populations: A literature review

Porównanie gęstości minerału kostnego u zdrowych dzieci z różnych populacji. Przegląd piśmiennictwa

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Summary

The aim of this study was to compare bone mineral density data assessed in healthy children from different populations in order to evaluate whether there are substantial differences among children bone mineralization data-sets worldwide. A literature search was performed for papers published during the last 15 years. We found 184 papers providing BMD data assessed in healthy children. To be eligible for the further analysis, the papers had to fit to selected criteria, such as the DXA pencil beam device used for total body, lumbar spine, or femur measurements; BMD data presented as g/cm^2; and Caucasian children aged 4-20 years. Finally, 37 papers matched our criteria and the BMD data-sets were analyzed according to age and gender as well as the origin of the DXA devices (Hologic and Lunar). GraphPad Prism software was used to analyze the 139 groups of data-sets.

Significant differences in age-, gender-, and device-matched BMD data were found in 38 of the 139 analyzed groups (27.3%). Two population-specific BMD data-sets assessed in healthy children markedly differed from the other data-sets in the whole analyzed age range. The apparent differences found in nearly 30% of the analyzed data-sets suggested that the tempo of bone mineralization as well as the amount of achieved BMD might be population specific. However, those differences might also be the consequence of different study design (cohort, prospective) as well as their varied scientific purposes. Moreover, the numbers of children included in the age and sex groups differed markedly.

Analysis of published data on many populations indicates that substantial differences in bone mineral density data exist at least in some age groups of healthy children. However, these differences might also reflect different study purposes and designs. Therefore there is a substantial need to establish population-specific reference BMD data based on studies with a consistent study design.

Key words: bone mineral density • healthy children • comparison of reference data • densitometry

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Introduction

Osteoporosis is traditionally considered as a disease of elderly, but the risk of osteoporosis in later life, at least in part, is influenced by the amount of bone accrued during childhood and adolescence years. Therefore, the increasing interest has been noted concerning bone mineral acquisition during growth and maturation period due to identify bone mass determinants and risk factors.

Because of its precision and low radiation dose, dual energy x-ray absorptiometry is broadly considered the preferred diagnostic method both in adults and children. The main advantages of this technique are related to reproducibility and high degree of achieved standardization (although not in children) supported by a great number of clinical evidences and agreements between many researchers, including World Health Organization [1, 2] experts. The pitfalls are generally related to complexity of the measured system and technical limitation of densitometry.

The DXA-assessed results are expressed as bone mineral content (BMC) in g per unit of the projected area of the corresponding bone(s) (BMD). The interpretation of DXA data in children is based on Z-score values, derived from age- and gender- matched reference groups of healthy children [3].

The DXA reference data are available for different races and for country-specific populations. However, in the case of children, the references are not as well established as in adults and the consistency of pediatric normative data seems to be unclear. This can be related to the fact, that most pediatric bone mineral density (BMD) reference data sets contain relatively small numbers of subjects within each age category. Further, it is noteworthy that DXA scanners markedly differ in their calibration for bone and soft tissue masses. Moreover, even within the same brand, differences between densitometers may exist due to software versions and technical changes in novel models. In consequence, the marked differences are expected between age-specific BMD means and standard deviations [4–7].

The aim of this study was to compare bone mineral density data assessed in healthy children from different populations in order to evaluate whether or not substantial differences are present or not in the worldwide available data sets.

A literature search was performed for papers published during the last fifteen years. Medline, subscription ″on-line″ via internet, personal contact with authors and citations from other papers were used as sources for the collection of data. Fifty-one journals in the fields of pediatric research, bone metabolism, endocrinology, physiology, epidemiology, radiology, nutrition, orthopedic issues and sport medicine were included in the search. Key words were: ″bone mineral density″, ″densitometry″ and ″healthy children″. The total number of 184 papers was found at the first step of the searching process. In the next step, the manuscripts showing only volumetric bone mineral density (vBMD, g/cm3) or bone area (BA, cm2) data were excluded, because the number of data sets was not suitable for statistical comparisons. We have not found a sufficient number of data sets either assessed using either Norland devices or fan-beam devices. Furthermore, the manuscripts, in which DXA measurements were done at sites other than total body, anterio-posterior lumbar spine (A-P) and femur, were also excluded. Moreover, due to diversity of statistical adjustments, the papers containing BMD values normalized for Tanner stage, age of menarche, bone age, body height, weight or body mass index were omitted. Finally, the following eligibility criteria for further selection of papers were chosen: (i) the total body, lumbar spine or femoral neck bone mineral density (BMD) data were obtained using the pencil beam devices, (ii) the BMD data were expressed in g/cm2 and were obtained from Caucasian children aged 4–20 yrs.

Statistical analysis

Statistical analyses were performed using GraphPad Prism software. The ANOVA or Student t-tests were used to compare DXA variables from different populations. All p values <0.05 were considered significant.

In the case of graphical data presentation, the mean bone mineral density (BMD) and standard deviation (SD) values were read from charts. If the standard deviation was not shown in the paper, SD values were calculated as the non-weighted mean of SD's from other data-sets, according to DXA device manufacturer, measurement type, age and gender.

Results

Fifty-seven papers that matched our eligibility criteria were analyzed according to age and gender as well as the DXA device manufacturer. In general, the collected papers had different study design. The typical purposes of analyzed papers were as follows: to establish reference data in local population, to assess the factors that modulate BMD including calcium dietary intake, the physical activity, the skin synthesis of vitamin D3, the breast feeding or artificial feeding in infants. The other purposes included the influence of smoking during pregnancy, the maternal peak bone mass, race, environmental factors, bone turnover, the muscle and fat masses and genetic factors and its relation to bone metabolism.

Summary of the data concerning Hologic apparatus

There were 31 papers concerning measurements on Hologic pencil beam apparatuses, in which 58% were cross-sectional, 26% were prospective and 16% joined both types of study design. The 58% of papers were focused on factors which can modulate BMD. The 42% were done to establish reference data in local population. In 48 % of analyzed papers the total body, lumbar spine and femoral neck were measured. The total body and lumbar spine were assessed in 7% of manuscripts, whereas 19% showed femoral neck and lumbar data. Further, 23% of total number of papers showed only the total body data and 3% presented only lumbar spine results. The commonly used data presentation form was tables (68%), whereas graphs were used in 6% of papers. Both forms of data presentation were used in 26% of papers. In 52% of papers DXA data were limited to females. Three percent of papers were focused on male DXA data. The BMD data analyzed in both genders were noted in the 45% of the manuscripts.

Since several papers studied nearly the same population but in a different manner, finally 20 papers [8–27] (Table 1) and BMD data-sets were analyzed according to age and gender as well as the site of measurements. A total of 3770 children of both genders were analyzed for the femoral neck BMD, 3556 for total body BMD and 1417 for lumbar spine BMD. The number of children in the population specific age groups varied from 2 to 316 (according to gender and the measured site). The results of these studies are presented in figures 1–6. Most of the papers included results assessed in the femoral neck in both girls and boys (fig. 1, 2). The biggest differences between population specific data-sets were observed in ages 9–12 and 14 yrs in both genders. In children younger than 8 yrs of age the comparison analyzes were not performed due to absence of data-sets. In the case of total body BMD in girls (fig. 3) statistically significant differences were observed in 18 yrs and 20 yrs groups. Data-sets slightly differed also in the ages 11–13 yrs but without reaching significance. On the contrary, in boys, statistically significant differences between data sets were observed in 14 yrs old group (fig. 4). However, the difference in g/cm2 was not so big, but due to the relatively high number of children in this population specific age group, significance level was reached. In boys and girls aged 7 yrs and less, only a few data-sets were presented, so analysis for this site could not be performed. In girls, in A-P spine measurements (fig. 5), statistically significant differences were observed in ages 10–19 yrs, with the exception of 11, 13 and 15 yrs. Most of the differences concerned the Swiss population [16], which differed significantly from others in the whole of its age range. Only in the 13 and 15 yrs age groups the differences did not reach significance level due to the small number of children. Difference in g/cm2 in this group was not smaller than in other groups which showed statistical significance. On the contrary, in boys (fig. 6), there was significant difference only in 14 yrs group, partially due to the small number of data-sets.

Summary of the data concerning Lunar apparatuses

There were 26 papers concerning measurements on Lunar pencil beam systems. Seventy-three percent of papers were cross-sectional, 8% were prospective and 19% included data of both types of study design. Most of studies (62%) were done for establishing reference data for local populations, 38% for studying factors affecting bone mineral density. Nearly the half of the papers (44%) included 3 measurements sites, 8% included total body and lumbar spine, 12% femoral neck and lumbar spine, 4% total body and femoral neck, 20% only total body and 12% lumbar spine. The commonly used data presentation form was tables (58%), graphs were used in 19% of papers and both forms were used in 23% of papers. In 23% of papers only girls were under investigation, in 15% boys and in 62% both sexes.

Table 1. Populations of analyzed papers – Hologic.
Tabela 1. Populacje w analizowanych pracach – Hologic.

Number of paper	Country of origin
8	USA
9	Canada
10	USA
11	Iceland
12	Australia
13	Australia
14	Holland
15	Spain
16	Swiss
17	Swiss
18	USA
19	France
20	Australia
21	USA
22	USA
23	England
24	USA
25	USA
26	USA
27	USA

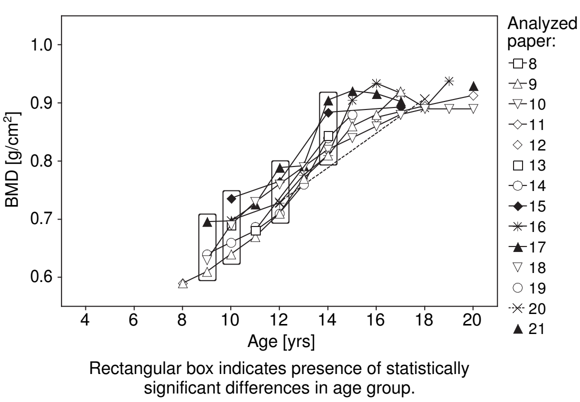


Figure 1. Femoral Neck BMD in Girls (Hologic).
Rycina 1. Gęstość minerału kostnego szyjki kości udowej u dziewcząt (Hologic).

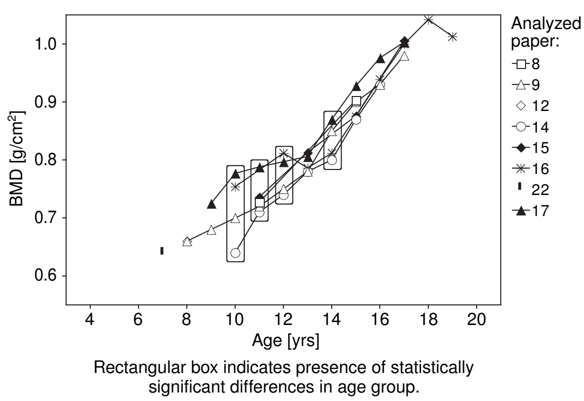
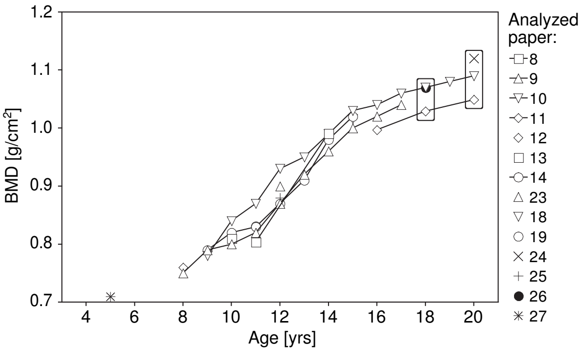
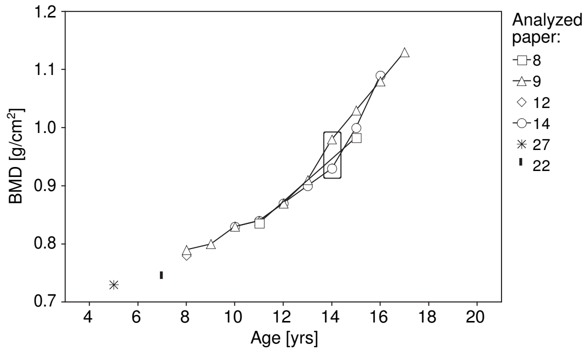


Figure 2. Femoral Neck BMD in Boys (Hologic).
Rycina 2. Gęstość minerału kostnego szyjki kości udowej u chłopców (Hologic).



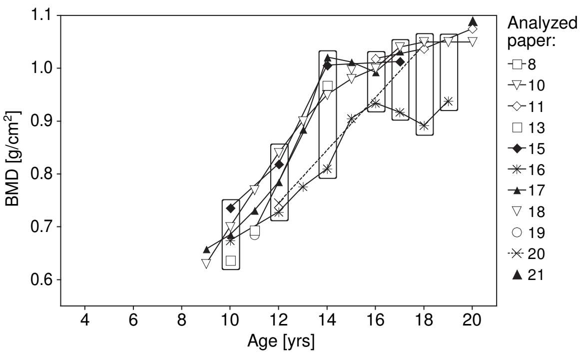
Rectangular box indicates presence of statistically significant differences in age group.

Figure 3. Total Body BMD in Girls (Hologic).
Rycina 3. Gęstość minerału kostnego całego kośćca u dziewcząt (Hologic).



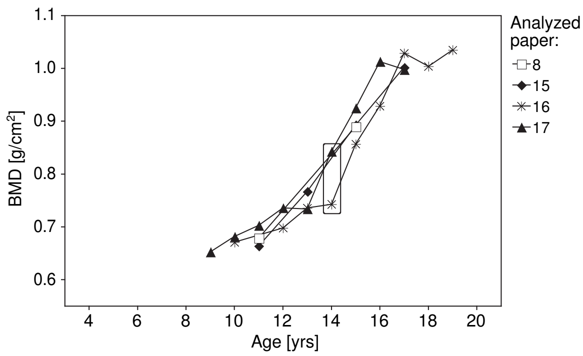
Rectangular box indicates presence of statistically significant differences in age group.

Figure 4. Total Body BMD in Boys (Hologic).
Rycina 4. Gęstość minerału kostnego całego kośćca u chłopców (Hologic).



Rectangular box indicates presence of statistically significant differences in age group.

Figure 5. AP Spine BMD in Girls (Hologic).
Rycina 5. Gęstość minerału kostnego kręgosłupa lędźwiowego u dziewcząt (Hologic).



Rectangular box indicates presence of statistically significant differences in age group.

Figure 6. AP Spine BMD in Boys (Hologic).
Rycina 6. Gęstość minerału kostnego kręgosłupa lędźwiowego u chłopców (Hologic).

Since several papers studied nearly the same population but in a different manner, finally 17 papers [28–44] (Table 2) and BMD data-sets were analyzed according to age and gender as well as the site of measurements. 1967 children of both sexes were analyzed for total body, 1956 for lumbar spine and 676 for femoral neck. Numbers of children in population specific age groups varied from 2 to 212 (according to sex and kind of measurements). Results are presented in figure 7–12. In the case of femoral neck (fig. 7, 8) there was a small number of papers and data-sets were difficult to analyze due to the narrow age range presented in the papers. Although, statistically significant differences were detected in girls (age 13 and 15 yrs) as well as in boys (age 10 yrs). Large number of the papers includes total body measurement. In girls (fig. 9) in this site, statistically significant differences between data-sets were observed in age 5 and 10. However, the small number of data-sets in this age range made statistical analyses difficult. The observed differences concerned mostly the Australian data-sets [32], which differed from others in 2 of 4 studied in that paper's age groups. In boys (fig. 10) Australian children differed from others, too. Papers for A-P spine presented a large number of data-sets but, in contrast to total body, most of them had a wide age range. In girls (fig. 11) statistically significant differences were observed in age 5–9 yrs and 12–13 yrs. In older girls differences in g/cm2 were also big but due to the relatively large standard deviation the differences were not statistically

Table 2. Populations of analyzed papers – Lunar.
Tabela 2. Populacje w analizowanych pracach – Lunar.

Number of paper	Country of origin
28	Sweden
29	Finland
30	Sweden
31	New Zealand
32	Australia
33	USA
34	Sweden
35	Holland
36	Sweden
37	Australia
38	USA
39	Australia
40	USA
41	Czech Republic
42	Spain
43	Brazil
44	New Zealand

significant. In boys (fig. 12) statistically significant differences were present in age groups 5–7 yrs and 13–14 yrs. In others age groups data-sets were close.

There were also observed systematic differences between Hologic and Lunar apparatuses. Evaluation of the data in the corresponding measurement site shows that Lunar densitometers give higher BMD values than Hologic instruments in the whole age range. However, population evaluated on Lunar and Hologic instruments are not the same.

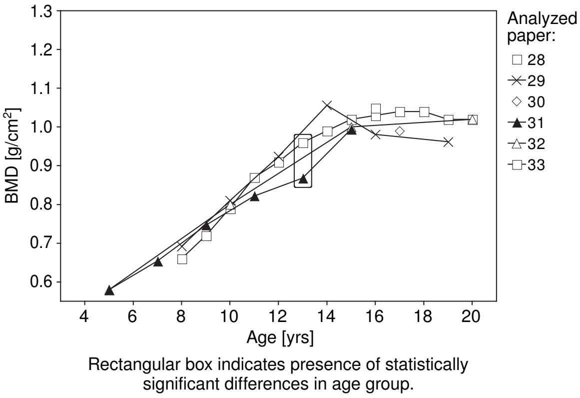


Figure 7. Femoral Neck BMD in Girls (Lunar).
Rycina 7. Gęstość minerału kostnego szyjki kości udowej u dziewcząt (Lunar).

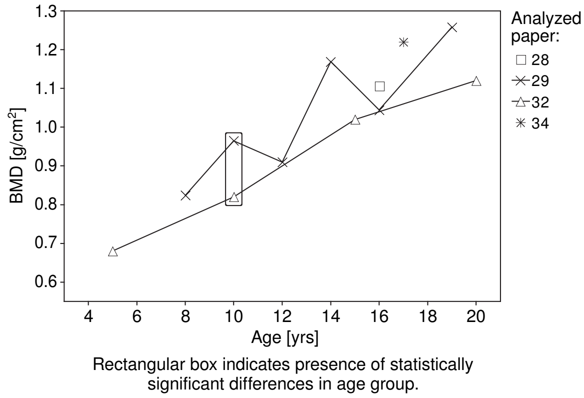


Figure 8. Femoral Neck BMD in Boys (Lunar).
Rycina 8. Gęstość minerału kostnego szyjki kości udowej u chłopców (Lunar).

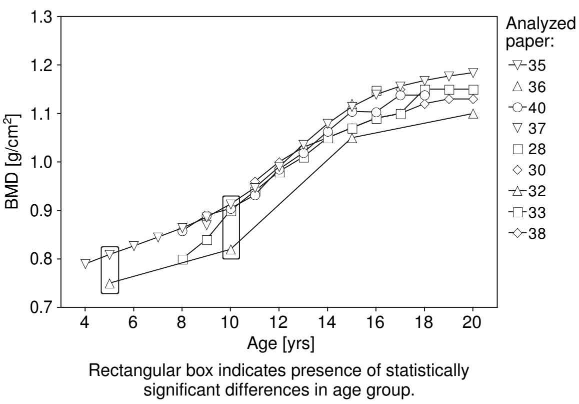


Figure 9. Total Body BMD in Girls (Lunar).
Rycina 9. Gęstość minerału kostnego całego kośćca u dziewcząt (Lunar).

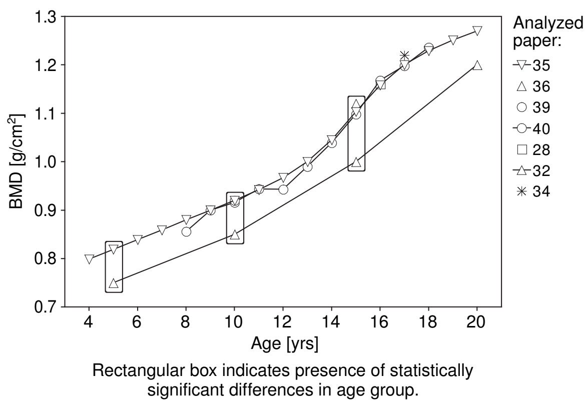


Figure 10. Total Body BMD in Boys (Lunar).
Rycina 10. Gęstość minerału kostnego całego kośćca u chłopców (Lunar).

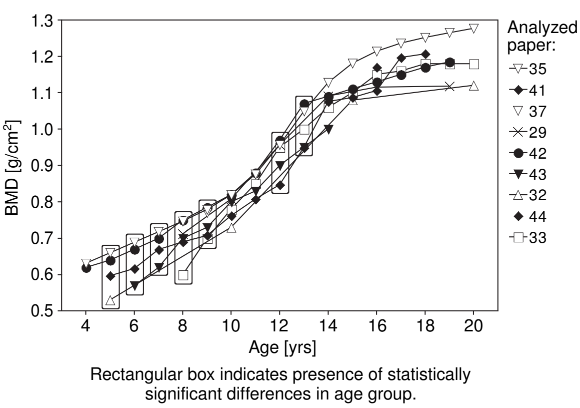


Figure 11. AP Spine BMD in Girls (Lunar).
Rycina 11. Gęstość minerału kostnego kręgosłupa lędźwiowego u dziewcząt (Lunar).

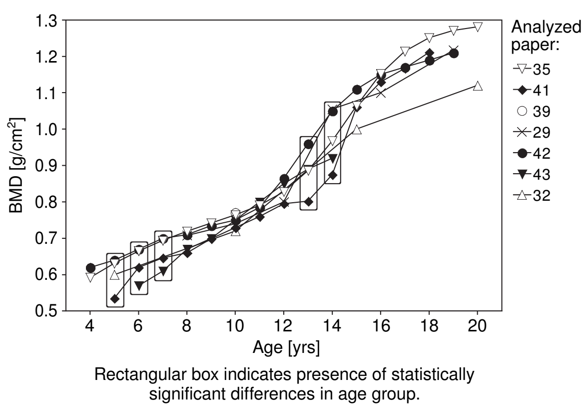


Figure 12. AP Spine BMD in Boys (Lunar).
Rycina 12. Gęstość minerału kostnego kręgosłupa lędźwiowego u chłopców (Lunar).

Discussion

The analysis of papers concerning bone mineral density in healthy children from different populations, published to date, showed big discrepancies in study designs. These discrepancies include different numbers and age range of children, different types of studies regarding time-pattern (cross-sectional, prospective) and time of duration as well as the purposes of studies. However, the analyzed papers are, in general, consistent concerning the race, measurement sites, age and DXA devices and data-sets were analyzed by age; according to type of densitometer, measurement site and sex. Overall, statistically significant differences were detected in nearly 30% of the analyzed age groups. There were 2 populations which differed markedly from others. The Swiss population [16] differed significantly in girls (A-P spine). Interestingly, girls in femoral neck and boys in lumbar spine and femoral neck from the same population did not differ significantly from others. Australian boys and girls [32] differed from others in total body, especially in the younger age range. In older children the difference did not reach statistically significance due to relatively larger standard deviation (data not shown). These Australian children had nearly the same BMD in both lumbar spine and femoral neck as in other populations. There were also statistically significant differences observed concerning a single age group between populations. Moreover, some of the data-sets had only one age group, which makes it difficult to compare to other populations.

Observed differences may be related to different velocity in bone mineralization as well as to amount of accrued BMD. However, its interpretation is difficult due to the large number of factors influencing BMD. In general, BMD values correlate with anthropometric parameters such as body height, weight and BMI [45] and depend strongly on Tanner stage. Unfortunately, the analyzed papers do not include such data in sufficient amount which makes it impossible to analyze probable differences between populations concerning these parameters. On the other hand, BMD values are also influenced by muscle mass [46–53]. It is possible that muscle mass could differ between populations and may partially explain differences in BMD, as it was demonstrated between boys and girls [54–57]. Moreover, BMD does not represent real ″bone tissue mineralization″ but depends also on bone size, cortical layer thickness and cortical/trabecular compartments ratio, which may be different in the populations studied.

The observed differences are relatively high and, in some age groups, they reach about 0.15 g/cm2, so it can exceed 1 SD of normative data. A similar observation was made by Leonard et all [4] who compared diagnostic classification of diseased children using different reference values. The authors concluded, that the use of different published reference data causes inconsistent diagnostic classification of patients. This indicates, that choosing the appropriate reference data-set is crucial for proper diagnostic classification of patients and should be done with concentrated attention, especially when native reference data are unavailable.

Among the different measurement sites, femoral neck seems to be the most difficult from a methodological point of view. Proper rotation of the leg is difficult as well as fixing the region of interest, especially in younger children. This caused relatively low number of papers in which such kind of measurement was utilized. On the contrary, lumbar spine appeared as the best described site owing to relatively big number of broad-age studies, especially by Lunar. Interestingly, in puberty, there were no statistically significant differences between populations, so in this period selection of reference data is not as important as in younger children and teenagers, when differences between populations were apparent. A-P spine measurement also has advantage in relation to bone composition and development. Vertebrae were more trabecular than other bones and only about 50% of the change in BMD is due to expansion of bone volume [45], whereas in long bones it could be about 95%. These make A-P spine measurements attractive in diseases which affect mostly trabecular bone. However, total body measurement provides information about development of skeleton in global and could be a source of additional information concerning body composition, especially lean body mass, which may help to recognize muscle-skeletal interactions and, could be the basis for the diseases.

Conclusion

Analysis of published data concerning many populations indicates, that substantial differences in bone mineral density data are existent at least in some age groups of healthy children. However, those differences might also reflect different study purposes and study designs. Therefore, there is substantial need to establish population specific reference BMD data based on studies with a consistent study design.

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