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■ Review article ■

Pediatric dual-energy X-ray absorptiometry: interpretation and clinical and research application

Jung Sub Lim, M.D.

Department of Pediatrics, Korean Cancer Center Hospital

= Abstract =

Peak bone mass is established predominately during childhood and adolescence. It is an important determinant of future resistance to osteoporosis and fractures to gain bone mass during growth. The issue of low bone density in children and adolescents has recently attracted much attention and the use of pediatric dual-energy X-ray absorptiometry (DXA) is increasing. The process of interpretation of pediatric DXA results is different from that of adults because normal bone mineral density (BMD) of children varies by age, body size, pubertal stage, skeletal maturation, sex, and ethnicity. Thus, an appropriate normal BMD Z-score reference value with Z-score should be used to detect and manage low BMD. Z-scores below -2.0 are generally considered a low BMD to pediatrician even though diagnoses of osteoporosis in children and adolescents are usually only made in the presence of at least one fragility fracture.

This article will review the basic knowledge and practical guidelines on pediatric DXA based on the International Society for Clinical Densitometry (ISCD) Pediatric Official Positions. Also discussed are the characteristics of normal Korean children and adolescents with respect to BMD development. The objective of this review is to help pediatricians to understand when DXA will be useful and how to interpret pediatric DXA reports in the clinical practice for management of children with the potential to develop osteoporosis in adulthood. (Korean J Pediatr 2010;53:286-293)

Key Words : Dual-energy X-ray absorptiometry, Osteoporosis, Low bone mineral density, Fracture, Child, Adolescent

Introduction

Osteoporosis is a major global public health concern. The incidence of osteoporosis and its subsequent morbidity is expected to increase dramatically over the coming decades in many regions, including Korea. Although it is considered as a disease of the elderly, there is now universal agreement that osteoporosis has a pediatric origin[1]. If individuals fail to achieve optimal peak bone mass (PBM) and strength childhood and adolescence, there is a likelihood of development osteoporosis later in life[2]. Genetic factors play an important role in the attainment of PBM. Lifestyle factors such as physical activity and nutrition are also important[3]. Chronic illness itself and various related treatments also tend to cause impairment of acquisition of bone mass, long-term adult bone health and to increase the risk of fracture[4, 5]. Furthermore, increased knowledge and improved care for children with chronic illness has led to many children living long enough to develop osteoporosis even in childhood or adolescence[4, 5].

Measurement of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) is the gold standard method for non-invasive diagnosis of osteoporosis[6, 7]. The World Health Organization (WHO) reported a classification of BMD for the diagnosis of osteoporosis based on DXA. DXA is easy to perform, safe, and clinically acceptable for children as well as adults. Thus, the use of pediatric DXA in the clinical and research fields has rapidly increased[8].

This article will discuss the basics of pediatric DXA and will review normal stages of BMD development of each region of interest (ROI) and PBM acquisition in Korean children and adolescents. The indications for pediatric DXA, clinical practice of pediatric DXA including cautions on interpretation, and other research applications of DXA will be described.

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Address for correspondence : Jung Sub Lim, M.D.
Department of Pediatrics, Korean Cancer Center Hospital, 215 Gongneung-dong, Nowon-gu, Seoul 139-706, Korea
Tel : +82.2-970-1224, Fax : +82.2-970-2403
E-mail : limjs@kcch.re.kr

Characteristics of bone mass acquisition in Korean children and adolescence

The most important aspect of pediatric DXA is to use an appropriate normative data set because the BMD and PBM differences are dependent on age, puberty, sex, and ethnicity[6, 9]. A BMD normative data set for Korean children and adolescents has been recently established and published[10, 11]. One notable characteristic of Korean children and adolescents is an earlier onset of BMD acquisition. Otherwise, the BMD and PBM trends are similar to those of other ethnicities.

BMD accretion at the lumbar spine in Korean girls has the highest rate between ages 11 to 13, while boys have the highest rate between ages 12 to 14, about six months after peak height velocity. Dutch children have the highest rate of lumbar spine BMD accretion that occurs one year later than in Korean children[10]. When compared with Korean adults, the lumbar spine BMD and femur neck BMD values of Korean girls over 18 yr and Korean boys over 19 yr were the same as the values measured for 20 to 30-yr-old Koreans[12]. Therefore, Koreans achieve essentially the same peak BMD in the lumbar spine and femur neck late in the second decade of life. On average, 90% of peak bone mass (PBM) is acquired by the age of 19 in other ethnicities[2, 7].

During puberty, Koreans have an increase in lumbar spine BMD, which is similar to that of other ethnic groups. The percentages of BMD acquisition at the lumbar spine in Koreans between Tanner stage (TS) 1 and TS 5 were found to be 65% in girls and 66% in boys. Koreans also tend to have a higher rate of trabecular bone mass (lumbar spine) acquisition than cortical bone mass acquisition (total body or femur neck) during puberty. The whole body BMD increases to 43% in girls and 51% in boys. Korean girls also have an earlier onset of the BMD plateau than boys, as observed for other ethnicities. The plateaus of the lumbar spine BMD and whole body BMD in girls occurred at ages 15 and 17 respectively. The plateaus of BMDs in each ROI occurred at age 17 in boys[10].

Bone mineral density and size in the prediction of fracture risk

Diagnosis of osteoporosis in children remains challenging. In adults, a DXA T-score is defined as the number of standard deviations (SDs) away from the mean BMD of a healthy young population. Several epidemiological studies have confirmed the association between a low BMD T-score and fracture risk in the elderly population. The fracture risk doubles for every SD decrease in BMD T-score [13]. Thus, DXA became the principal tool for diagnosing adult osteoporosis. In children, the association between low BMD Z-score and fracture risk is not well established. However, ISCD adopted DXA in assessing bone mass in children and growing evidence suggested that low bone mass might contribute to fracture risk in childhood[14, 15].

Fractures are common and the prime reason for hospitalization of children. Forty-two percent of boys and 27% of girls experience at least one fracture between the age of 0 to 16[16]. Studies in generally healthy children have found that those who sustain a forearm fracture have a lower mean bone density than peers without a history of fracture[17]. Recently, a systematic review and meta-analysis of the association between bone density and fractures in otherwise healthy children concluded that lower total body and spine BMD can be a predictor of an upper extremity fracture during puberty[14]. The total body less head (TBLH; the ROI of total body after subtraction of cranium) bone mineral content (BMC) adjusted bone area is expected to increase the risk of fracture by about 89% per each SD decrease. In the same cohort, it was found that fracture risk from both slight and moderate-severe trauma is related to changes in TBLH bone size relative to body size[18]. A small increase in the bone diameter will increase bone strength markedly[19].

Indications for pediatric DXA

Before ordering a DXA analysis, pediatricians should consider how the information will influence clinical management[6, 20]. In adults, DXA is performed to predict fracture, to decide which patients warrant treatment, and to monitor response to therapy. The rationale for pediatric DXA is potentially the same in children. The International Society for Clinical Densitometry (ISCD) has suggested that the DXA analysis be carried out for any child who is being treated or considered for treatment of osteoporosis[5]. Children whose potential fracture risk is likely to exceed that of normal children should obtain DXA measurements. This will include children with primary bone diseases (such as

osteogenesis imperfecta and idiopathic juvenile osteoporosis). Children with secondary conditions that affect bone health should also obtain DXA measurements (Such secondary conditions include immobilization, inflammation, endocrine disturbance, malignancy and treatment, transplantation recovery apparent osteopenia on radiographs, and systemic use of long-term steroids)[4, 5, 21]. Previous studies have established that children with chronic disease have lower BMD than their healthy counterparts[4, 5]. Certain children treated with specific medications, such as corticosteroids, anticonvulsants, and chemotherapeutic drugs, do not acquire adequate BMD during growth, and, thus, have an increased risk of fractures in later life[21, 22]. In addition, most children with chronic disease are subject to risks in skeletal health as a result of a combination of risk factors including malnutrition, malabsorption, vitamin D insufficiency, immobilization, deficiency or resistance to sex steroids or growth hormone, and increased cytokine production[5].

Pediatric DXA testing is not routinely indicated for the evaluation of all chronic disease. Any additional risk factors such as disease severity, dose and duration of exposure to potentially harmful medication, bone pain, a history of fracture after minimal trauma, osteopenia on a plain film, and recurrent or low-impact fractures history are useful parameters for identification of candidates for DXA testing. Causes of pediatric osteoporosis and commonly indicated diseases for DXA are listed in Table 1.

Table 1. Lists of Diseases Associated with Low Bone Mass or Fractures in Children and Adolescents

Genetic Defects
Osteogenesis imperfecta
Turner's syndrome (XO)
Klinefelter's syndrome (XXY)
Down's syndrome (21 trisomy)
Ehlers-Danlos syndrome
Marfan syndrome
Phenylketonuria
Glycogen storage disease
Wilson disease
Gaucher disease
Cystic fibrosis
Heredity hemochromatosis
Endocrine disorders
Hypogonadism
Growth hormone deficiency
Cushing's syndrome
Primary hyperparathyroidism
Acromegaly
Diabetes
Chronic diseases
Rheumatic disorders (juvenile rheumatic arthritis, systemic lupus erythromatosis and others)
Renal disease
Inflammatory bowel disease
Liver disease
Malabsorption (celiac disease)
Chronic obstructive lung disease
Congenital heart disease
Hemophillia
Leukemia
Lymphoma
Solid tumors
Iatrogenic disorders causing osteopenia/osteoporosis
Glucocorticoid excess-either systemic or inhaled
Anticonvulsants
Chemotherapy
Central Precocious Puberty
Immune suppressant (Cyclosporin)
Radiotherapy
Nutritional Disorders
Malnutrition
Vitamin D deficiency
Vitamin K deficiency
Anorexia Nervosa
Total parenteral nutrition
Preterm infants
Calcium deficiency
Disorders causing disuse osteoporosis
Chronic diseases
Celebral palsy
Huntington disease
Burns
Muscular dystrophy
Others
Idiopathic juvenile osteoporosis
Constitutional delay of puberty

Ordering a pediatric DXA analysis

The posterior-anterior (PA) lumbar spine and TBLH are recommended sites for performing BMC and areal BMD measurements in both children and adolescents because the most accurate and reproducible measurements can be obtained in these areas. The hip (including proximal femur and total hip) is not a reliable site for measurement in growing children due to significant variability in skeletal development, lack of reproducibility and limited normal reference data[6]. However, selection of regions of interest (ROI) for DXA analysis depends upon clinical concerns and the options within the clinical setting[8].

For example, sex steroid deficiency typically causes greater loss in trabecular bone[23]. Selecting lumbar spine as the ROI to be scanned is appropriate as spine is rich in trabecular bone. On the other hand, growth hormone deficiency causes a predispositions to greater loss of cortical

bone. In that case, total body scans may be needed[24]. In the evaluation of localized osteoporosis in osteosarcoma patients, the hip scan is advised in case of appropriate pediatric reference data are available. In osteosarcoma patients, comparisons of both extremities and follow-up studies of the affected limbs are needed.

There is a significant association between TBLH and fractures. As a result, the ISCD recommends TBLH measurements instead of total body measurements. However, many studies show that the total body BMD scan is used clinically because most pediatric-based software can only provide total body results. The pediatric normal references of TBLH are limited.

Analysis of Pediatric DXA Results

In a pediatric DXA report, the Z-score should be assessed instead of the T-score. Subsequently, the patient's anthropometric data, including age, gender, ethnicity, weight, height, and Tanner stage should be verified. Next, the patient's position and analyzed ROIs should be verified as appropriate, and it should be confirmed that no artifacts exist, which would lead to abnormal results. The proper patient position for DXA scanning is illustrated in Fig 1. The lumbar spine should be straightened and centered in the image with visualization of the last rib pair and the upper sacrum. The femur neck and the femoral shaft should be parallel to the long axis of the image with only a small portion of the lesser trochanter visualized. Total body scanning after proper positioning according to the machine type provides measurements of total body BMC, BMD, and body composition including fat, lean body mass, bone mineral content, and percentage of fat. Extraneous artifacts, including buttons, coins, enteric tubes, and orthopedic hardware should be excluded from the image. The next step is to check the Z-score. The Z-score is a standard deviation score compared to a Korean normal control adjusted for age and sex. A proper control should be obtained for interpretation of pediatric DXA results. A common mistake of erroneous interpretation of pediatric DXA is to use a T-score based upon a comparison with peak adult BMD. In one report, 62% of children for referred for osteoporosis were misdiagnosed because adult reference data was used rather than pediatric norms[25]. The T-score measures the bone density loss occurring from early adulthood. Its use for analyzing pediatric data will cause a significant misdiagnosis[6]. When T-scores are obtained, adult software is used to analyze BMD instead of pediatric software. The analysis algorithm of the adult software significantly overestimates the lumbar BMD and underestimates the lumbar BMC relative to the pediatric software because pediatric bone is naturally less dense than adult bone[26]. The algorithm used in the pediatric DXA software is adapted for improved edge detection of lower density pediatric bone in order to address this problem[7, 20]. The final step is to verify that the correct version of the DXA software was used and include this verification in the DXA reports.

Interpretation of Pediatric DXA

In children and adolescents, the terms "low bone mineral content" or "low bone mineral density for chronological age" have been recommended for use in DXA reports rather than the terms osteopenia and osteoporosis[6]. Importantly, the diagnosis of osteoporosis should not be made solely on the basis of DXA results . Diagnosis of osteoporosis requires a clinically significant fracture history such as one long-bone fracture of the lower extremity, vertebral compression fracture, and two or more long-bone fractures of the upper extremities in addition to low bone mass. Low bone mass is diagnosed when a BMC or areal BMD Z-score of known ROI is less than or equal to −2.0 (with the Z-score adjusted for age, sex, and body size). If Z scores are not provided by the DXA software, published pediatric reference data can be used to calculate them. Several DXA studies providing normative data from healthy Korean children are summarized in Table 2. It is essential to use a normal reference obtained from the same instrument because there are systematic differences among the different DXA machines.

The pattern of mineral accrual is linked more closely to pubertal and skeletal maturation than to chronologic age, and these processes tend to vary with gender and ethnicity [6, 27]. For example, children with precocious puberty have abnormally increased BMD relative to chronological age. On the other hand, children with constitutional delay exhibit decreased BMD. For this reason, the influence of height, bone size, and maturation must be considered during evaluation of DXA results. Korean children and adolescents often have a discrepancy between chronological age and bone age[10]. In particular, many children and adolescents

Table 2. Normative Data for DXA in Korean Pediatric Subjects.

Year of Publication (Ref.)	Authors	DXA machine	Number	Age	Site
2009[10]	Lim JS et al.	Lunar Prodigy	514	5-20	Spine, femur, total body, TBLH, BMAD
2007[11]	Lee SHet al.	Hologic QDR Discovery	446	2-18	Spine, femur
2009[33]	Oh YJ et al.	Hologic QDR Discovery	135	6-14	Spine, femur
1998[34]	Cho HJ et al.	Norland XR 26	75	2-15	Spine, femur
1995[35]	Kim BY et al.	Hologic QDR 2000	53	4-13	Lumbar

with chronic disease have a delayed growth, absent or arrested puberty, and altered body composition.

The DXA-derived BMD is based upon two dimensional projection areas of three dimensional structures and provides an areal BMD rather than volumetric (true) BMD. This can causes several problems[5, 6], the most significant of which is that areal bone density may be underestimated in children with smaller bones and overestimated in larger children[5, 6]. Thus several methods have been proposed to solve this problem. One of the commonly used methods makes use of the ""apparent BMD (BMAD)", a mathematically calculated volumetric BMD. The calculation for BMAD is: BMAD (g/cm^3)=$BMD_{LS}\times[4/(\pi\times width)]$[28]. Another measure is the "adjusted bone mass" that is obtained by correcting the lean body mass or height to minimize the influence of bone size or lean body mass[29, 30]. Another possible way of making corrections to the BMD is to use bone age. Height and skeletal maturation generally correlate with bone age rather than chronological age. Bone age is more accurate than chronological age in assessing each individual BMD[6, 10]. However, none of the abovementioned correction methods has been established as the best method according to the gold standard of successful prediction of childhood fracture. Nonetheless, it is possible to estimate how much a reduced BMD can be attributed to smaller bone size by calculating volumetric BMD or using other corrective methods.

Clinical case studies

The following common examples are pediatrics DXA studies interpreted at the Korea Cancer Center Hospital. The reference BMD employed for each ROI is obtained from '*Bone Mineral Density according to Age, Bone Age, Pubertal Stages in Korean Children and Adolescents*'[10]. Subject 1 was a 11.1-year-old male without chronic disease. He was in Tanner stage 1 and weighed 32 kg. His lumbar BMD, left femur neck BMD, and total body BMD were 0.671 g/cm^2, 0.762 g/cm^2, and 0.833 g/cm^2 (normal mean BMD values for a male at the age of 11 are: 0.871±0.137 g/cm^2, 0.786±0.102 g/cm^2, and 0.913±0.070 g/cm^2). According to our normal database, this subject's lumbar, femur neck, and total body BMD were lower than normal, with Z-scores of −1.5, −0.2, and −1.1 respectively. However, his bone age was 9 years. The normal mean lumbar, femur neck, and total BMD of male bone age of a 9 year old male is 0.700±0.076 g/cm^2, 0.731±0.087g/cm^2, and 0.841±0.051 g/cm^2 respectively. Therefore, the corrected BMD Z-scores were −0.4, 0.4, and −1.2 respectively. His diagnosis was constitutional delay. Thus, he was found to have a normal BMD according to bone age. On follow-up DXA, his lumbar BMD, left femur neck BMD, and total body BMD were 0.701 g/cm^2, 0.782 g/cm^2, and 0.862 g/cm^2 (the normal mean BMD for a male at the age of 13 are 0.996±0.127 g/cm^2, 0.731±0.087 g/cm^2, and 0.841±0.051 g/cm^2) respectively and the normal mean BMD values for a male with a bone age of 11 are 0.789±0.075 g/cm^2, 0.813±0.072 g/cm^2, and 0.896±0.041 g/cm^2. The bone age corrected BMD Z-scores were −1.1, −0.4, and −0.8 respectively. His BMD increase at each ROI was found to be within normal range.

Subject 2 was a 15.4-year-old female with panhypopituitarism following an operation for intracranial germinoma. She presented for a baseline study and was in Tanner stage 1 with a body weight of 40 kg. Her lumbar BMD was 0.740 g/cm^2. Using our normal database, the patient's lumbar BMD Z-score was found to be much less than −4.8. The left femur neck BMD was 0.694 g/cm^2 with a Z-score of −1.6. The total body BMD was 0.805 g/cm^2 with a Z-score of −4.3. The patient was reported as having markedly reduced bone density. However, her bone age was 10 years (the normal mean BMD at bone age 10 years for a female is 0.765±0.059 g/cm^2). The corrected BMD Z-scores were −1.1, −0.7, and −2.0 respectively. Her follow-up BMD Z-scores were same for a period of 3 years after growth hormone treatment. It should be noted that a patient with chronic disease exhibits a severe decrease in BMD Z-

score at each ROI with respect to chronologic reference data. Bone age reference values would better reflect the patient's actual bone status. Thus, we used the patient's bone age in interpreting the DXA results.

Subject 3 was a 12.3-year-old male with osteosarcoma in the left femur. On baseline DXA the lumbar BMD was 0.783 g/cm^2 (normal mean BMD at bone age 12 years male; 0.820±0.098 g/cm^2). The left femur neck BMD was 0.785 g/cm^2 and right femur neck BMD was 0.773 g/cm^2 (the normal mean BMD for a male12 years of age is 0.842±0.087 g/cm^2). The Z-score of −0.4, −0.7, and −08 determined using our database was considered to be within normal values. During the next 12 months, the patient underwent a limb salvage operation and chemotherapy with MTX and lost 7 kg while remaining at Tanner stage 2. On follow-up, the DXA analysis indicated that the lumbar BMD was 0.971 g/cm^2 (the normal mean lumbar BMD for a male at age 13 years of age is 0.954±0.161 g/cm^2). The left femur neck BMD was 0.480 g/cm^2 and the right femur neck BMD was 0.700 g/cm^2 (the normal mean femur neck BMD for a male 13 years of age is 0.996±0.127 g/cm^2). The Z-score of each ROI was 0.1, −4.1, and −2.3. Thus, the patient had a slight increase in lumbar BMD value at a time when rapid bone mineral accrual was expected. However, both femur neck measurements indicated a decreased BMD, particularly in the left femur neck. This decrease was rather evident in the Z-score, ranging from −0.7 to −4.1 in the left femur neck. Immobilization might have been the cause of the decreased femur neck BMD. After informing the patient of the DXA results, calcium and vitamin D intake was recommended. Further recommendations for proper exercise were made to increase BMD, and the patient was counseled to manage risks of fracture.

Treatment of osteoporosis

Until recently, there has been no consensus on the treatment of osteoporosis in children and adolescents with the exception of osteogenesis imperfecta. However, the need for osteoporosis therapy is increasing. The basic approach for young osteoporotic patients is to first identify and then eliminate all the known risk factors. Effective control of the underlying disease, adequate supplementation of calcium and vitamin D, and advising increased physical activity are essential and represent the simplest course of action. The advanced approach involves correcting hormonal deficiency and using antiresorptive drugs such as bisphosphonates. The complex issue of treatment with about bisphosphonates is has been addressed in my previous review[21].

Other indication of pediatric DXA

Bone mineral contents and bone mineral density is an important part of body composition together with lean body mass and fat mass. The total (whole) body DXA reports include not only total body BMD but also lean body mass, fat mass, percentage of fat and fat distribution (Fig 1). The body composition difference (especially fat distribution) between age groups, sex, and ethnicity explain the different risk profiles for metabolic disease[31]. The DXA-based body composition reference data of children and adolescents of diverse ethnicities including Korean have been published[32].

Conclusion

The gain of optimal PBM during growth is important for future resistance to osteoporosis and fractures. Because pediatric DXA is a useful tool for evaluation of the skeletal health of children and adolescents with chronic disease, the demand for DXA for children is likely to increase. Pediatricians treating chronic diseases should be aware of pediatric DXA techniques and know when pediatric DXA analysis is recommended, as well as knowing how to interpret DXA reports.

Pediatricians should remember that 1) DXA analysis is the preferred method for assessing BMC and areal BMD, 2) Z-scores (not T-scores) adjusted for with Korean normative children and adolescent data sets should appear on the pediatric DXA reports generated using pediatric software, 3) PA spine and TBLH are the preferred sites for measurements of BMC and BMD, 4) a Z-score less than or equal to −2.0 is indicates "low bone mass,"and 5) the diagnosis of osteoporosis in children and adolescents can be made if low bone mass is observed with clinically significant fragile fractures.

When diagnosed with low bone mass, pediatricians should inform children and their parents of the DXA results. Pediatricians should undertake preventive measures for all skeletal risk factors by optimizing calcium and vitamin D intake, addressing deficiencies of sex steroids and recommend as much weight-bearing activity as possible.

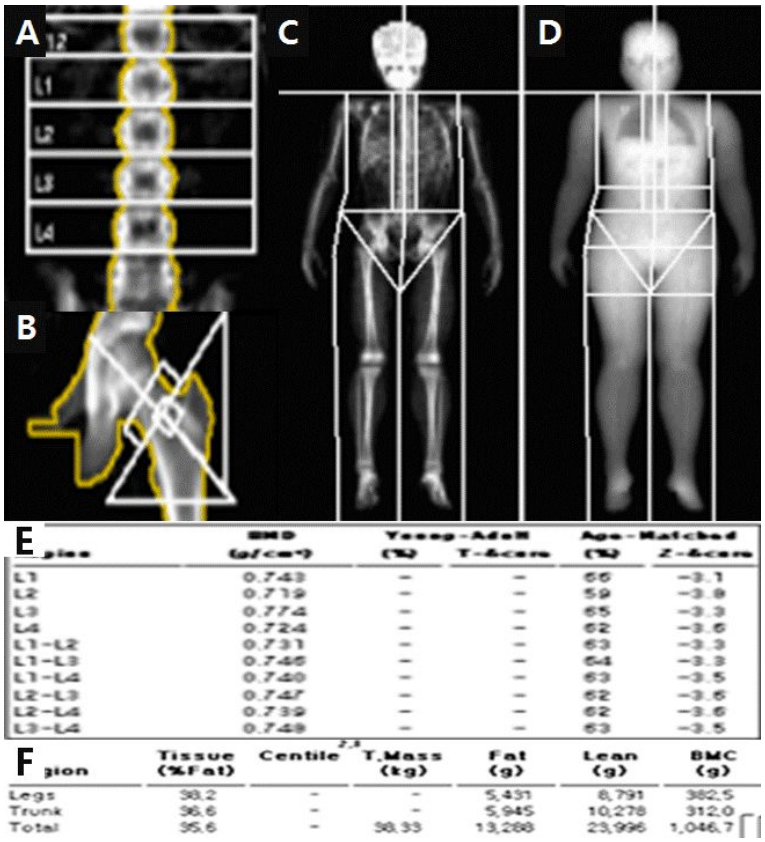

Fig. 1. DXA images. (A) AP image of the lumbar spine showing regions of interest from L1 to L4. Note the presence of the transitional lumbosacralvertebral body. (B) AP DXA image of the left hip shows regions of interest of the femoral neck, greater trochanter, and total hip. (C) Total body scan with sub-regions of interests for trunk, extremities, and head (D) Total body scan of body composition (E) Results of lumbar spine. Note bone mineral density at each level of vertebra and total L1 to L4 is expressed by the Z-score not by the T-score. (F) Expression of body composition including fat, lean body mass, bone mineral content, and fat percentage is expressed.

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