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Evaluation of mandibular cortical bone in a healthy paediatric population

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«Αξιολόγηση του συμπαγούς οστού της κάτω γνάθου σε υγιή παιδιά και εφήβους»

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Contents

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ABSTRACT

Summary

Introduction

The skeletal system plays a pivotal role in children's growth, development, and overall health. Bones provide structural support, protect vital organs, facilitate movement, and serve as a reservoir for minerals essential for numerous physiological processes. Understanding the intricacies of bone health in a healthy paediatric population is of utmost importance, as it lays the foundation for lifelong musculoskeletal well-being.
Bone mineral density, is one of the most important factors to measure bone quality, as it is a reliable and non-invasive method. There are various available techniques that have been used to assess and/or quantify bone density. Radiographic imaging, such as dual-energy X-ray absorptiometry (DXA), remains the gold standard for evaluating bone mineral density. Another frequently used technique is panoramic radiography. Many valid indicators have been developed and used to analyze bone quality and quantity in panoramic radiographs, two of which are the Mandibular cortical index (MCI) and Mandibular Cortical Width Index (MCW). These two indices were created during the past several decades to evaluate the mandibular bone mass's quality and quantity and detect resorption in panoramic radiography.

Aim

The primary aim of the study is to systematically record and evaluate qualitatively and quantitatively the cortical bone of healthy children aged 6-18 years.

Secondary objectives are:

1. To evaluate the distribution of bone density in different gender and age groups.
2. To evaluate cortical bone quality in different gender and age groups.
3. To investigate the possibility that bone density is affected by factors that generally alter occlusion and indirectly masticatory forces such as the presence of extensive carious lesions, missing teeth, extensive resin composite restorations, and Stainless-Steel Crowns.

The ultimate goal of the study is to create reference tables of the thickness of the cortical bone in a healthy Greek population of children and adolescents.

Material and Methods

It was a double-blinded retrospective cohort study evaluating mandibular cortical bone of healthy children and adolescents through dental panoramic radiographs

taken in the context of the patient's dental needs. The dental records of all patients from the Department of Paediatric Dentistry and the Department of Orthodontics (Dental School, National and Kapodistrian University of Athens) treated between 2012 and 2021 were searched for patients, aged 6-18 years of age, with a dental panoramic radiograph available. The period selected ensured that all radiographs are comparable as they have been performed with the same radiographic machine and the possible magnification is the same.

Panoramic radiographs of 660 children aged 6-18 were divided into different groups according to age and gender. The inclusion criteria were panoramic radiographs of good quality of patients with updated medical and dental records. Exclusion criteria were panoramic radiographs of poor quality of patients with diseases/ conditions/ treatments affecting the bone e.g. eating disorders, prematurity, early puberty, musculoskeletal disorders, etc. and of patients undergoing/ undergone orthodontic treatment.

Quantitative assessment was performed by measuring the cortical bone width bilaterally using the Mandibular cortical width (MCW) Index (according to Paulsson-Björnsson et al. 2015) and qualitative assessment using mandibular cortical index (MCI) (according to Klemetti et al 1994). MCI is a qualitative index that evaluates the morphology of the threshold of the cortical bone with the trabecular bone distally to the mental foramen at both sides of the mandible. It is categorized according to a three-point scale C1, C2, C3. MCW is a quantitative index that evaluates the thickness of the cortical bone in both sides of the mandible. In each side a line was drawn along the lower border of the mandible, followed by four perpendicular lines to the tangent at the following points:

1. Antegonion
2. the mesial cementoenamel junction of the first molar perpendicular to the mandibular base
3. the most superior cusp tip of the second premolar perpendicular to the mandibular base
4. the most superior cusp tip of the first premolar perpendicular to the mandibular base

The thickness of the cortical bone was measured using the software Image J (Image J 1.50c4 for Windows XP). As the software measures length in pixels (1024x1024 pixels; 8-bit; 1 MB), all measurements were converted into mm using a calculated coefficient factor. The examiners were calibrated prior to the initiation of the study for both qualitative and quantitative evaluation.

Results

The mean age of the patients was 11.7 years (SD: 3.37 years). Regarding the stage of dentition, for 30.6% of the patients it was early mixed, 23.3% late mixed and 46.1% permanent.

A statistically significant correlation was observed between bone morphology and gender, with girls having more frequent even and sharp endosteal margin of the cortex(C1) compared to boys and boys having more frequent endosteal margin which shows semilunar defects(C2). When bone was evaluated on both the right and left side as in total, a statistically significant correlation was observed with age groups. In particular, the endosteal margin of the cortex was even and sharp on both sides frequently in patients aged 8 to 11 years old compared to other ages. On the other hand, the endosteal margin showed semilunar defects (lacunar resorption) and/or seems to form endosteal cortical residues on one or both sides were more frequent in patients 14+ years old.

In addition, a statistically significant positive relationship was found between all points assessing bone thickness and age (years), meaning that as age increases, bone thickness also increases. Our study also showed statistical differences in terms of the correlation between cortical bone thickness and type of dentition, namely between mixed dentition and permanent dentition. We found that in mixed dentition C1 predominates and in permanent dentition decreases and increases C2.

No correlation was found between bone morphology according MCI Index or bone thickness and the presence of carious lesions, missing teeth, resin composite restorations, and stainless-steel crowns. Furthermore, we created reference tables of bone morphology and the thickness of the cortical bone in a healthy Greek population of children and adolescents.

Conclusions

Within the limitations of this study, it can be concluded that:

- A statistically significant difference was found between gender and bone morphology according to MCI Index. The endosteal margin of the cortex is even and sharp more frequent in girls compared to boys and shows seminular defects more frequent in boys than girls.
- The developmental stage of dentition was statistically significant correlated with the cortical bone thickness, i.e. cortical bone thickness was significantly higher in permanent dentition compared to early or late mixed dentition.
- There is no correlation between cortical bone thickness or bone morphology and factors such as the existence of extensive caries, composites, stainless steel crowns and missing teeth.
- More broad and well-designed studies are required to support the correlations between age/gender and bone morphology or thickness.

- The results of this study can be an important guide for the clinical dentist, who may check the cortical bone thickness in a panoramic radiograph and refer the patient for further examination. Early detection and adequate treatment of low BMD is essential especially when osteoporosis prevention should occur on time or when orthodontic treatment will occur (bone density affects tooth movement).

Key Words: cortical bone, mandible, panoramic radiography, radiomorphometric indices, children

LIST OF ABBREVIATIONS

aBMD	Areal bone mineral density, mg/cm²
BMD	Bone mineral density, mg/cm³
BMI	Body mass index, kg/m²
DM1	Type 1 diabetes mellitus
DXA	Dual-energy X-ray absorptiometry
HbA1c	Long-term blood glucose, % glycated hemoglobin
HR-pQCT	High-resolution peripheral quantitative computed tomography
IGF-1	Insulin-like growth factor 1
pQCT	Peripheral quantitative computed tomography
QCT	quantitative computed tomography
QUS	Qualitative ultrasound
SSC	Stainless Steel Crown
CVM	cervical vertebral maturation method
MCW	Mandibular Cortical Width
MCI	Mandibular Cortical Index
PMI	Panoramic Mandibular Index
AGI	Antegonial Index
MRI	Magnetic resonance imaging

GENERAL PART

Introduction

The skeletal system plays a pivotal role in children's growth, development, and overall health. Bones provide structural support, protect vital organs, facilitate movement, and serve as a reservoir for minerals essential for numerous physiological processes. Understanding the intricacies of bone health in a healthy paediatric population is of utmost importance, as it lays the foundation for lifelong musculoskeletal well-being.

Bone's development is a complex process of interrelated events in space and time. Bone tissue rigidity occurs from the deposition of calcium and phosphorus as hydroxyapatite during the mineralization process. The remaining 30% of the bone is made up of organic material, primarily collagen, with those two minerals making up 70% of the bone. (Kälebo & Strid, 1988a; Field, 1999).

There has been growing concern regarding the prevalence of bone-related disorders among children and adolescents in recent years. Factors such as sedentary lifestyles, poor nutrition, and the increasing prevalence of obesity have contributed to a higher incidence of bone-related issues, including fractures, osteoporosis, and reduced bone mineral density (Gkastaris K,2020). Consequently, there is a critical need to investigate bone health in an otherwise healthy paediatric population to identify potential risk factors, implement preventive measures, and optimize interventions.

Assessing bone health in paediatric populations necessitates the utilization of reliable and sensitive diagnostic tools and techniques. Radiographic imaging, such as dual-energy X-ray absorptiometry (DXA), remains the gold standard for evaluating bone mineral density. However, emerging methodologies, such as quantitative ultrasound (QUS) and peripheral quantitative computed tomography (pQCT), offer additional means of assessing bone quality, microarchitecture, and biomechanical properties (Guerri S,2018).

Another frequently used technique is panoramic radiography. Many valid indicators may be used to analyze bone quality in panoramic radiographs, two of which are the Mandibular cortical index (MCI) and Panoramic Mandibular Index (PMI). These two indices were created during the past several decades to evaluate the mandibular bone

mass's quality and detect resorption in panoramic radiography. Recent studies have reported significant correlations between BMD and either MCI or PMI (Kwon et al. 2017; Hastar 2011).

The use of panoramic radiographs as an indicator of alterations in BMD has been used mainly in adults with osteoporosis (Alonso et al. 2011; Taguchi et al. 1996). Based on the results of the 3-year OSTEODENT project a 3mm limit for the cortical width, in the mental foramen region, was established and patients with a cortical width less than that should be referred for definitive diagnosis (Karayianni et al. 2007).

Relative studies in children are rare and focus mainly on changes in bone mass density in pathological conditions. Up to date, panoramic radiographs had been used in studies that record bone density in children with conditions that impair growth such as preterm births (Paulsson- Bjornsson et al. 2015), osteogenesis imperfecta (Apolinário et al.2015), HIV-infection and cancer (Frascino et al. 2019). Additionally, Yasa et al.'s study on the impact of obesity on the mandibular cortical bone (2020) revealed that individuals who are obese and overweight had bigger mandibular cortexes than those who are of normal weight. Mandibular cortical width has even been utilized as an auxiliary diagnostic criterion for the identification of sleep disordered breathing in a study (Eimar et al. 2019).

A very interesting parameter is the alterations in bone mass density in puberty, a period during which there is a large increase in BMD (Annemieke et al. 1997). During puberty, growth hormone as well as sex steroid levels increase, both of which have a positive influence on BMD (Albertsson-Wikland et al. 1994). Bone strength is mostly influenced by bone mass and density. The elastic modulus of bone is conceptually linked to its fragility and is proportional to the cube of its density. As a result, minor changes in bone density are linked to more significant changes in bone strength (Nobakhti S,2018).

Bone mineral density (BMD) rises during childhood and adolescence until peak bone mass is attained. Those periods are critical as high skeletal growth of up to 90% of adult bone mass is acquired (Bachrach et al., 2007). Thus, it is necessary to define

normal values for bone density during this period to allow for the determination of deviations. Early detection and adequate treatment should be essential for the prevention of osteoporosis and fractures in the elderly.

2.1. Basic Bone Biology

Bone tissue serves a multitude of purposes in the body and is the main load-bearing component of the endoskeleton of vertebrates. It is crucial for the physical protection of the interior organs and tissues in addition to preserving body structure and enabling movement. In addition, nutrients, lipids, and growth hormones can be stored in bone and released as needed (Clarke, 2008). In addition to serving as a source for stem cell regeneration, the marrow present in the cancellous bones' interstices and voids is crucial for hematopoiesis, the process of producing new blood cells (Taichman, 2005).

According to Rho et al. (1998), there are two main macrostructures of bone: cancellous (trabecular) and cortical (compact) bone (Figure 1). Trabecular struts make up cancellous bone, which develops into a honeycomb structure with bone marrow-filled pores (Rho et al., 1998). The position of the trabecular struts of this cancellous structure, which is in the center of the bone, enables it to endure forces. Osteoblasts, osteocytes, and osteoclasts remodel cancellous bone, which is also more metabolically active than cortical bone (Rho et al., 1998). The architecture of cortical bone is more well-defined and compact, and it undergoes less frequent remodeling.

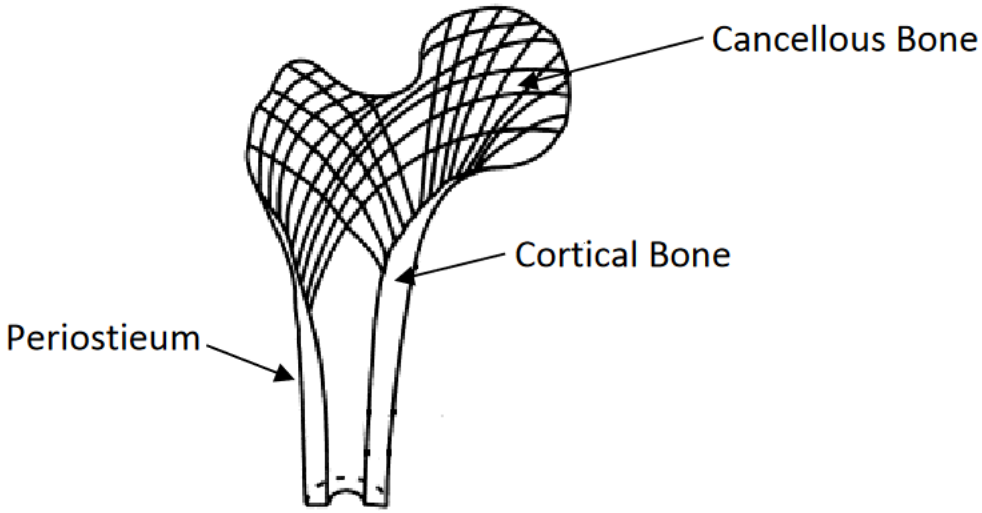


Figure 1: The position of the cortical and cancellous bone as well as the position of the periosteum are shown in the structure of a long bone. (Rho et. al., 1998)

2.2. Skeletal development and growth

Skeletal development and growth are crucial components of overall child development, as they lay the foundation for proper physical growth and function throughout life (Levine MA.2012).

The skeleton develops and grows, through the coordinated interaction of osteoblasts and osteoclasts.

Osteoblasts are mesenchymal stem cells that can develop into muscle, adipocytes, cartilage, or fibrous tissue. They are the cells that make bones. Large, multinucleated cells called osteoclasts, can break down minerals and release calcium and phosphorus into the extracellular fluid, reabsorbing bone. Monocyte and macrophage cells have a connection to osteoclasts. The skeleton continues to alter in size and shape during embryogenesis and as the child develops after birth, a process known as "modeling," which is accompanied by corresponding increases in bone mineral mass and density. Through consistent modeling during puberty, these changes are accomplished. In addition to modeling, remodeling refers to the ongoing reshaping of bones by removing and replacing existing skeletal structures (Figure 2) (Naik P.,2021).

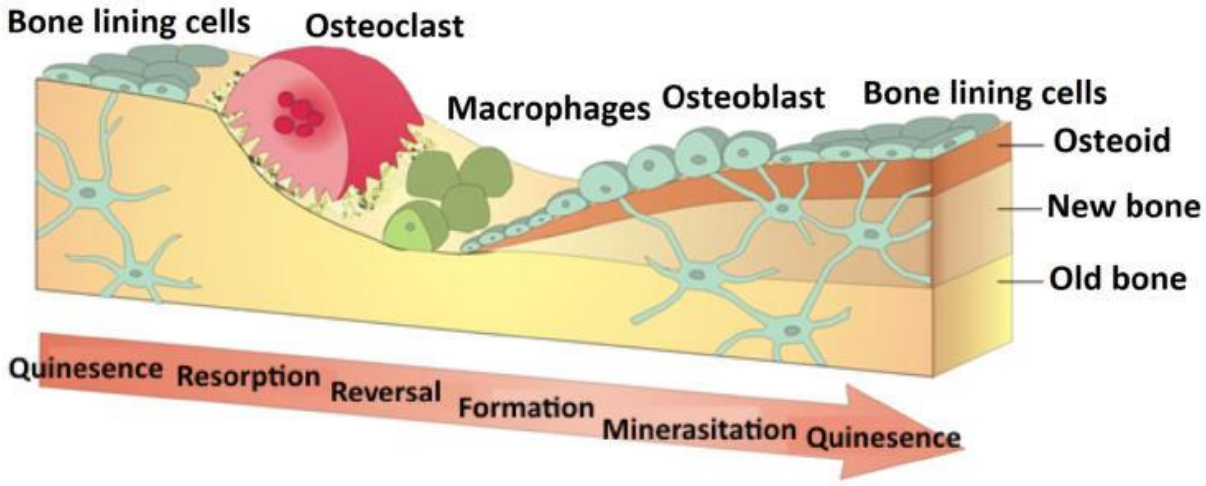


Figure 2: Schematic view of bone remodeling phases (Naval,2015)

To bring about these changes through remodeling old bones and modeling new ones, osteoblasts and osteoclasts must engage in incredibly sophisticated cross-talk as bone growth continues. Growing cartilage at the end plates of long bones causes linear growth during childhood and adolescence, which is followed by the production of endochondral bones. The process of periosteal apposition widens the bones. Peak bone mass is produced during puberty and the early years of adulthood by endosteal apposition and trabecular thickening. To maintain structural strength, these processes are influenced by locally and systemically generated variables and mechanical forces, which in turn regulate the coordinated actions of osteoblasts and osteoclasts. (Rauch F.,2007) The adult skeleton continues to remodel throughout a person's lifetime, losing about 15% of its mature mass per year to preserve mineral homeostasis, mend broken bones, and adapt to alterations in skeletal stress (Feng X, 2011).

The proximal femur, calcaneus, and ultra-distal radius are only a few examples of the skeletal areas where bone remodeling is most common. The second type of bone, known as cortical bone, is less metabolically active but gives the skeleton a lot of strength and stability. All skeletal structures are made of cortical bone, which makes up 80% of the skeleton and is thick and compact (Levine MA.,2012).

The skeleton expands in both size and density over the first two decades of life, and more than half of peak bone mass is thought to be acquired during adolescence

(Bachrach LK., 2001). Axial and appendicular skeletons expand in size at various rates because bone growth is not a homogeneous process **(**Tanner JM, 1976).
Particularly, before puberty, the limbs expand proportionately more than the trunk. Early and middle puberty sees a rise in the relative rate of spine growth, while late puberty sees a slowdown in growth at all sites (Bradney M et al., 2000). As a result of the skeleton's rapid development during puberty outpacing the rate of mineralization, the accumulation of bone minerals takes 8 months longer than growth in height **(**Bailey DA et al., 2000).

During peripuberty, the areal bone mineral content and bone mineral density in the lumbar spine and proximal femur increase fourfold to sixfold. At the same time, the diaphyses of the long bone increase twofold (Maggioli C et al.,2017).

Mandibular alveolar bone undergoes aging processes that are like other bones in the body. As bone ages, trabeculae thin and the bone becomes demineralized, whereas the inferior mandibular cortex becomes more porous and focally thin (Allen B,2016).

The bone mass continues to increase until around age 30 (Baxter-Jones AD et al., 2011). Peak bone mass, also referred to as maximum bone strength and density, is reached at that time. Between the ages of 30 and menopause, women's overall bone mass typically changes just slightly. However, many women undergo a period of fast bone loss in the first few years following menopause, which then decreases but persists throughout the post-menopausal years. Osteoporosis, a disorder of weaker bones and an increased risk of fragility fracture can result from this loss of bone mass. Age-related bone loss starts later and progresses steadily in men. Falling bone mass is the main factor in weak bones and fractures in both men and women (Baxter-Jones AD et al., 2011).

2.3. Mechanical properties of cortical bone tissue in adults

Bone tissue continues to grow and change in mechanical characteristics as it matures. Animal bone tissue has been utilized in several research to examine how mechanical behavior changes as a child grows (Öhman C et al.,2011). In those experiments, it was discovered that with maturity, ultimate displacement reduced while strength, stiffness, and density rose. Additionally, certain research (Nafei A et al.,2000) discovered a strong link between mechanical characteristics and mineral content/ash density.

The mechanical characteristics of cortical bone tissue taken only from adult human participants have been the topic of numerous investigations, including those on bending (Cuppone M. et al., 2004), tensile (Nyman JS et al., 2007), compressive (Grimal Q et al., 2009), toughness (Ohman C et al., 2008), fracture development (Akkus O,2001), and hardness properties (Zwierzak I et al., 2009). Additionally, substantial research has been done on the use of mathematical connections to forecast the mechanical behavior of human bone tissue (Ait Oumghar I,2016).

Osteous tissue, the main component of bone, is a hard but lightweight tissue made primarily of the protein collagen type I and the mineral hydroxyapatite (Clarke, 2008). Although bone has a low tensile and shear stress strength (Table 1), it has a high compressive strength. These characteristics make bone rather brittle, however, due to the high collagen concentration in osseous tissue, it does have considerable flexibility (Hutmacher et al., 2007).

	Cortical Bone	Cancellous Bone
Compressive Strength (MPa)	100-230	2-12
Tensile Strength (MPa)	50-150	10-20
Fracture Toughness (Mpam $^{1/2}$)	2-12	-
Young's Modulus (GPa)	7-30	0.5-0.05

Table 1: The mechanical strengths of cortical and cancellous bone (Hutmacher et al.,2007)

Numerous studies have shown that density is a reliable predictor of the compressive and bending mechanical properties of bone tissue (Cuppone M et al., 2004), but it appears that other factors, such as bone composition, collagen fiber orientation, and age, must be taken into account to predict the tensile and toughness mechanical properties (Yeni YN et al., 1998).

2.4. Mechanical properties of cortical bone tissue in children

On the other hand, there are very few studies that have looked into the mechanical characteristics of children's bone tissue, maybe because it is very difficult, if not impossible, to acquire such tissue. Only three studies (Currey JD et al.,1996) (Martin RB,1989) (Mueller KH,1966) that the authors are aware of have examined and contrasted human juvenile bone tissue with adult bone tissue.

In 1966, Muller et al. (Mueller KH,1966) studied changes in bone density and composition with age. Trabecular bone samples from the iliac and lumbar vertebral bodies (ranging in age from newborn to 85 years old) were examined. It was discovered that the organic portion of human trabecular bone stays rather stable throughout life, although the percentage of water content is reduced with aging. On the other hand, it was discovered that from birth until ages 60 to 70, the percentage of ash content increases (Mueller KH,1966).

Research by Currey and Butler (Currey JD,1975) verified the reduced ash content in youngsters. In that study, the bending fracture characteristics of human cortical bone specimens taken from the mid-shaft of the femur (aged between two and forty-eight) were also examined. Young bone specimens were found to deflect and absorb more energy before failing than adult counterparts, despite being weaker and less rigid. Additionally, it was discovered that ash density and bending elastic modulus had a somewhat positive correlation (r= 0.78 and r= 0.63, respectively).

According to a study by Caroline Oman et al. (2008), the compressive Young's modulus, yield stress, ultimate stress, and ash density of the infant bone tissue were all much lower than those of the adult tissue. The juvenile group, however, had a higher compressive final strain (+ 24%). Despite samples being taken from both adults and children, ash density (R 2 = in the range of 0.86-0.91) primarily explained the variation in tissue strength and stiffness. Furthermore, it appeared that subject age and tissue density had little effect on yield strain. These findings support the notion that the mechanical characteristics of cortical bone tissue in children differ from those of adult tissue. However, these variations are linked to variations in tissue ash density. Even with cortical bone samples from young infants, it was observed that ash density was a good indication of strength and stiffness (Caroline Oman et al.,2008).

2.5. Bone mass- Timing of Peak Bone Mass (PBM) accumulation

The primary assumption of the peak bone mass concept is that achieving peak bone mass throughout childhood and adolescence will avoid fractures in later life. This idea is based on the observation that areal bone density peaks at roughly age 20 and subsequently declines as people get older. Fractures may occur later in life for one of two reasons: either these people have lost more bone mass than people without fractures, or their peak bone mass was lower in adolescence, and they subsequently lost bone mass at the same rate and for the same period of time as people without fractures (Faulkner RA, 2017) (Bachrach LK, et al., 1999) (Fig. 3,4).

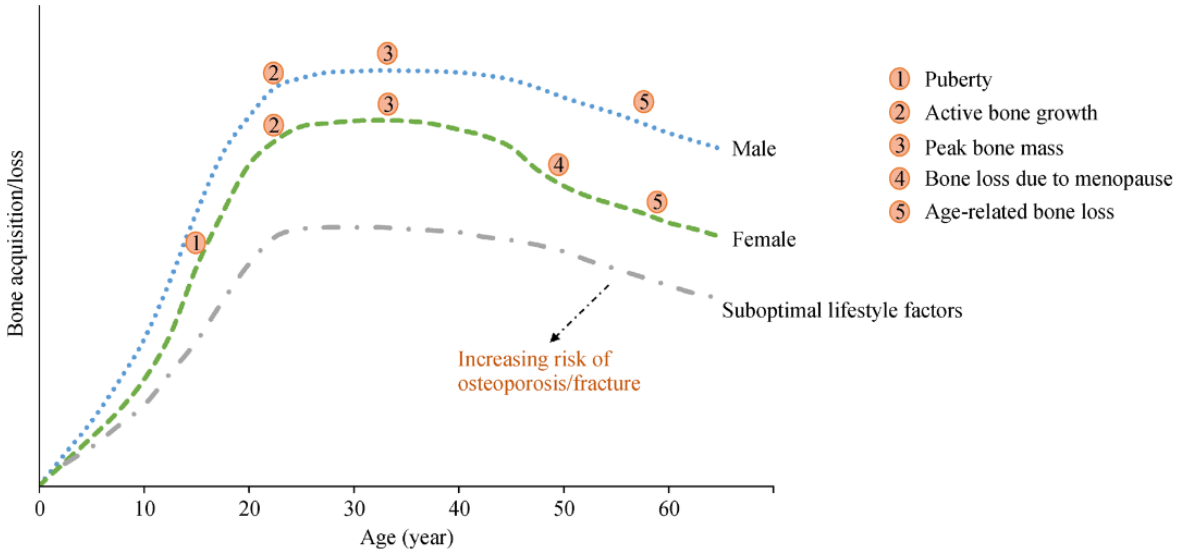


Fig. 3 Bone Mass throughout the lifespan (Zhu X, 2020)

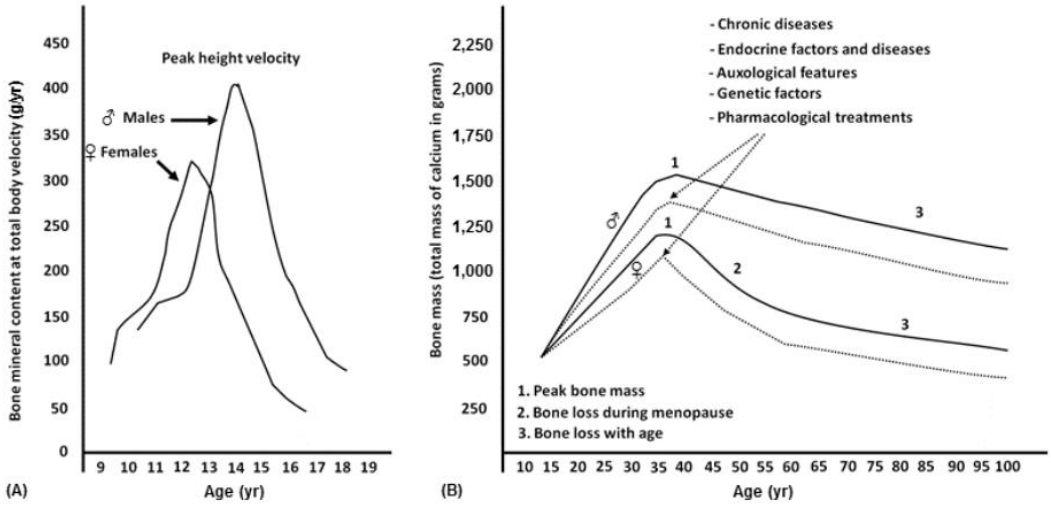


Fig. 4: (A) Increase of bone mass at a height-related growth rate and variance in peak bone mass between males (♂) and females (♀). (B) The variance in peak bone mass between males (♂) and females (♀) and factors and diseases that influence the peak bone mass and the risk of osteopenia/osteoporosis in adulthood (Maggioli C, 2017)

It's critical to understand the difference between bone mass and density: whereas physical bone density refers to the mineral content of the bone relative to the outer bone volume and is size-independent, bone mass equals the weight of the bone, which relies on bone size. Even though their physical densities are the same, a normal tiny bone will often have a lower areal density than a bigger one, and as a result, a

perceived bone mass deficit may disappear when the data are corrected for body height or bone size (Deng HW, 2002).

More than 94% of BMD is acquired by men and women by the age of 16 according to longitudinal data (Berger C et al., 2010). Puberty is a crucial time for bone growth and has a significant impact on PBM value (Bonjour JP,2014). The exact date of PBM is still up for debate. According to additional evidence, bone mineral continues to accumulate until the third decade of life (Recker RR,1992) (Teegarden D,1995).

2.6. Bone accretion and the effects of puberty

Beyond the alterations brought on by growth, pubertal maturation has significant impacts on bone accretion and strength. Bonjour et al. (1991) shown, in a cross-sectional sample, the impact of pubertal stage of maturation on spinal and femoral bone mass accumulation.

The delayed increase in lumbar spine BMC in boys was connected to the later date of pubertal onset compared to girls, and they demonstrated a substantial increase in bone mass accumulation at the later phases of puberty. Similar findings were made by Gilsanz et al.(1991), who discovered that girls in pubertal stages 4 and 5 had a considerable rise in trabecular volumetric BMD as measured by QCT of the spine.

Bone accretion and PBM are similarly impacted by the speed of puberty. Reduced BMD was observed at the spine and radius in a study of young adult men who had a history of constitutionally delayed puberty (Finkelstein JS et al., 1992). Since then, longitudinal studies have shown that pubertal timing has an adverse impact on PBM. Gilsanz et al. (2011) found that BMC and BMD attained by Tanner Stage 5 at all skeletal sites were inversely related to the age at which boys and girls transition from Tanner Stage 1 to Stage 2 in the multicenter Bone Mineral Density in Childhood Study, which included a large cohort of children followed for 7 years. It's interesting to note that Chevalley et al.'s research (2009) found that girls who menstruated earlier had higher

BMD z-scores at all assessment ages, both before and after menarche, from age 7.9 to 20.4 years.

2.7. What affects bone mass in children?

A complex interplay of environmental, behavioral, and hereditary variables determines bone mass. Although not all the necessary genes have yet been discovered, it is believed that between 60% and 80% of the contribution to peak bone mass is genetically determined (Heaney RP et al., 2000) (table 2). Before puberty, the effects of heredity and genetics become apparent in childhood (Liu CT et al., 2012).

Receptors	Hormones/ cytokines	Enzymes	Bone matrix proteins
Vitamin D*	IL-6*	Aromatase	COLIA1*
Oestrogen (ERα)*	IGF-1*	Collagenase	Osteocalcin*
LRP-5*	Leptin*	BMP-4	
Leptin*	PTH		
Androgen	TNF-α		
Glucocorticoid	TGF-β		
PTH	Osteoprotegerin		
TNF			
Calcium			
Calcitonin			
TSH			

*Indicates influence on BMD shown during childhood.
BMP, bone morphogenetic protein; COLIA1, type I collagen; IGF-1, insulin-like growth factor 1; IL, interleukin; LRP-5, low density lipoprotein related protein 5; PTH, parathyroid hormone; TGF, transforming growth factor; TNF, tumour necrosis factor; TSH, thyroid stimulating hormone.

Table 2. Gene polymorphisms that influence bone mass (Davies JH et al., 2005)

Genome-Wide Association Studies have pinpointed certain genetic variations linked to variables connected to bones. As an illustration, a sizable GWAS that was published

in Nature Genetics in 2012 looked at the genetic basis of BMD in kids and teenagers. The study revealed several genetic loci linked to BMD, underlining the genetic influences on bone mass (Kemp JP et. al., 2014).

Additionally, several uncommon genetic disorders shed light on the genetic elements influencing bone health. For instance, the hereditary condition osteogenesis imperfecta (OI) is characterized by brittle bones and low bone mass. The genetic basis of bone fragility is highlighted by the association of OI with mutations in collagen-producing genes such COL1A1 and COL1A2 (Van Dijk FS.,2014).

The remaining 20% to 40% of the variance in bone mass is caused by environmental and behavioral factors, with dietary considerations (especially calcium and vitamin D) and physical activity plays a significant role. (Demay MB et al.,2007).

It's also crucial to keep in mind that several other nutrients, including vitamin D and K, copper, protein, phosphorus, magnesium, manganese, zinc, energy, and iron (Prentice A et al., 2006), seem to be crucial for maintaining healthy bones.

Exercise, especially physical activity, is a key factor in determining bone mass in addition to food. A network of osteocytes found in bone functions as a bio-mechanostat that can sense loads and stresses placed on the skeleton. Increased bone mass results from signals sent by bone stress that encourages osteoblast bone growth and inhibit osteoclast bone resorption (Abdel Gader AM.,2018).

Body mass is one of the other crucial parameters. Although obese children often have larger, denser, and higher-density bones (Leonard MB et al., 2004), visceral fat content is inversely correlated with bone mass, increasing the risk of fracture.

2.8. Syndromes and diseases that affect bone mass in children

There are several children's chronic disorders that are linked to poor bone health, and they span almost all paediatric specialties (Table 3,4). These illnesses are varied, and there is a broad range of clinical characteristics, including the course and prognosis. Any element that has a negative impact on bone quality, strength, or mass may raise the risk of fracture and should be viewed as a danger to bone health. Common risk factors for poor bone health include: (1) decreased loading of bones owing to inactivity or weak muscles; (2) inadequate diet; and (3) use of bone-toxic medications. (4) Hormonal deficits that impair development and growth, and (5) persistent inflammation (Pouresmaeili F, 2018).

Primary bone disorders
o Idiopathic juvenile osteoporosis
o Osteogenesis imperfecta
Potential secondary bone diseases
o Chronic inflammatory disorders
- Inflammatory bowel disease
- Juvenile idiopathic arthritis
- Celiac disease
- Cystic fibrosis
o Chronic immobilization
- Cerebral palsy
- Myopathic disease
- Epidermolysis bullosa
o Endocrine disturbance
- Turner syndrome
- Anorexia nervosa
- Type 1 diabetes
o Cancer and therapies with adverse effects on bone health
- Acute lymphoblastic leukemia
- Chemotherapy for childhood cancer
- Transplantation (nonrenal)
o Hematologic disorders
- Thalassemia
- Sickle cell disease
o Genetic disorders
- Ehlers Danlos syndrome
- Galactosemia
- Marfan syndrome

Table 3: Diseases or Therapies that may affect the skeleton (Bishop et al., 2013

Classification	Disease
Endocrine diseases	Hypogonadism; insensitivity syndrome of estrogen; panhypopituitarism; growth hormone deficiency; hyperthyroidism; Cushing syndrome; primary hyperparathyroidism; primary hypoparathyroidism; McCune-Albright syndrome
Iatrogenic causes	Anticonvulsants; gonadotropin-releasing hormone analogue; L-thyroxine (high dose); antiretroviral drugs; anticoagulants; chemotherapeutic drugs; corticosteroids treatments
Genetic syndromes	Turner syndrome; Klinefelter syndrome; 22q11 deletion syndrome; Down syndrome; Williams-Beuren syndrome
Malignancies	Leukemia; lymphoma; solid tumors
Nutritional problems	Nervous anorexia; lactose intolerance; deficiency of calcium, copper, etc.; vegetarian diets; malnutrition; total parenteral nutrition
Chronic diseases	Juvenile idiopathic arthritis; systemic lupus erythematosus; dermatomyositis; chronic renal failure; renal tubular acidosis; idiopathic hypercalciuria; cholestatic forms; celiac disease; Crohn disease; ulcerative Colitis; congestive heart failure; thalassemia; hereditary hemochromatosis; haemophilia; sickle cell anemia; systemic mastocytosis; hyper-IgE syndrome; overweight/obesity
Other	Immobilization/little use; intense physical activity; posttransplant; prematurity

Table 4: Main conditions potentially causing an altered density and/or quality in childhood (Maggioli C, 2017)

Here are a few instances of disorders associated with impaired bone health:

Neurologic disorders

Cerebral palsy (CP): CP is a neuromuscular condition that does not progress and results from harm to the developing brain. All ages of children with CP have been found to have deficiencies in bone mineral density (BMD), which have been linked to the severity of motor deficits, feeding difficulties, and the use of antiepileptic medicines (AEDs) (Henderson RC,2002). Longitudinal studies indicate that CP patients build bone throughout childhood, albeit more slowly than children who are regularly developing.

Neuromuscular disorders: The most prevalent heritable neuromuscular illness in children is Duchenne muscular dystrophy (DMD). It is a chronic illness that always leaves patients unable to walk by late childhood or early adolescence. A significantly increased fracture prevalence is caused by the risk factors of muscular weakening, immobilization, and chronic glucocorticoid exposure coupled (Morgenroth VH, 2012).

Epilepsy: The possibility of severe skeletal effects from therapies like AEDs and the ketogenic diet is a major worry for kids with seizure disorders. There has been a thorough analysis of the connections between AEDs and bone mineral metabolism. Numerous traditional AEDs activate the CYP-450 enzyme system, which lowers the levels of vitamin D. There have also been reports of AEDs having direct detrimental effects on skeletal cells (Pitetzis DA,2017). Although they have not been well investigated, newer-generation AEDs seem to have less of an effect on mineral metabolism (Fu J. et al.,2019). The use of ketogenic diets to treat refractory epilepsy is growing, although they may have negative effects on the skeleton due to acidosis, hypercalciuria, and nutritional shortages (Ruiz Herrero J. et al.,2020). There have been reports of BMD deficiencies getting worse in longitudinal studies of kids on ketogenic diets (Simm PJ,2017).

Neurodevelopment disorders: It has been established that the bones of children with autism are smaller, weaker, and less thick than those of their counterparts who are typically developing (Neumeyer AM,2017). These deficiencies

might be caused by insufficient protein, calcium, and phosphorus intake as well as decreased time spent engaging in physical exercise (Neumeyer AM,2018). Additionally, skeletal issues in girls with Rett Syndrome have been linked to scoliosis, poor BMD, and fragility fractures.

Chronic kidney disease (CKD): The physiologic causes of CKD metabolic bone disease (CKD-MBD) include phosphate retention, elevated levels of parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23), reduced renal 1-hydroxylase activity, and hypocalcemia (Hanudel MR,2017). Skeletal metabolism is impacted; symptoms include skeletal fragility, abnormal mineralization, and altered bone turnover. Children with CKD have fracture rates that are 2–3 times higher than those of the general population (Denburg MR,2016). It has been documented that BMD, bone structure, and muscle size deficiencies exist (Tsampalieros A,2012).

Inflammatory disorders: Skeletal injury can be brought on by inflammatory bowel disease (IBD), juvenile idiopathic arthritis (JIA), inflammatory arthritis, and systemic lupus erythematosus (SLE). By inhibiting osteoblast-mediated bone production and encouraging osteoclast resorption, inflammatory cytokines have a detrimental effect on bone. In the first stages of treating inflammatory diseases, glucocorticoids are routinely used, but they also damage bone. Nutritional deficiencies are possible, particularly in IBD when there may be reduced absorption (Huber AM,2016).

Liver disease: Poor development, low BMD, deficiencies in the mineralization of the bone (including rickets), and fracture are skeletal symptoms of severe liver illness in children (Hogler W,2012). Fat malabsorption can seriously impede vitamin D absorption, necessitating the use of very high dosages of vitamin D supplements.

Cancer: In some types of juvenile cancer, glucocorticoids are used during induction chemotherapy. Deconditioning and immobility are also frequent. Some kids need skeletal radiation, which worsens bone deterioration. Acute lymphoblastic leukemia (ALL) in children treated with glucocorticoids has been associated with VF in 25% of cases (Cummings EA,2015). Patients receiving hematopoietic stem cell

transplantation (HSCT) may have much greater rates of BMD deficiency, fracture, and avascular necrosis (Kuhlen M,2019).

Diabetes: One well-known consequence of type 1 diabetes (T1D) is impaired bone health. In comparison to children without T1D, fracture risk was found to be 14% higher in males and 35% higher in girls (Weber DR, 2015).

Cystic fibrosis (CF): Some studies of young people with CF, although not all of them, have mentioned low BMD (Ubago-Guisado E.et al,2019). Studies confined to individuals with severe CF have shown substantial BMD deficiencies and fracture risk, suggesting that this discrepancy may be the result of variability in CF severity (Cairoli E. et al. 2019). Risk factors for inadequate bone accumulation include nutritional inadequacy that results in low body weight, malabsorption of fat-soluble vitamins D and K, decreased development, and pubertal delay.

Congenital heart disease (CHD): Several children with CHD are in the early stages of skeletal development when they are dangerously unwell. Deficits in bone and lean mass that worsen over time may be a particular danger for kids with single ventricle illness who need Fontan palliation. The use of diuretics, secondary hyperparathyroidism, and protein-losing enteropathy have all been linked to decreased bone health (Diab SG. et al. 2019).

Metabolic: Skeletal fragility and bone deformities can be caused by lysosomal storage diseases (Langeveld M, 2018). Rickets, osteoporosis, and CKD-MBD are just a few of the severe skeletal repercussions that cystinosis in particular can have.

Eating disorders: Impaired bone health is linked to the female athletic triad, bulimia, and anorexia nervosa (Williams NI,2017). Low body mass, an energy deficiency, and hormonal issues, particularly hypogonadism, all contribute to deficiencies in BMD and bone formation. Young athletes who are underweight are more likely to suffer from stress fractures (Nose-Ogura S.,2019) and the presence of both should raise the possibility of an eating issue.

2.9. What affects bone mass in adults?

Osteoporosis is a common condition that affects bone health, particularly in adult women. It is characterized by low bone mass and deteriorated bone tissue, which can increase the risk of fractures and other bone-related problems. Osteoporosis is more common in women than in men, particularly after menopause when estrogen levels decrease. Approximately 1 in 2 women over the age of 50 will experience an osteoporosis-related fracture in their lifetime. Several factors can increase a woman's risk of developing osteoporosis, including age, family history of the condition, low body weight, smoking, excessive alcohol consumption, and a sedentary lifestyle (Sözen T et al., 2017).

One typical kind of secondary osteoporosis is **drug-induced osteoporosis.** Drug-induced osteoporosis is most frequently brought on by glucocorticoids, while other medications like proton pump inhibitors (PPIs), heparin, and anticonvulsants can also impact how bones are metabolized. Upper gastrointestinal tract diseases are treated with PPIs. PPIs may reduce calcium absorption and have detrimental effects on skeletal homeostasis by raising stomach pH [130]. Heparin coupled with OPG, the RANKL decoy receptor, enables RANKL to stimulate osteoclastogenesis, which increases bone resorption as a potent medication for the treatment of thromboembolic illnesses (Mirza F,2015). Although the exact causes are unclear, anticonvulsants may lead to bone loss. Anticonvulsants may hasten vitamin D metabolism, which raises the risk of bone loss by causing low 25-OHD levels, rapid bone turnover, and secondary hyperparathyroidism (Fitzpatrick LA., 2004).

Secondary causes of osteoporosis and low BMD are frequent **endocrine conditions**, such as glucocorticoid osteoporosis, growth hormone insufficiency, diabetes, and primary hyperparathyroidism. The primary characteristic in the pathophysiology of glucocorticoids on bone loss is that glucocorticoids reduce the quantity and function of osteoblasts, which inhibits bone production and increases the activity of osteoclasts (Canalis E et al., 2007).

The development and reduction of bone mass throughout the course of a person's life are dependent on **socioeconomic circumstances** (Crandall CJ et al., 2012). Osteoporosis is among the acute and chronic disorders that have been linked to socioeconomic status (SES) (Navarro MC, et al. 2013 (Du Y et al., 2017). The currently accessible literature, meanwhile, continues to be debatable (Myong JP et al., 2012) (Brennan SL et al.,2013). The risk of hip fracture in the elderly is increased by low SES, which has a substantial and well-documented relationship with several negative health outcomes (Brennan SL et al.,2013). However, there is no correlation between low SES and femoral neck BMD, the primary predictor of the risk of hip fracture (Brennan SL et al., 2010).

Bone mass can also be affected by **alcohol and smoking.** Nicotine alters the blood vessel wall's permeability and prevents the flow of chemicals between the inside and outside of the blood vessels, which results in inefficient absorption and utilization of nutrients like calcium and protein. Other harmful components in cigarettes also make the blood more acidic and hasten bone deterioration. Uncertainty surrounds the pathophysiology of alcohol-induced osteoporosis, and it is thought that both direct and indirect actions of alcohol affect bone health (Mikosch P.,2014). Alcohol directly affects the function of bone cells by preventing the proliferation of marrow mesenchymal stem cells and their differentiation into osteoblasts (Suh KT et al., 2005).

The immune system and immunological-related variables are crucial in the emergence of osteoporosis. For instance, bone loss can be caused by rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), and multiple sclerosis (MS). A prevalent rheumatic condition, RA, can increase the risk of fractures and bone loss due to the underlying disease activity and continuing glucocorticoid use (Maruotti N, 2014).

Increased bone absorption, increased intestinal calcium absorption, and decreased renal tubular calcium reabsorption are the characteristics of **hypercalciuria**, which is linked to low bone density and an increased incidence of

fractures and causes net calcium loss (Coe FL et al,2026). There are higher levels of fibroblast growth factor (FGF23) in people with chronic kidney disease (CKD) due to the high incidence of Klotho deficiency and low expression of Klotho (Khairallah P,2018).

2.10. Techniques to Assess Bone Mineral Density

Bone mineral density, a biophysical parameter of critical experimental importance, is one of the most important factors to measure bone quality, as it is a reliable and non-invasive method. The amount of bone in the skeletal system determines BMD; hence, the higher the BMD, the stronger the bones are, and vice versa (Carl E. Misch,2015).

There is still much debate on the best method for determining a kid's or adolescent's bone mass. In clinical practice, a proper procedure is not always available or standardized, and the results could raise more questions than answers. In addition, other factors including the expense and usage of ionizing radiation should be considered in kids, especially if the exam is meant to be preventive (Levine MA.,2012).

Dual-energy radiograph absorptiometry (DXA), quantitative computed tomography (QCT), peripheral QCT (pQCT), high-resolution pQCT (HR-pQCT), quantitative ultrasonography, magnetic resonance imaging (MRI), or plain films (radiogrammetry) can all be used to evaluate the paediatric skeleton. Ultrasonography and MRI are techniques that do not require radiation.

Each modality has unique benefits and drawbacks (Bachrach LK, 2016).
Epigrammatically:

DXA, or dual-energy X-ray absorptiometry (Lewiecki EM et al., 2016). DXA is mainly used in adults for the detection of osteoporosis. According to the World Health Organization (WHO), osteoporosis is present when BMD (a T-score of 2.5 SD) is 2.5 SD or more below the typical value for young, healthy women. The term "low bone mass" or "osteopenia" is defined by a second, higher threshold as a T-score that ranges

between 1 and 2.5 SD. Osteoporosis that has been determined to exist in the presence of one or more verified fragility fractures is referred to as "severe" or "established" (Table 4) (Kanis JA, 2007). It also continues to be the method of choice for clinical assessments of bone density in children, due to its accessibility, reproducibility, speed, low radiation dose, and extensive paediatric reference data. However, it cannot reveal details about the geometry or structure of bones instead, it assesses areal bone mineral density (aBMD), a two-dimensional measure (Pezzuti IL et al., 2017). Once it faces the same direction as the X-ray beam, the third dimension, depth, cannot be directly measured. In contrast to adults, children's bones develop with time, however, this growth is not constant in all three dimensions. Young children have a substantially bigger area in ratio to bone volume compared to older children because skeletal growth results in a significantly higher rise in volume than in bone area. Therefore, aBMD underestimates the real bone density in smaller children and overestimates it in larger ones.

Classification	Bone Mineral Density	T Score
Normal	Within 1 SD of the mean level for a young adult reference population	T score at −1.0 and above
Low bone mass (Osteopenia)	Between 1 and 2.5 SD below that of the mean level for a young adult reference population	T score between −1.0 and −2.5
Osteoporosis	2.5 or more below that of the mean level for a young adult reference population	T score at or below −2.5
Severe or established osteoporosis	2.5 or more below that of the mean level for a young adult reference population with fractures	T score at or below −2.5 with one or more fractures

Table 5: WHO definitions of osteoporosis based on BMD (Kanis JA, 2007)

QCT, or quantitative computed tomography (Rüegsegger P, 1982). BMD in the spine may be accurately measured using QCT, which can also reveal details on the strength and geometry of the bones. It is helpful for evaluating changes in bone density over time since it can measure BMD in three dimensions. However, compared to DXA, QCT is more expensive and exposes users to more radiation. Additionally, it is less accessible, and the size of the region being scanned can have an impact on the outcomes.

Quantitative computed tomography in the periphery (pQCT)(Zemel B et al., 2008). BMD in the peripheral skeleton can be measured using pQCT, a QCT variant. Additionally, it might reveal details about the strength and bone shape. pQCT may not be appropriate for those with limited mobility because it is less accurate than DXA or QCT at measuring BMD.

Ultrasound (Dumitriu D et al., 2022). Ultrasound is a rapid, painless, and non-invasive method for calculating BMD in small bones. It is less expensive than other procedures and does not expose the user to radiation. Ultrasound may not be appropriate for patients with very thin or very big bones since it is less accurate than DXA or QCT.

Magnetic resonance imaging (MRI) (Natascia Di Iorgi et al., 2018) (Bachrach LK, 2016). MRI may give precise details about the density and structure of bones as well as other soft tissues. Nevertheless, for measuring BMD, MRI is not as commonly used as DXA or QCT. It is more time-consuming and expensive, and some medical conditions or implanted equipment may prevent some people from using it.

2.11. Panoramic radiomorphometric indices for bone assessment

It has been suggested that morphometric analysis of panoramic jaw radiographs could be a good alternative to DXA in the screening, diagnosis, and evaluation of low BMD.

Many valid indicators may be used to analyze bone quality in panoramic radiographs (Table 6).

Index	Description	Normal Value
Panoramic Mandibular Index (PMI)	Calculated as the ratio of the mandibular cortical thickness measured on the line perpendicular to the bottom of the mandible, at the middle of mental foramen, by the distance between the superior margin of mental foramen and bottom of the mandible.	>0.3
Mental Index (MI)	The measurement of the mandibular cortical thickness on the line perpendicular to the bottom of the mandible at the middle of the mental foramen.	>3.1 mm
Antegonial Index (AI)	The measurement of the mandibular cortical thickness measured on the line perpendicular to the mandibular cortex at the intersection with the tangent line to the anterior border of the ramus.	>3.2 mm
Gonial Index (GI)	The measurement of the mandibular cortical thickness measured on the bisectrix of the angle between the tangent lines to the posterior border of the ramus of mandible and the bottom of the mandible.	>1.2 mm

Table 6: Description of radiomorphometric indices (Anju P David et al., 2017)

Among the often-used indices are (Taguchi A et al., 1996)(Dagistan S et al., 2010):

- **Mandibular cortical width (MCW)** is a radiographic indicator that quantifies the thickness of the mandibular cortical bone. A decrease in MCW has been linked to a higher risk of fractures and osteoporosis.

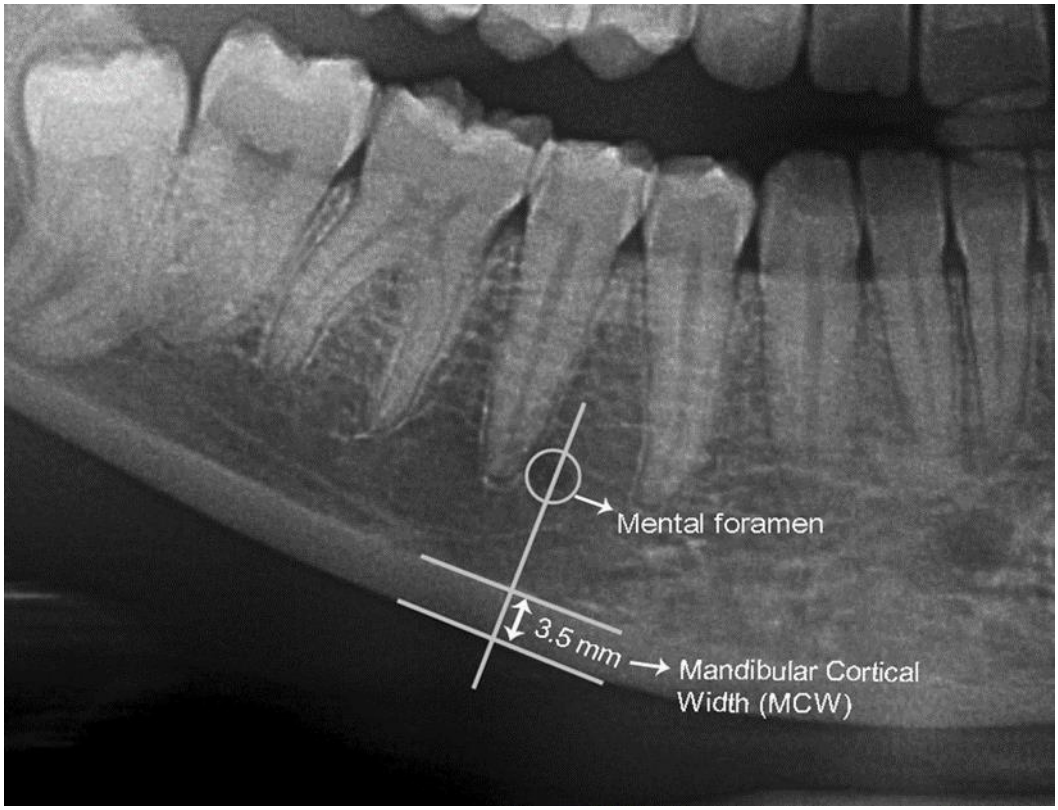


Figure 5: MCW index is visible in a cropped panoramic radiograph. (Camila NAO Kato,2020).

- **Mandibular cortical index (MCI):** On a panoramic radiograph, this index assesses how the mandibular cortical bone appears. On a scale from 0 to 3, the MCI is graded; higher grades denote a more porous look of the cortical bone. Having a higher MCI has been linked to a higher risk of fractures and osteoporosis (Hastar E, 2011).

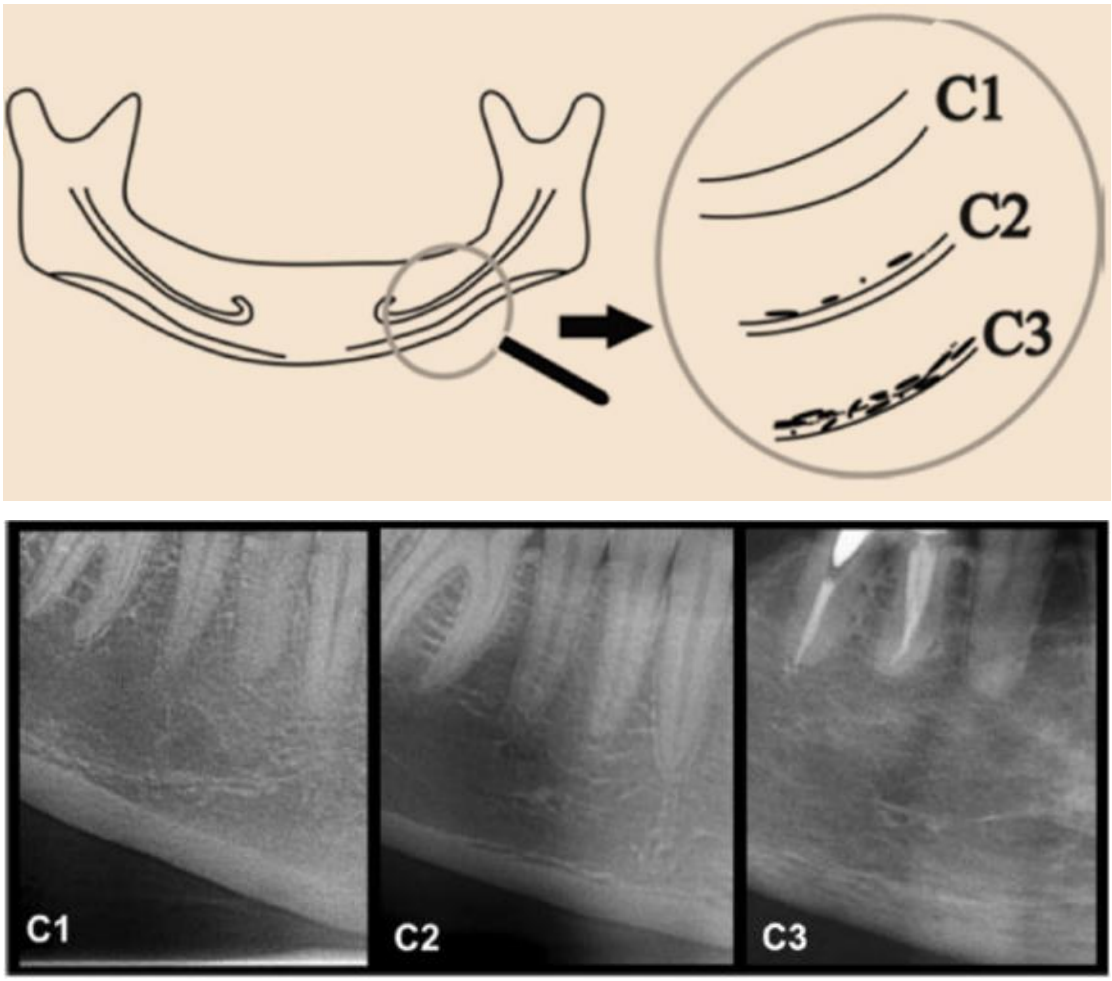


Figure 6: According to Klemetti, this is an illustration of the mandibular cortical index (MCI). C1: normal cortex, with both sides of the endosteal edge still being clearly visible. C2: Cortex that was only mildly or moderately degraded, with semi-lunar flaws at the endosteal boundary, C3: Cortical layer with extensive erosive damage (Binetou Catherine Gassama,2021).

- **Mental Index:** The mental foramen's thickness is measured by the mental index (MI) on a panoramic radiograph. A thinner MI has been linked to a higher incidence of fractures and osteoporosis (Hastar E, 2011).
- **The antegonial index (AGI)** on a panoramic radiograph measures the separation between the antegonial notch and the mandibular angle. Osteoporosis and fracture risk have been linked to greater AGI levels (Sghaireen MG,2020).
- **The gonial angle:** On a panoramic radiograph, the angle created by the intersection of the mandibular ramus and the body of the jaw is measured as the gonial angle (GA). The risk of osteoporosis and fractures has been linked to a smaller GA (Upadhyay RB, 2012).

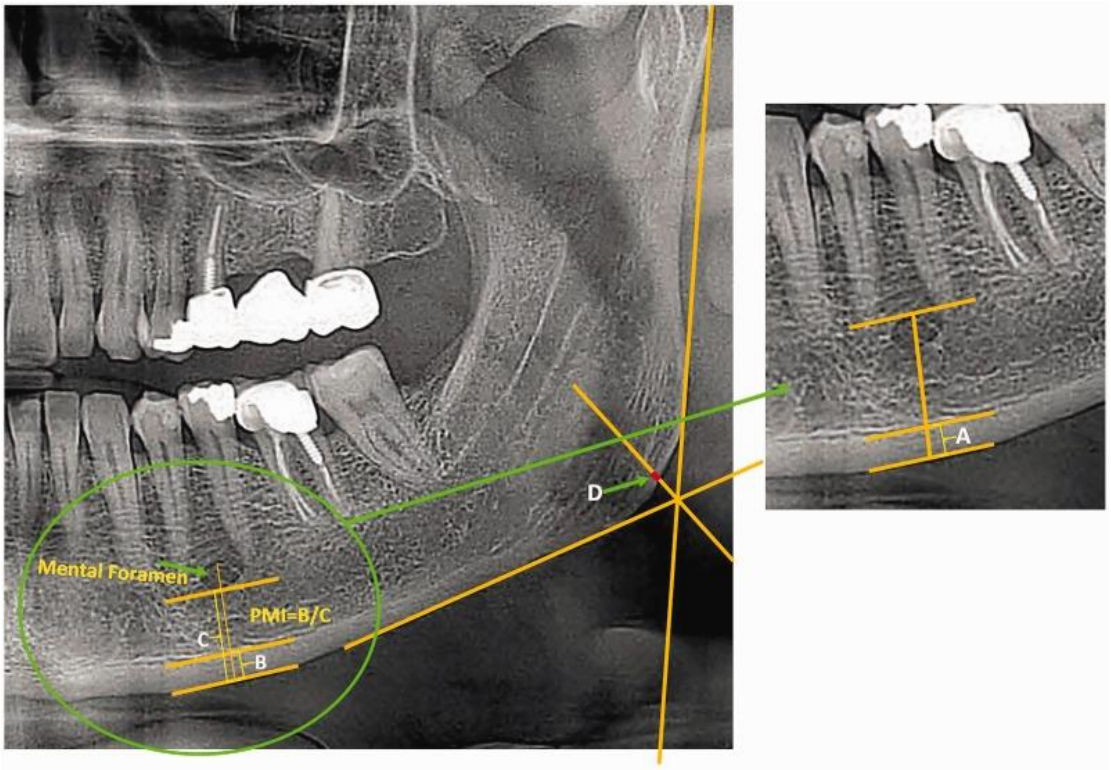


Figure 7: MI width (width A) as measured on an orthopantomogram. Orthopantomogram used to calculate PMI (PMI = B/C). Orthopantomogram showing AGI measurement (width D). AGI stands for antegonial index; PMI stands for panoramic mandibular index. (Sghaireen MG,2020)

Mandibular cortical index (MCI), was developed for panoramic radiography in 1994 by Klemetti and collaborators (Klemetti E et al,1994). It is a qualitative index that evaluates how the mandibular endosteum appears. It classifies the mandibular cortex as C1, C2, C3 due to the severity. Since that, it is a visual classification, the MCI's key benefit is that dentists may easily use it. This index was initially used to identify postmenopausal females using conventional radiographs as an adjunct tool. Since then, several researchers have argued in favor of the MCI's applicability and effectiveness as a precise supplemental tool for low BMD. (Munhoz L et al.,2021; Karayianni et al., 2007; Devlin et al., 2007; Horner et al., 2007).

The mandibular cortical width (MCW) index, which measures the thickness of the mandibular cortical bone distal to the mental foramen, will be used for the quantitative evaluation. A decrease in MCW has been linked to a higher risk of fractures and osteoporosis. According to research, postmenopausal women, the elderly, and patients with a history of skeletal fractures can all benefit from using the MCW index to determine their risk of osteoporosis and fracture. The gold standard for determining bone mineral density (BMD), dual-energy X-ray absorptiometry (DXA), has been found to correlate well with MCW measures. MCW can be used as a diagnostic tool, although it has several drawbacks. The index can only evaluate the mandible's quality of bone; it cannot reveal information about the density of bone in other skeletal locations. Additionally, operator variability makes the MCW measurement method less trustworthy than other imaging methods like DXA. Despite these drawbacks, the MCW index is a quick and painless way to evaluate the mandible's bone integrity, and it may be able to tell some patients at risk for osteoporosis and fractures (Klemetti E, 1994).

These indices have been developed over past decades to assess and quantify the quality of mandibular bone mass and to observe signs of resorption in panoramic radiographs. Recent studies have reported significant correlations between BMD and either MCI, PMI, or MCW (*Kwon et al. 2017; Hastar 2011*).

Kwon et al concluded that **PMI** had limited usability when the margin of the mental foramen was not clear. Contrarily, MCW, a factor used to calculate the PMI, showed a strong association with patient age, and had fewer limitations regarding assessments of bone mineral density than the PMI (*Kwon et al. 2017*).

The use of panoramic radiographs as an indicator of alterations in BMD has been used mainly in adults with osteoporosis (*Alonso et al. 2011; Taguchi et al. 1996*). Based on the results of the 3-year OSTEODENT project a 3mm limit for the cortical width, in the mental foramen region, was established and patients with a cortical width less than that should be referred for definitive diagnosis (Karayianni et al. 2007).

Relative studies in children are rare and focus mainly on changes in bone mass density in special groups of population. Up to date, panoramic radiographs had been used in studies that record bone density in children with systemic diseases or pathological conditions which can affect jawbone quality.

2.12. Studies in special groups of the paediatric population where radiomorphometric indices had been used

Preterm births are one of the conditions that have been researched in the literature (Paulsson-Bjornsson et al. 2015). This study compared the mandibular cortical thickness on panoramic radiographs of 8 to 10-year-old children with or without a history of preterm or full-term deliveries. At the ages of 8 to 10 years old, panoramic radiography was done on 42 full-term children, 36 extremely preterm children, and 38 very preterm children. Between extremely preterm and very preterm children, there were significant variations in mandibular cortical width, with the very preterm displaying the highest value. Except for one measurement point, where the extremely preterm showed the lowest value, there were no significant differences between full-term and either very preterm or extremely preterm. They hypothesized that these results may reflect the effect of mineral supplementation given to premature infants, causing a "shifting up" of bone mineral status relative to the full-term peer group while

maintaining the difference between very preterm and extremely preterm-born children. The evidence showed that very preterm children had significantly thicker mandibular cortices than extremely preterm children (Paulsson-Bjornsson et al. 2015).

Another relative study is about **osteogenesis imperfecta** (Apolinário AC, 2015). The objective of this retrospective study was to validate radiomorphometric indices and fractal dimension in DPRs of children with various forms of osteogenesis imperfecta as well as to validate the therapeutic impact of pamidronate (PAM) in such panoramic assessments. They chose 197 DPRs from 62 children with OI Types I, III and IV who were receiving treatment with a comparable dosage of intravenous PAM. They concluded that PAM therapy caused cortical bone changes in children with OI. Following PAM therapy, children with OI had greater Mandibular Cortical Width (MCW) and Fractal Dimension of the cortical bone. It is believed that cortical bone should be taken into account when examining patients with OI and tracking the effectiveness of PAM therapy.

Bone density has also been studied in **cancer survivor children** (Frascino et al. 2019). 52 panoramic radiographs of childhood HSCT survivors aged 3.69–18.88 years and controls were used to measure BMD using two radiomorphometric indices (MCW, MCI). Compared to healthy controls, the mandibular cortical bone width was 17% smaller in childhood HSCT survivors. Although no statistically significant difference was found, the qualitative analysis showed a higher frequency of severe mandibular cortical erosion in children HSCT survivors.

In addition, the effect of **obesity** on the mandibular cortical bone was studied. According to Yasa et al. (2020), they evaluated the mental index (MI) and panoramic mandibular index (PMI) of a group of adolescent patients in different body mass index (BMI) percentile. According to their BMI percentile status, the subjects were classified into three groups: normal weight (35 subjects; mean age, 14.81 2.12 years); overweight (32 subjects; mean age, 14.77 2.56 years); and obese (33 subjects; mean age, 14.06 2.59 years). In people who are obese and overweight compared to patients who are of normal weight, the mandibular cortex was observed to be thicker.

Another study (Tercanlı Alkış, H. et al.,2022) is about mandibular bone changes in children and adolescents with **Type 1 Diabetes Mellitus (DM)** in different metabolic control states. The study included 57 patients for the type 1 DM group with a mean age of 11.5±2.4 years and 57 patients for the control with a mean age of 10.5±2.1 years. Both the panoramic mandibular index (PMI) and mandibular cortical width (MCW) were measured. In contrast to the control group, children and adolescents with type 1 DM did not exhibit any cortical and trabecular bone alterations in the mandibula, according to this study. Additionally, the bone structure was unaffected by the metabolic control stages of DM.

The cortical and trabecular mandibular bone morphology of children and adolescents who have **beta-thalassemia major (ß-TM)** had also been evaluated (Yagmur B. et al., 2022). There were 80 patients total in the trial (40 ß-TM sufferers and 40 control individuals). Simple visual estimation (SVE), the mandibular cortical index (MCI), the panoramic mandibular index (PMI), and the mandibular cortical width (MCW) were assessed. They showed that the ß-TM group had lower MCW and PMI values. While the trabecular bone's mean fractal dimension (FD) values are comparable to those of the control groups, the ß-TM group's cortical bone's mean FD value is lower.

Another study (Firman et al., 2020) aims to assess the mandibular bone quality in 43 panoramic radiographs of **HIV-infected children** using the mandibular cortical index (MCI) and panoramic mandibular index (PMI). The mandibular cortical index (MCI) with the highest value was C2 (cortex with mild to moderate erosion), and the mandibular panoramic index (PMI) with the highest number was lower than normal in children with HIV infection.

Mandibular cortical width was even employed in a study (Eimar et al. 2019) as an additional diagnostic measure for the identification of **sleep-disordered breathing (SDB)**. There were two cross-sectional retrospective studies. The first study evaluated the MCW between 24 children with OSA who had been polysomnographically (PSG) diagnosed and 72 age- and sex-matched control children. The Paediatric Sleep

Questionnaire's recommendation for SDB was used in the second study's cohort of kids. From panoramic radiographs, MCW was calculated. According to research, children who are at risk for or who have been diagnosed with SDB have reduced mandibular cortical width, which may indicate changes in bone homeostasis.

Additionally, some research has revealed that children who receive psychostimulant treatment for **attention-deficit hyperactivity disorder (ADHD)** have lower bone mineral density (BMD) (Kostiner H, 2022). They compared the MCW of 58 children and adolescents without ADHD (control) to the MCW of 38 children and adolescents with ADHD who were treated with methylphenidate for at least 12 months using digital panoramic radiographs (DPR). Youngsters with ADHD had considerably lower mean MCW than youngsters in the control group.

2.13. Gap in the existing literature

Although there is enough literature on the use of panoramic radiography in special groups of paediatric population, namely children with diseases, syndromes or children who are taking any medication that affect bone density, the bone in healthy children has not yet been studied in a corresponding way, so that there is a measure of comparison. These data could be useful for future studies as a control group. From this study we can derive new data that are missing from the literature for the quantitative and qualitative evaluation of mandibular cortical bone in a healthy population.

During childhood and adolescence, bone mineral density (BMD) increases until peak bone mass is reached. Those periods are critical as high skeletal growth up to 90% of adult bone mass is acquired (*Bachrach et al., 2007*). **Thus, it is necessary to define normal values for bone density during this period to allow for the determination of deviations.**

MAIN PART

3.1. Aim of the study

The primary aim of the study is to systematically record and evaluate qualitatively and quantitatively the cortical bone of healthy children aged 6-18 years.

Secondary objectives are:

4. To evaluate the distribution of bone density in different gender and age groups.
5. To evaluate cortical bone quality in different gender and age groups.
6. To investigate the possibility that bone density is affected by factors that generally alter occlusion and indirectly masticatory forces such as the presence of extensive carious lesions, missing teeth, extensive resin composite restorations, and Stainless-Steel Crowns.

The ultimate goal of the study is to create reference tables of the thickness of the cortical bone in a healthy Greek population of children and adolescents.

3.2 MATERIALS AND METHOD

The study was performed according to the Declaration of Helsinki (WMA 2013) and the research protocol was submitted and approved by the Ethics Committee of the School of Dentistry, National & Kapodistrian University of Athens (NKUA), Greece (N449, approved on 21/12/2020).

Study design

It was a double-blinded retrospective cohort study evaluating mandibular cortical bone of healthy children and adolescents through dental panoramic radiographs taken in the context of the patient's dental needs. The sample was retrieved from the electronic database of the Dental School of National and Kapodistrian University of Athens.

Study population

The dental records of all patients from the Department of Paediatric Dentistry and the Department of Orthodontics (Dental School, National and Kapodistrian University of Athens) treated between 2012 and 2021 were searched for patients, aged 6-18 years of age, with a dental panoramic radiograph available. The radiograph was taken for diagnostic reasons. The period selected ensured that all radiographs are comparable as they have been performed with the same radiographic machine (Planmeca ProMax Elsinki Finland 50/60 Hz) and the possible magnification is the same.

The inclusion criteria were panoramic radiographs of:

- good quality of
- patients with updated medical and dental records

Exclusion criteria were panoramic radiographs of:

- patients with diseases/ conditions/ treatments affecting the bone e.g. eating disorders, prematurity, early puberty, musculoskeletal disorders, etc.,
- patients undergoing/ undergone orthodontic treatment,
- poor quality.

The imaging parameters may have varied according to the patient's age. Normal quality criteria for panoramic radiography were used (Table 7). Since all images have been performed with the same panoramic equipment the vertical magnification factor in the radiographs was calculated according to the manufacturer.

A: Patient preparation/ instruction adequate • Edge to edge incisors. • No removable metallic foreign bodies (e.g. earrings, spectacles, dentures). • No motion artefacts. • Tongue against roof of mouth. • Minimisation of spine shadow.
B: No patient positioning errors • No antero-posterior positioning errors (equal vertical and horizontal magnification). • No mid sagittal plane positioning errors (symmetrical magnification). • No occlusal plane positioning errors. • Correct positioning of spinal column.
C: Correct anatomical coverage • Appropriate coverage depending upon the clinical application. Field size limitation should have been used (if available) to exclude structures irrelevant to clinical needs (e.g. limitation of field to teeth and alveolar bone for everyday dental use).
D: Good density and contrast • There should be good density and adequate contrast between the enamel and the dentine.
E: No cassette/ screen problems • No light leaks. • Good film/screen contact. • Clean screens.
F: Adequate processing and darkroom techniques • No pressure marks on film, no emulsion scratches. • No roller marks (automatic processing only). • No evidence of film fog. • No chemical streaks/splashes/contamination. • No evidence of inadequate fixation/washing. • Name/date/left or right marker all legible.

Table 7: Quality standards for panoramic radiography (http://europa.eu.int/comm/energy/nuclear/radioprotection/ No.136)

A power analysis was performed with a strength of 0.8. The required sample size was calculated with STATISTICA for Windows 12.5 (Power Analysis module) which led to an even distribution of patients in different age and gender groups. This resulted in a total sample of 660 patients. The 660 patients were divided into groups by age and gender.

Study Procedure

Dental panoramic radiographs were assessed and the mandibular cortical bone was evaluated qualitatively and quantitatively using two distinct anthropometric indices.

Assessment and analysis of all radiographs were performed in random order by two calibrated observers. The evaluators acted blindly concerning the patient's demographic characteristics since all radiographs were initially mixed up by a third researcher not involved in the evaluation process. The third researcher, who was also calibrated, was involved in the preparation of the radiographs for the quantitative analysis, i.e. drawing the lines required for the analysis and cropping of the radiographs so that only the lower jaw was visible in order to facilitate the analysis.
Any discrepancies between evaluators were resolved through discussion and if agreement was not reached, a third evaluator not previously involved in the above processes was consulted.
100 x-rays were re-examined after one month by the same examiners to check the intra- and inter- observer reliability.

The indexes used were:

a. **Mandibular Cortical Index (MCI)**,
A qualitative index that evaluates the morphology of the threshold of the cortical bone with the trabecular bone distally to the mental foramen at both sides of the mandible. (Figure. 8). It is categorized according to a three-point scale described by Klemetti et al. (*1994*):
C1: the endosteal margin of the cortex is even and sharp on both sides
C2: the endosteal margin shows semilunar defects (lacunar resorption) and/or seems to form endosteal cortical residues on one or both sides

C3: the cortical layer forms heavy endosteal cortical residues and is clearly porous

Each side was evaluated separately and the worst value was the one recorded for each patient.

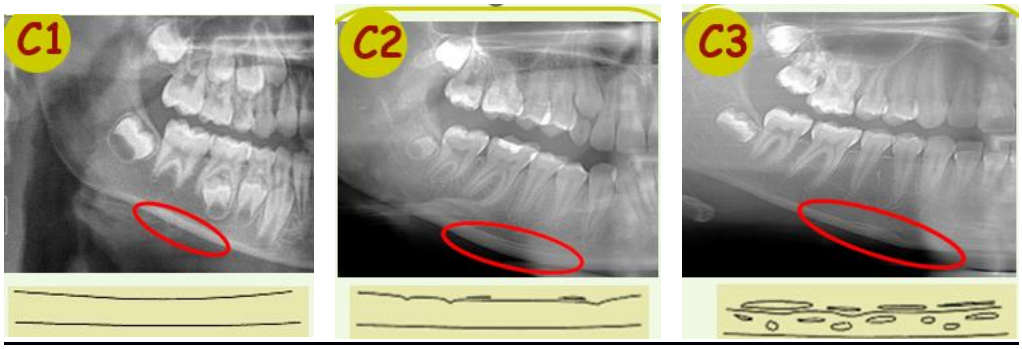


Figure 8: The C1, C2 and C3 classification of the mandibular cortex index (MCI) (Gulsahi et al. 2010).

b. **Mandibular Cortical Width (MCW)**

A quantitative index that evaluates the thickness of the cortical bone in both sides of the mandible. In each side a line was drawn along the lower border of the mandible, followed by four perpendicular lines to the tangent at the following points (Figure 9):

5. Antegonion—the deepest point of the antegonial notch concavity (A, H)
6. the mesial cementoenamel junction of the first molar perpendicular to the mandibular base(B, G)
7. the most superior cusp tip of the second premolar perpendicular to the mandibular base (C, F)
8. the most superior cusp tip of the first premolar perpendicular to the mandibular base(D, E)

At the points where the vertical lines intersect the cortical bone, the thickness of the cortical bone was measured using the software Image J (Image J 1.50c4 for Windows XP). As the software measures length in pixels (1024x1024 pixels; 8-bit; 1 MB), all measurements were converted into mm using a calculated coefficient factor. The pixel to physical-world dimensions, was based on the size of pixels using a known sample. For each radiograph, the mean value from the two measurements for each site and the overall mean value from all sites was calculated and recorded in a specially designed recording sheet.

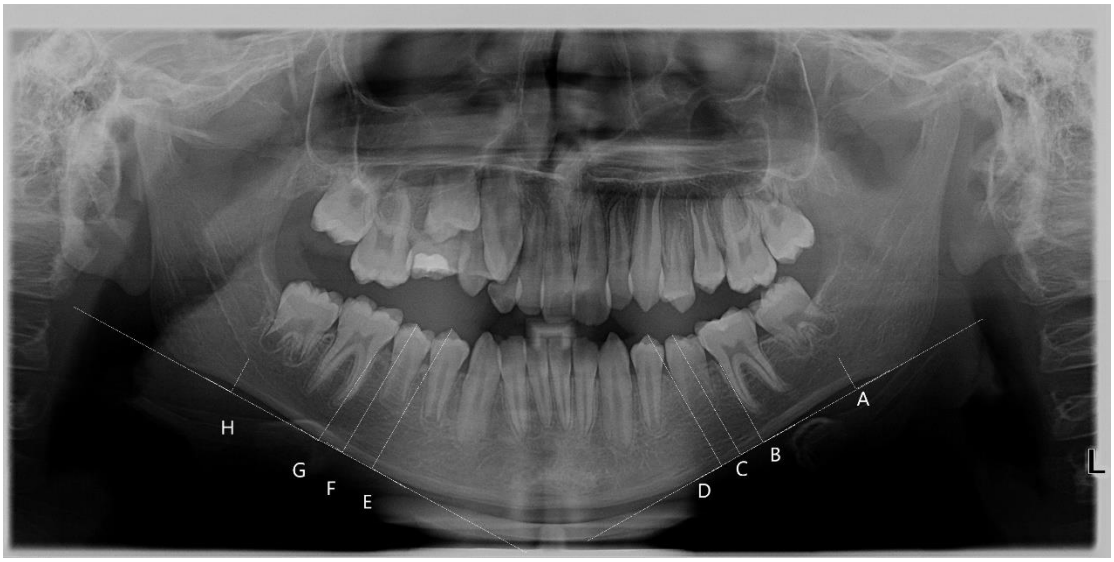


Figure 9: Panoramic radiograph showing the sites (A–H) where measurements of the width of the cortical bone were done. Lines were drawn perpendicular to a tangent at the lower border of the cortex to the inner border of the cortex at A and H (the deepest points of the antegonial notch concavity), at the cementoenamel junction of the crown of the first molar (B, G) and at the highest cusp of the premolars (C, D, E, F). The width of the cortex was measured along these lines.

Calibration of the examiners

The examiners were calibrated prior to the initiation of the study for both qualitative and quantitative evaluation. An adequate number of radiographs of healthy patients not included in the sample were evaluated by the examiner until intra-examiner reliability of $k>0.8$ was reached.

Secondary objectives

In order to detect the effect of various occlusion-related factors on the quality and quantity of cortical bone, the radiographs were also evaluated regarding the state of dentition (primary, mixed, permanent) as well as the oral condition, i.e. number of teeth with deep carious lesions, number of missing teeth, number of primary or permanent teeth with caries, composite resin restorations and teeth with stainless-

steel crowns. All the above parameters were also recorded in a separate sheet by the researcher that prepared the radiographs.

3.3 Statistical analysis

Mean values for the cortical bone thickness at each site were calculated and age and gender distribution are presented. The prevalence of bone morphology (left, right and total) was also calculated for each age group and gender. Total bone morphology was defined as the maximum condition (C1< C2< C3) observed in either the left or right side. In order to evaluate the correlation between bone morphology and demographic characteristics, Fisher's exact test and z-test for comparing 2 proportions were applied. The agreement of calculated values of cortical bone thickness between the 2 examiners was assessed by applying Lin's concordance correlation coefficient, Pearson's r correlation coefficient and calculating the 95% Limits of Agreement (LoA). Lin's concordance correlation coefficient passes values from 0 to 1 and the closer the value is to 1 the more statistically significant the correlation is. The correlation between characteristics of the samples' dentition and demographic characteristics and bone morphology was evaluated by applying the chi-square test (or in the case that the assumptions did not hold, Fisher's exact test). Spearman's rho correlation coefficient was calculated to assess the correlation of samples' characteristics by age (years), one-way analysis of variance (ANOVA) to assess differences in samples' characteristics by mean age and by total cortical bone thickness, followed by Bonferroni correction for multiple comparisons.

All analysis was done using STATA version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Two-tailed p-values are reported. A *p*-value less than 0.05 was considered as statistically significant.

3.4. Results

A) Demographic characteristics

Table 8 depicts the demographic characteristics of the present sample. Half of the participants (49.4%) were boys. The mean age of the patients was 11.7 years and standard deviation 3.37 years, with the minimum age being 6 years old and the maximum 18 years old. The distribution of age was also showed in age groups, 21.8% of the patients are 8 to 9 years old, while 19.9% were 10 to 11 years old.

Table 8. Distribution of demographic characteristics of patients (N=660).

Demographic characteristics	Descriptive statistic
Gender n (%)	**N(%)**
Boy	326 (49.4)
Girl	334 (50.6)
Age yrs: mean (SD)	11.7 (3.37)
Age groups n (%)	**N(%)**
6-7	67 (10.2)
8-9	144 (21.8)
10-11	131 (19.9)
12-13	114 (17.3)
14-15	90 (13.6)
16-17	78 (11.8)
18	36 (5.5)

SD: Standard Deviation

Table 9 shows the distribution of the dentintions' characteristics. The majority of patients (90%) did not have caries or composites (79.2%), or SCC (95.2%). 10.2% of the patients had a least one missing tooth. 30.6% of the patients were in the early mixed, 23.3% were in the late mixed and 46.1% in the permanent dentition. Early mixed we consider the period when we have the eruption of 1st permanent molars and the exchange of incisors and late mixed the period when 2nd permanent molars erupt and canines and premolars exchange.

Table 9. Distribution of dentitions' characteristics.

Characteristics	Frequency (Percent)
Caries n (%)	
0	594 (90.0)
1	18 (2.7)
2	16 (2.4)
3+	32 (4.9)
Composites n (%)	
0	523 (79.2)
1	42 (6.4)
2	39 (5.9)
3	21 (3.2)
4+	35 (5.3)
SCC n (%)	
0	628 (95.2)
1	17 (2.6)
2	10 (1.5)
3	5 (0.8)
Missing teeth n (%)	
0	592 (89.8)
1	37 (5.6)
2	24 (3.6)
3	4 (0.6)
4	2 (0.3)
Dentition n (%)	
Early mixed	202 (30.6)
Late Mixed	154 (23.3)
Permanent	304 (46.1)

Table 10 shows the results of the correlation between samples' characteristics and gender. The distribution of caries, composites, SCC and missing teeth did not differ statistically significant between boys and girls (p-value> 0.05) in our study sample.

Table 10. Results of correlation between samples' characteristics and gender.

	Gender n(%)			
Characteristics	Boys	Girls	Total	**p-value**
Caries				
0	298 (50.2)	296 (49.8)	594	
1	11 (61.1)	7 (38.9)	18	0.168[1]
2	5 (31.3)	11 (68.8)	16	
3+	12 (37.5)	20 (62.5)	32	
Composites				
0	256 (49.0)	267 (51.1)	523	
1	22 (52.4)	20 (47.6)	42	
2	21 (53.9)	18 (46.2)	39	0.970[1]
3	10 (47.6)	11 (52.4)	21	
4+	17 (48.6)	18 (51.4)	35	
SCC				
0	315 (50.2)	313 (49.8)	628	
1	5 (29.4)	12 (70.6)	17	0.217[2]
2	3 (30.0)	7 (70.0)	10	
3	3 (60.0)	2 (40.0)	5	
Missing teeth				
0	297 (50.2)	295 (49.8)	592	
1	17 (46.0)	20 (54.1)	37	
2	8 (33.3)	16 (66.7)	24	0.406[2]
3	3 (75.0)	1 (25.0)	4	
4	1 (50.0)	1 (50.0)	2	
Dentition				
Early mixed	113 (55.9)	89 (44.1)	202	
Late Mixed	59 (38.3)	95 (61.7)	154	0.004[1]*
Permanent	154 (50.7)	150 (49.3)	304	

[1]Chi square test
[2]Fisher's exact test
*statistically significant result (α=5%)

Table 11 presents the results of the correlation between samples' characteristics and age (years). A statistically significant negative correlation was observed between age and a. caries, b. SCC and c. missing teeth (p-value< 0.05). Therefore, the older in age the patients the less they had caries, SCC and missing teeth. Moreover, a statistically significant difference in mean age was observed over dentition (p-value<0.001). Mean age differed significantly between all possible dentition pairs (Bonferroni p-value< 0.001).

Table 11. Results of correlation between samples' characteristics and age (years).

Characteristics	**Spearman rho correlation coefficient**	**p-value**
Caries	-0.09	0.018[1]*
Composites	0.03	0.484[1]
SCC	-0.13	0.001[1]*
Missing teeth	-0.21	<0.001[1]*
Dentition	Mean (SD)	
Early mixed	8.3 (1.5)	
Late Mixed	11.0 (2.0)	<0.001[2]*
Permanent	14.3 (2.5)	
Bonferroni		
Early-late mixed		<0.001[3]*
Early mixed-permanent		<0.001[3]*
Late mixed-permanent		<0.001[3]*

[1]Spearman rho correlation coefficient
[2]One-way analysis of variance (ANOVA)
[3]Bonferroni p-value for multiple comparisons
SD: Standard Deviation
*statistically significant result (α=5%)

B) Qualitative Bone assessment

Table 12 presents the distribution for the qualitative analysis done to evaluate the morphology of the threshold of the cortical bone with the trabecular bone at the distal of mental foramen. The prevalence of endosteal margin of the cortex was even and sharp on both sides is 87.9% (right) and 84.6% (left), while in total 80.3%. The endosteal margin showed semilunar defects (lacunar resorption) and/or seems to form endosteal cortical residues on one or both sides in 12%, 15.3% and 19.3% of the cases, right, left and in total, respectively. While only 0.1% of the cases showed that the cortical layer forms heavy endosteal cortical residues and was clearly porous. The distribution of morphology did not differ between left and right (p-value> 0.05).

Table 12. Distribution of the morphology of the endosteal margin of the cortical bone with the trabecular bone at the distal of mental foramen.

Morphology n (%)	Right	Left	p-value[1]	Total
C1	580 (87.9)	558 (84.6)	0.078	530 (80.3)
C2	79 (12.0)	101 (15.3)	0.074	127 (19.3)
C3	1 (0.1)	1 (0.1)	0.999	1 (0.2)

[1]z-test for comparison of proportions

Table 13 and Figure 10 presents the prevalence of bone morphology (both right and left), by gender. In both cases, a statistically significant correlation was observed between bone morphology and gender (p-value= 0.017, 0.027 and 0.026< 0.05, right, left and in total, respectively). Specifically, the endosteal margin of the cortex, which was even and sharp on both sides, was more frequent in girls compared to boys (91% vs 87.7%, 84.7% vs 81.3% and 84.1% vs 76.9%, right, left and in total respectively). On the other hand, the endosteal margin which showed semilunar defects (lacunar resorption) and/or seems to form endosteal cortical residues on one or both sides, was more frequent in boys than girls (15% vs 9%, 18.4% vs 12.3% and 22.8% vs 15.9%, right, left and in total respectively).

Table 13. Distribution of bone morphology according to MCI Index, by gender.

	Morphology (right) n (%)				
	C1	C2	C3	Total	
Gender					**p-value[1]**
Boys	276 (84.7)	49 (15.0)	1 (0.3)	326	0.017*
Girls	304 (91.0)	30 (9.0)	0 (0.0)	334	
	Morphology (left) n (%)				
Gender					**p-value[1]**
Boys	265 (81.3)	60 (18.4)	1 (0.3)	326	0.027*
Girls	293 (87.7)	41 (12.3)	0 (0.0)	334	
	Morphology (Total) n (%)				
Gender					**p-value[1]**
Boys	250 (76.9)	74 (22.8)	1 (0.3)	325	
Girls	280 (84.1)	53 (15.9)	0 (0.0)	333	0.026*

[1]Fisher's exact test
*statistically significant result (α=5%)

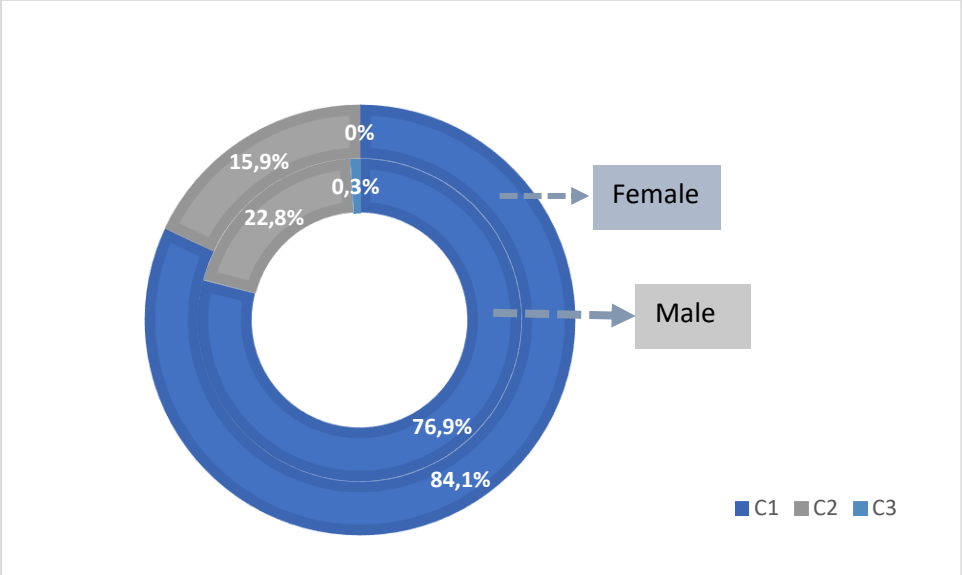


Figure 10: Distribution of Bone Quality by gender

Table 14 and Figure 11 shows the prevalence of bone morphology (both right and left), by age groups. In both right, left bone morphology as in total, a statistically significant correlation was observed with age groups (p-value= 0.001, 0.048 and 0.013< 0.05, respectively). In particular, the endosteal margin of the cortex was even and sharp on both sides was more frequent in patients aged 8 to 11 (93.8% and 95.4% on the right side, 90.3% and 89.3% on the left side and 86.6% and 88.5% in total bone morphology) compared to other ages. On the other hand, the endosteal margin showed semilunar defects (lacunar resorption) and/or seems to form endosteal cortical residues on one or both sides were more frequent in ages 6 to 7 and in patients 14+ years old (about 20%, right and left respectively and 32.8% in total).

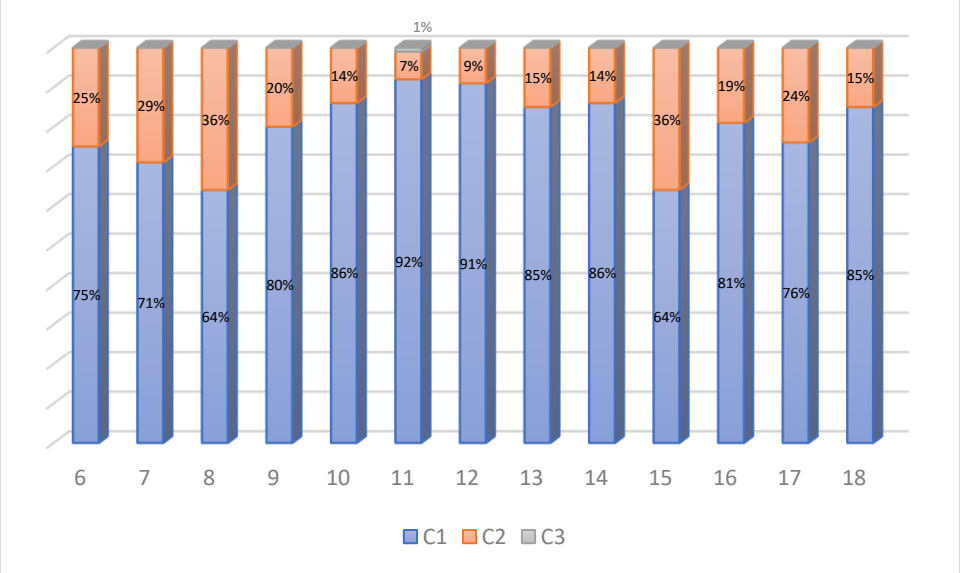


Figure 11: Distribution of cortical bone quality by age.

Table 14. Distribution of bone morphology according to MCI Index, by age groups.

	Morphology (right) n (%)				
Age groups n (%)	C1 n%	C2 n%	C3 n%	Total n%	**p-value[1]**
6-7	52 (77.6)	15 (22.4)	0 (0.0)	67	
8-9	135 (93.8)	8 (5.6)	1 (0.7)	144	
10-11	125 (95.4)	6 (4.6)	0 (0.0)	131	
12-13	100 (87.7)	14 (12.3)	0 (0.0)	114	0.001*
14-15	70 (77.8)	20 (22.2)	0 (0.0)	90	
16-17	66 (84.6)	12 (15.4)	0 (0.0)	78	
18	32 (88.9)	4 (11.1)	0 (0.0)	36	
	Morphology (left) n (%)				
Age groups n (%)	n%	n%	n%	n%	**p-value[1]**
6-7	54 (80.6)	13 (19.4)	0 (0.0)	67	
8-9	130 (90.3)	13 (9.0)	1 (0.7)	144	
10-11	117 (89.3)	14 (10.7)	0 (0.0)	131	
12-13	95 (83.3)	19 (16.7)	0 (0.0)	114	0.048*
14-15	71 (78.9)	19 (21.1)	0 (0.0)	90	
16-17	62 (79.5)	16 (20.5)	0 (0.0)	78	
18	29 (80.6)	7 (19.4)	0 (0.0)	36	
	Morphology (Total) n (%)				
Age groups n (%)					**p-value[1]**
6-7	45 (67.2)	22 (32.8)	0 (0.0)	67	
8-9	124 (86.6)	17 (12.0)	1 (0.7)	142	
10-11	116 (88.5)	15 (11.5)	0 (0.0)	131	
12-13	90 (78.9)	24 (21.1)	0 (0.0)	114	0.013*
14-15	65 (72.2)	25 (27.8)	0 (0.0)	90	
16-17	61 (78.2)	17 (21.8)	0 (0.0)	78	
18	29 (80.6)	7 (19.4)	0 (0.0)	36	

[1]Fisher's exact test
*statistically significant result (α=5%)

Table 15 shows the prevalence of bone morphology in each age group, stratified by gender. Bone morphology and age was correlated in boys (p-value< 0.001), but not in girls (p-value> 0.05). Regarding boys, the endosteal margin of the cortex is even and sharp on both sides is more frequent in patients aged 8 to 11 (90.1% and 92.6%) compared to other ages. On the other hand, for girls aged 14-15 the endosteal margin of the cortex is even and sharp on both sides is more frequent (92.7%) compared to other age groups. However, the result did not reach statistical significance.

Table 15. Correlation between bone morphology and age groups, stratified by gender.

Boys	**Bone morphology n (%)**				
Age groups n (%)	C1	C2	C3	Total	**p-value[1]**
6-7	23 (63.9)	13 (36.1)	0 (0.0)	36	
8-9	64 (90.1)	6 (8.5)	1 (1.4)	71	
10-11	50 (92.6)	4 (7.4)	0 (0.0)	54	
12-13	45 (77.8)	12 (22.2)	0 (0.0)	54	<0.001*
14-15	27 (55.1)	22 (44.9)	0 (0.0)	49	
16-17	31 (70.5)	13 (29.5)	0 (0.0)	44	
18	13 (76.5)	4 (23.5)	0 (0.0)	17	
Girls	**Bone morphology n (%)**				
Age groups n (%)	C1	C2		Total	**p-value[1]**
6-7	23 (71.0)	9 (29.0)		31	
8-9	60 (84.5)	11 (15.5)		71	
10-11	66 (85.7)	11 (14.3)		77	
12-13	48 (80.0)	12 (20.0)		60	0.291
14-15	38 (92.7)	3 (7.3)		41	
16-17	30 (88.2)	4 (11.8)		34	
18	16 (84.2)	3 (15.8)		19	

C1: the endosteal margin of the cortex is even and sharp on both sides
C2: the endosteal margin shows semilunar defects (lacunar resorption) and/or seems to form endosteal cortical residues on one or both sides
C3: the cortical layer forms heavy endosteal cortical residues and is clearly porous
[1]Fisher's exact test
*statistically significant result (α=5%)

C) Quantitative Bone assessment

Table 16 summarizes the magnitude of the agreement and the correlation of cortical bone thickness values calculated by the 2 examiners. Lin's concordance correlation coefficient was 0.90, meaning excellent agreement of calculated values between the 2 examiners. Moreover, Pearson's correlation coefficient was 0.96 (excellent linear correlation). Both measures were statistically significant (p-value< 0.001). The mean difference of cortical bone thickness values between Examiner 1 and Examiner 2 was very small (0.17 with SD: 0.15), while the 95% Limits of Agreement were estimated from -0.13 to 0.46. Figure 12 is a scatterplot of the average calculated values of cortical bone thickness between the 2 examiners vs their difference (red points). The grey shaded area represents the 95% LoA between the 2 examiners. Only few points lay outside the LoA, indicating an excellent agreement.

Table 16. Cortical bone thickness measurement of agreement and correlation, between Examiner 1 and 2.

	Concordance coefficient Lin's r_c (p-value)	**Correlation coefficient Pearson's r (p-value)**	**Mean Difference (SD)**	**95% Limits of Agreement**
Cortical bone thickness	0.90 (<0.001*)	0.96 (<0.001*)	0.17 (0.15)	(-0.13 to 0.46)

SD: Standard Deviation
*statistically significant result (α=5%)

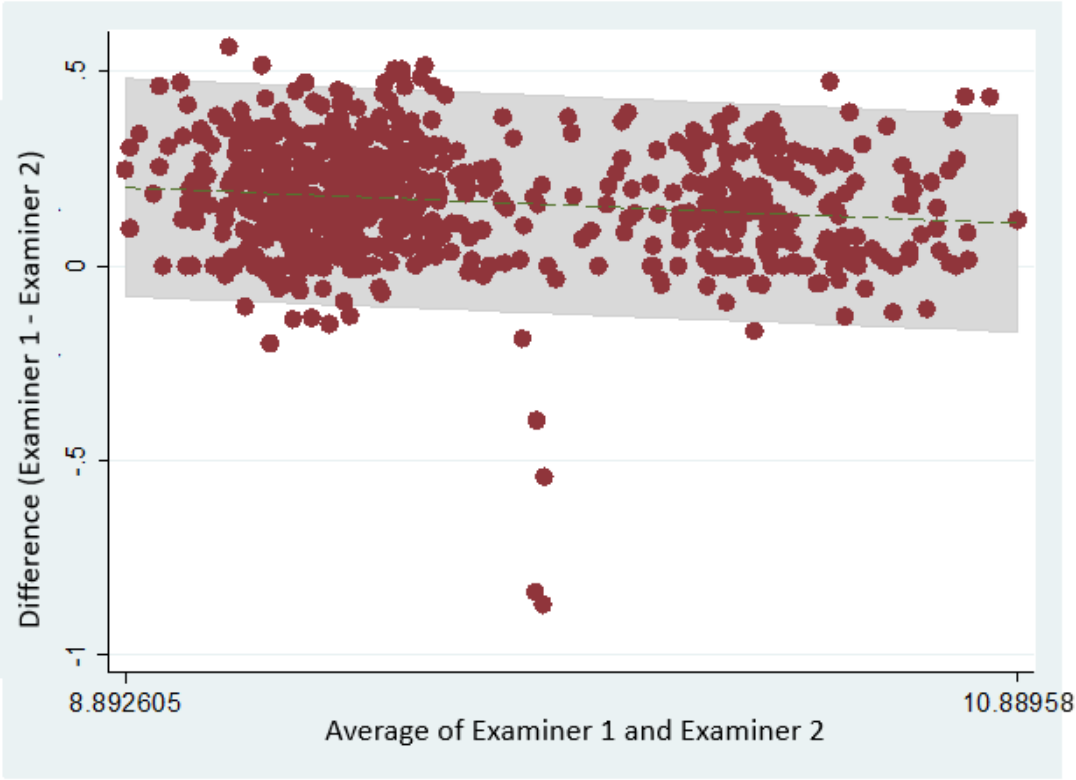


Figure 12. Bland-Altman scatterplot plot of the difference of calculated values of cortical bone thickness between the 2 examiners (Examiner 1 – Examiner 2) and the corresponding mean value and 95% Limits of Agreement.

Table 17 and Figure 13 summarizes the results of comparing mean cortical bone thickness, by age group. A statistically significant difference was found in all areas (p-value< 0.05). Regarding cortical bone thickness:

a. "Antegonion—the deepest point of the antegonial notch concavity (A,H)": multiple comparisons corrected Bonferroni p-values revealed a statistically significant lower mean value in ages 8-9 years compared to ages 14-15 years (mean difference: -0,7109 p-value= 0.029);

Table 17a. Results of correlation between age groups and cortical bone thickness.

Antegonion—the deepest point of the antegonial notch concavity (A,H)

Age (yrs)	N	Mean (mm)	95% Confidence Interval for Mean Lower Bound	95% Confidence Interval for Mean Upper Bound	**p-value[1]**
6-7	67	2,4944	2,1280	2,8607	
8-9	141	2,5624	2,3376	2,7873	
10-11	131	2,8282	2,5631	3,0931	0.010*
12-13	114	2,8742	2,5762	3,1722	
14-15	90	3,2733	2,8656	3,6809	
16-17	78	3,1280	2,6993	3,5567	
18	36	3,1327	2,4896	3,7760	
Total	657	2,8584	2,7318	2,9849	

b. "Along the mesial cementoenamel junction of the first molar perpendicular to the mandibular base (B,G)" statistically significant lower mean values in ages 8-9 years compared to ages 14-15 years (mean difference: -0,9291, p-value= 0.023) and also to ages 16-17 years (mean difference: 1,0204, p-value= 0.013);

Age (yrs)	N	Mean (mm)	95% Confidence Interval for Mean Lower Bound	95% Confidence Interval for Mean Upper Bound	**p-value[1]**
6-7	67	3,2296	2,8082	3,6511	
8-9	141	3,1978	2,9104	3,4853	
10-11	131	3,5453	3,1993	3,8911	
12-13	114	3,5898	3,2033	3,9760	0.002*
14-15	90	4,1269	3,6202	4,6338	
16-17	78	4,2182	3,6180	4,8184	
18	36	4,0871	3,3153	4,8587	
Total	657	3,6356	3,4724	3,7984	

c. “Along the most superior cusp tip of the second premolar perpendicular to the mandibular base (C,F)” multiple comparisons corrected Bonferroni p-values resulted in statistically significant lower mean values in ages 6-7 years compared to ages 18 years (mean difference:-1,4002, p-value= 0.037), in ages 8-9 years compared to ages 14-15 years, 16-17 years and 18+ years (mean difference: -1,1334, -0,9774 and -1,52729, p-value= 0.002, 0.030 and 0.003, respectively) and in ages 10-11 years compared to ages 18 years (mean difference: -1,2849, p-value= 0.035).

Table 17c. Results of correlation between age groups and cortical bone thickness.

Age (yrs)	N	Mean (mm)	95% Confidence Interval for Mean Lower Bound	95% Confidence Interval for Mean Upper Bound	**p-value[1]**
6-7	67	3,3967	2,9633	3,8300	
8-9	141	3,2524	2,9678	3,5371	
10-11	131	3,5120	3,1736	3,8504	
12-13	114	3,6980	3,2947	4,1013	<0.001*
14-15	90	4,3858	3,8182	4,9531	
16-17	78	4,2298	3,6584	4,8011	
18	36	4,7969	3,9211	5,6724	
Total	657	3,7522	3,5836	3,9207	

d. “Along the most superior cusp tip of the first premolar perpendicular to the mandibular base(D,E)” statistically significant lower mean value in ages 6-7 compared to 18 years (mean difference: -1,53, p-value= 0.028), in ages 8-9 years compared to ages 14-15 years (mean difference: -1,0069, p-value= 0.026) and also ages 18 years (mean difference: -1,5611, p-value= 0.006) and in ages 10-11 years compared to ages 18 years (mean difference: -1,4146, p-value= 0.024).

Table 17d. Results of correlation between age groups and cortical bone thickness.

Age (yrs)	N	Mean (mm)	95% Confidence Interval for Mean Lower Bound	95% Confidence Interval for Mean Upper Bound	**p-value[1]**
6-7	67	3,6442	3,2256	4,0631	
8-9	141	3,6131	3,2878	3,9382	
10-11	131	3,7596	3,4067	4,1124	
12-13	114	3,9853	3,5282	4,4424	<0.001*
14-15	90	4,6200	4,0300	5,2098	
16-17	78	4,3064	3,7262	4,8867	
18	36	5,1742	4,2462	6,1020	
Total	657	4,0158	3,8373	4,1944	

e. multiple comparisons, between total bone thickness and age groups, corrected Bonferroni p-values resulted in statistically significant lower mean values in ages 8-9 years compared to ages 14-15 years (mean difference: -0,9449, p-value= 0.010) and compared to ages 18 years (mean difference: -1,1412, p-value= 0.046).

Table 17e. Results of correlation between age groups and cortical bone thickness.

Total					
Age (yrs)	N	Mean (mm)	95% Confidence Interval for Mean Lower Bound	95% Confidence Interval for Mean Upper Bound	**p-value[1]**
6-7	67	3,1913	2,7987	3,5838	
8-9	141	3,1564	2,8876	3,4253	
10-11	131	3,4113	3,0947	3,7280	
12-13	114	3,5367	3,1618	3,9118	<0.001*
14-15	90	4,1013	3,5956	4,6073	
16-17	78	3,9704	3,4358	4,5053	
18	36	4,2976	3,5229	5,0724	
Total	657	3,5653	3,4111	3,7198	

[1]One-way analysis of variance (ANOVA)
SD: Standard Deviation
*statistically significant result (α=5%)

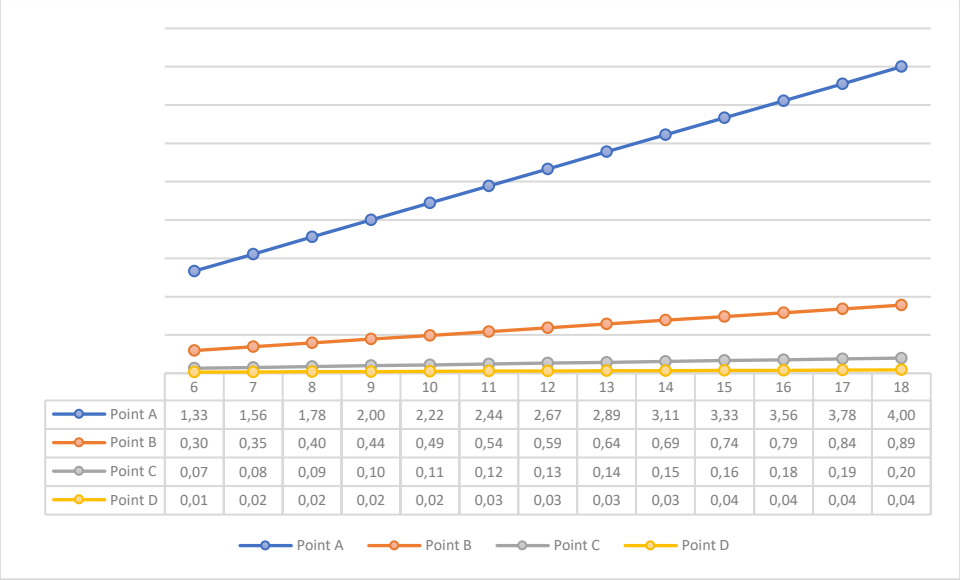


Figure 13: **Distribution of mean cortical width on each point according to age.**

Table 18 shows the correlation between age and bone thickness. A statistically significant positive relationship was found between all points assesing bone thickness and age (years), meaning that as age increases, bone thickness also increases (p-value< 0.001).

Table 18. Correlation between age (years) and bone thickness.

Bone thickness	**Pearson correlation coefficient r**	**p-value**
Antegonion—the deepest point of the antegonial notch concavity (A,H)	0.154	<0.001*
Along the mesial cementoenamel junction of the first molar perpendicular to the mandibular base(B,G)	0.175	<0.001*
Along the most superior cusp tip of the second premolar perpendicular to the mandibular base (C,F)	0.205	<0.001*
Along the most superior cusp tip of the first premolar perpendicular to the mandibular base(D,E)	0.180	<0.001*
Total	0.186	<0.001*

*statistically significant result (α=5%)

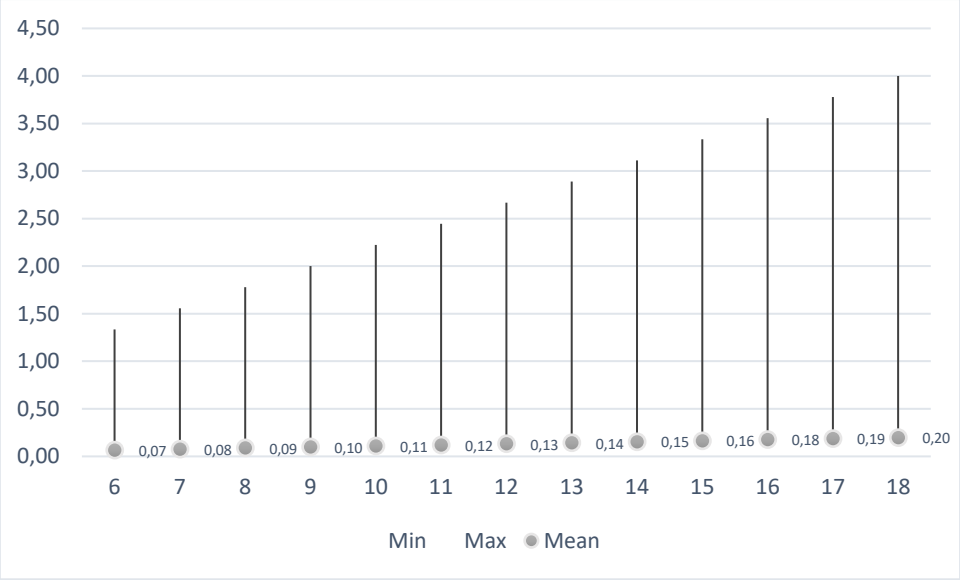
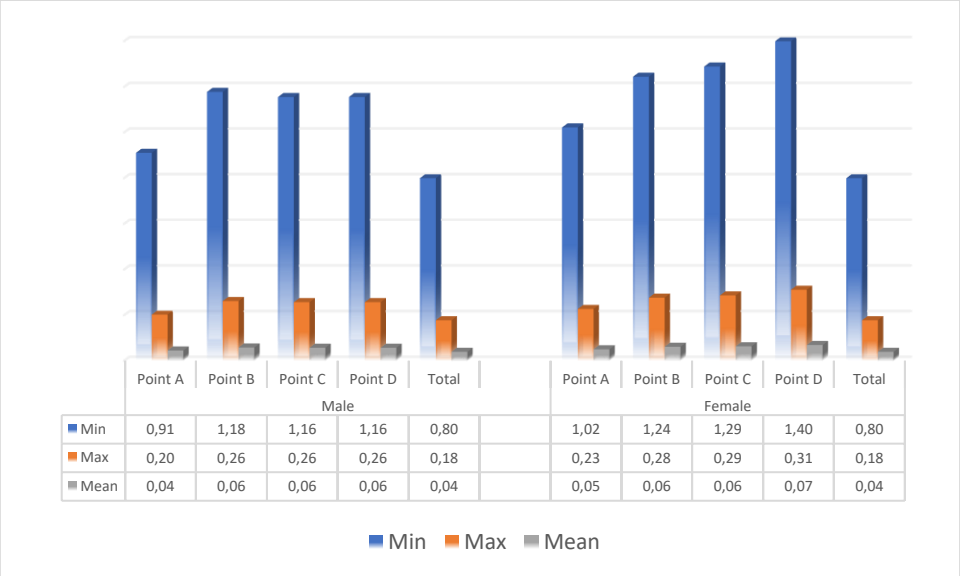


Figure 14: Distribution of min, max and mean values of cortical bone width by age.



	Male					Female				
	Point A	Point B	Point C	Point D	Total	Point A	Point B	Point C	Point D	Total
Min	0,91	1,18	1,16	1,16	0,80	1,02	1,24	1,29	1,40	0,80
Max	0,20	0,26	0,26	0,26	0,18	0,23	0,28	0,29	0,31	0,18
Mean	0,04	0,06	0,06	0,06	0,04	0,05	0,06	0,06	0,07	0,04

Figure 15: Distribution of cortical width (mean, minimum and maximum values) by gender.

Table 19 and Figure 15 summarizes the results of comparing mean cortical bone thickness, by age group and stratified by gender. A statistically significant difference was found in total cortical bone thickness (p-value< 0.05) in both boys and girls. Specifically, for boys, multiple comparisons corrected Bonferroni p-values revealed a statistically significant lower mean value in ages 8-9 years compared to age 18 years (mean difference: -1,653, p-value= 0.026). Regarding girls, a statistically significant lower mean value of total bone thickness was found in ages 6-7 years compared to ages 16-17 years (mean difference: -0,1116, p-value= 0.040) and in ages 8-9 years compared to ages 16-17 years (mean difference: -0,2374, p-value= 0.016).

Table 19. Results of correlation between age groups and cortical bone thickness, stratified by gender.

Boys					
			95% Confidence Interval for Mean		
Age (yrs)	N	Mean (mm)	Lower Bound	Upper Bound	
6-7	36	3,3822	2,8189	3,9453	
8-9	72	3,2564	2,8744	3,6384	
10-11	54	3,3682	2,8747	3,8618	
12-13	54	3,5338	3,0429	4,0244	0.034*
14-15	49	3,9662	3,3256	4,6069	
16-17	44	3,4938	2,9418	4,0458	
18	17	4,9089	3,5200	6,2978	
Total	326	3,5596	3,3524	3,7669	
Girls					
			95% Confidence Interval for Mean		
Age (yrs)	N	Mean (mm)	Lower Bound	Upper Bound	
6-7	31	2,9696	2,4044	3,5344	
8-9	72	3,1142	2,7262	3,5022	
10-11	77	3,4413	3,0193	3,8636	
12-13	60	3,5393	2,9664	4,1124	0.005*
14-15	41	4,2629	3,4302	5,0958	
16-17	34	4,5876	3,5924	5,5824	
18	19	3,7507	2,9102	4,5911	
Total	334	3,5798	3,3511	3,8084	

[1]One-way analysis of variance (ANOVA)
SD: Standard Deviation
*statistically significant result (α=5%)

Table 20 shows the correlation between age (years) and bone thickness, stratified by gender. A statistically significant positive relationship was found between all total bone thickness and age (years) in both boys and girls, meaning that as age increases, bone thickness also increases (p-value< 0.05). The relationship found was stronger for girls compared to boys (r= 0.216 vs r= 0.155, respectively).

Table 20. Correlation between age (years) and bone thickness, stratified by gender.

Total bone thickness	**Pearson correlation coefficient r**	**p-value**
Boys	0.155	0.005*
Girls	0.216	<0.001*

*statistically significant result (α=5%)

D) Characteristics of samples' dentition

Table 21 presents the association of samples' characteristics and total cortical bone thickness value. The differences were not statistically significant (p-value> 0.05), except for the dentition (p-value< 0.001): it was observed that the mean value of cortical bone thickness was significantly higher in permanent dentition compared to both early and late mixed dentition (p-value<0.001 and p-value= 0.049< 0.05, respectively).

Table 21. Results of correlation between samples' characteristics and total critical bone thickness.

Characteristics	Total Cortical bone thickness Mean	p-value[1]
Caries		
0	3,6311	
1	3,0969	0.083
2	2,6996	
3+	3,0482	
Composites		
0	3,5458	
1	3,3291	
2	3,8376	0.791
3	3,7524	
4+	3,7178	
SCC		
0	3,5878	
1	2,7611	
2	3,7000	0.398
3	3,2364	
Missing teeth		
0	3,5944	
1	3,2060	
2	3,6282	0.575
3	3,0624	
4	1,9198	
Dentition		
Early mixed	3,2142	
Late Mixed	3,4024	<0.001*
Permanent	3,8778	
Bonferroni		
Early-late mixed		0.999
Early mixed-permanent		<0.001*
Late mixed-permanent		0.049*

[1]One-way analysis of variance (ANOVA)
[2]Bonferroni p-value for multiple comparisons

Table 22 summarizes the correlation between the bone morphology according the MCI Index and samples' characteristics. We apply the statistical tests using the bone morphology according to the Index in total. Moreover, in order to have sufficient frequency in all categories to be able to perform the statistical test, we evaluated only C1 and C2, since only one patient was characterized with C3. Samples' characteristics and stage of the dentition were not statistically significant associated with bone morphology according the MCI Index in total (p-value> 0.05).

Table 22. Results of correlation between bone morphology and samples' characteristics.

	Bone morphology n(%)			
Characteristics	C1	C2	Total	**p-value**
Caries				
0	476 (80.5)	115 (19.5)	591	
1	18 (100.0)	0 (0,0)	18	0.074[1]
2	13 (81.3)	3 (18.8)	16	
3+	23 (71.9)	9 (28.1)	32	
Composites				
0	427 (82.0)	94 (18.0)	521	
1	32 (78.0)	9 (22.0)	41	
2	29 (74.4)	10 (25.6)	39	0.252[2]
3	18 (85.7)	3 (14.3)	21	
4+	24 (68.6)	11 (31.4)	35	
SCC				
0	503 (80.5)	122 (19.5)	625	
1	15 (88.2)	2 (11.8)	17	0.915[1]
2	8 (80.0)	2 (20.0)	10	
3	4 (80.0)	1 (20.0)	5	
Missing teeth				
0	477 (80.7)	114 (19.3)	591	
1	33 (89.2)	4 (10.8)	37	
2	15 (65.2)	8 (34.8)	23	0.194[1]
3	3 (75.0)	1 (25.0)	4	
4	2 (100.0)	0 (0.0)	2	
Dentition				
Early mixed	166 (83.4)	33 (16.6)	199	
Late Mixed	130 (84.4)	24 (15.6)	154	0.082[2]
Permanent	234 (77.0)	70 (23.0)	304	

[1]Fisher's exact test
[2]Chi square test
*statistically significant result (α=5%)

Table 23 a,b: The ultimate goal of the study was to create reference tables of the morphology and thickness of the cortical bone in a healthy Greek population of children and adolescents, separately for boys and girls in each age group. Table a shows the morphology of cortical bone according to MCI Index and Table b shows the thickness of the cortical bone in mm.

a)

Bone Quality	**C1**		**C2**		**C3**	
Gender / **Age**	Boys	Girls	Boys	Girls	Boys	Girls
6 years	76%	71%	24%	29%	0%	0%
7 years	65%	75%	35%	25%	0%	0%
8 years	59%	69%	41%	31%	0%	0%
9 years	84%	75%	16%	25%	0%	0%
10 years	82%	90%	18%	10%	0%	0%
11 years	88%	94%	8%	6%	4%	0%
12 years	91%	91%	9%	9%	0%	0%
13 years	86%	85%	14%	15%	0%	0%
14 years	88%	84%	12%	16%	0%	0%
15 years	77%	50%	23%	50%	0%	0%
16 years	76%	88%	24%	12%	0%	0%
17 years	65%	89%	35%	11%	0%	0%
18 years	94%	77%	6%	24%	0%	0%

b)

Bone Quantity	**Point A**		**Point B**		**Point C**		**Point D**		**Total**	
Gender / **Age**	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
6 years	2,02	2,16	3,49	4,04	3,62	4,13	3,84	4,40	3,24	3,68
7 years	3,51	2,38	4,20	3,20	4,29	3,18	4,84	3,49	4,21	3,06
8 years	3,22	2,84	4,16	2,84	4,51	3,93	4,78	4,42	4,17	3,51
9 years	3,16	2,82	3,84	3,51	4,13	3,58	4,60	4,24	3,93	3,54
10 years	2,93	2,76	3,96	3,51	4,09	3,53	4,44	3,87	3,86	3,42
11 years	3,04	2,84	3,58	3,53	3,58	3,44	3,82	3,64	3,51	3,36
12 years	3,20	2,60	3,91	3,33	3,87	3,36	4,13	3,58	3,78	3,22
13 years	2,82	2,42	3,44	3,20	3,62	3,00	4,02	3,16	3,48	2,95
14 years	2,78	2,20	3,40	2,80	3,53	2,73	3,51	2,96	3,31	2,67
15 years	2,36	3,58	2,91	4,51	2,84	4,58	2,78	4,71	2,72	4,35
16 years	3,18	2,56	4,11	3,47	4,16	3,71	4,27	3,87	3,93	3,41
17 years	2,36	3,20	3,07	4,64	3,16	4,76	3,18	4,82	2,94	4,36
18 years	3,87	3,62	5,31	4,58	5,11	4,62	5,20	4,76	4,87	4,4

3.5. Discussion

Dentists have the ability to identify paediatric patients at risk for bony defects, through panoramic radiographs that are part of their routine dental examination. These radiographs have been previously shown to serve as a screening tool for BMD deficits in adult populations (Klemetti et al. 1994; Taguchi et al., 2011). However, some studies failed to demonstrate a direct association between qualitative changes in the mandibular cortical bone and BMD deficits in children and young adults (Allen, 2016). A possible explanation is that this technique cannot capture subtle nuances in BMD in children's jaw that are in early stages of maturation.

Although various studies have evaluated the relationship between DPRs and BMD in adults and suggested that it is a useful screening tool for identifying low bone density, a similar relationship in the juvenile population has not yet been proven. The aim of the present study was to evaluate the quality and quantity of cortical bone in healthy children and adolescents, using anthropometric indices. To the best of our knowledge, this is the first study that evaluated the cortical bone quality and quantity in such detail and attempted to detect possible correlations with age and gender distribution as well as to investigate the possibility that bone density is affected by the presence of deep caries lesions, missing teeth, extensive resin composites and stainless-steel crowns.

The strength of the study was the large sample since 660 x-rays from children and adolescents with a mean chronological age of 11.7 years were used and the excellent reliability with intra- and inter-examiner reliability of ≥0.8.

Given that more than 1.5 billion X-rays are used annually in the world for dental purposes, it gives the dentist the opportunity to use them not only for the detection of caries etc. but also for the observation and evaluation of the bone of the jaw. According to our examination of the literature, there are currently no methods available for evaluating jaw bone changes in children. Despite the fact that the

Klemetti approach has only been tested on adults, we chose it since it is straightforward and simple to apply.

In our study, mean MCI values presented significant differences between the sexes, with girls showing more often even and sharp endosteal margin of the cortex (C1) than boys. This is in accordance with previous studies in the elderly, possibly related to discrepant aging trajectories mediated by hormonal variations (e.g., growth hormone and estrogen), body size, bone size, and geometry (Parfitt et al. 2000; Seeman 2003). Studies in medically compromised children failed to demonstrate such a correlation (Apolinário AC et al.,2015) (Eimar H et al., 2019). This could be attributed to the fact that our study sample includes children up to 18 years of age in which the effects of hormonal changes and development have already begun to become more apparent.

Significant differences were also recorded between the different age groups. Our study showed a statistically significant increase in bone thickness from the age of 8-9 and over. This is observed in all of the areas that were assessed(A,H-B,G,C-F,D-E, total). This is probably due to the onset of puberty and bone maturation (Zemel B.,2013) (Schoenau E,2006). The onset of puberty, the time in life when a person becomes sexually mature, typically occurs between ages 8 and 13 for girls and ages 9 and 14 for boys.

The results concerning the correlation between age and bone morphology can be interpreted in the same way. The results of our study showed a statistically significant increase in the prevalence of eroded bone in older patients, especially in patients 14 years old and over. The age of 14, which seems to be the threshold above which there is a statistically significant difference, is a little higher than the quantitative assessment, probably because there are many boys in our study in whom puberty starts late and therefore hormonal changes are expressed at an older age.
Furthermore, it is well known that girls reach mandibular peak height velocity (PHV) at the age of 12, whereas boys reach it around the age of 14 (Mellion, Z.J,2013)(Bjork, A,1966). The connection between skeletal development and facial growth in general and mandibular growth, in particular, is a matter of debate. Numerous studies have

shown a strong correlation between the speed of facial growth and, more specifically, the growth of the mandible, and skeletal maturity derived from the hand and wrist (Mellion, Z.J., 2013) (Verma, D., 2009). Delayed or accelerated skeletal maturity is frequently accompanied by a corresponding deceleration or acceleration in facial growth (Tofani, M.I., 1972) (Fishman, L.S., 1979).

However, some have suggested that velocity maxima in the face and stature do not happen at the same time. One theory holds that the face has its largest development spurt a little later than the body's height (Fishman, L.S.,1982). Others, however, were unable to discover any conclusive links between skeletal maturity and mandibular growth during adolescence (Gomes, A.S.,2006).

It is also generally known that sex steroids, such as estrogen, control the tumor-necrosis factor superfamily members RANK (receptor activator of nuclear factor-B), RANKL (receptor activator of nuclear factor-B ligand), and OPG (osteoprotegerin) axis. RANKL (Streicher C et al., 2017) is one of the most significant osteoclast differentiation, activation, and survival-related downstream mediators of estrogen action on bone. The RANK receptor on osteoclast precursor cells is activated by OPG, a soluble decoy receptor that binds RANKL and inhibits osteoclastogenesis (Lacey DL et al.,1998) (Kong YY et al., 1999). The receptor for RANKL, which is found on the cell membrane of osteoblasts and can also be secreted in soluble form, is found on the membrane of osteoclasts and osteoclast precursor cells (Li J et al., 2000). For osteoclast biology, RANK, RANKL, and OPG are crucial, non-redundant factors.

Low levels of estrogen have been shown to affect craniofacial development, osteoporosis, osteoporotic fractures, osteoporosis in the alveolar bone, and abnormalities in the microarchitecture of the femur and mandible in animal models (Hernandez RA et al., 2011) (Fujita T et al., 2006). In a study utilizing a mouse model, Küchler EC et al. (2021) hypothesized that one of the factors influencing the growth and development of the maxilla and mandible is estrogen. Low estrogen levels in women and teenage girls can be caused by a variety of disorders, and how they impact an individual depends on their age and general health. Clinicians should be aware of the potential effects of estrogen shortage on the development of girls' dental arches.

The cervical vertebral maturation (CVM) method has been proven to be a method for determining the various stages of the teenage growth spurt by a number

of research (Baccetti T et al., 2005) (Pasciuti E et al., 2013)(Franchi L et al.,2000) and a systematic review (Cericato GO eta al., 2015). The first and last stages of the accelerative component of the pubertal growth peak are designated by the CVM technique as cervical stages 3 (CS3) and 4 (CS4), respectively. According to longitudinal studies by Gu and McNamara (2007) and Perinetti et al. (2016), the mandibular development increment is greatest between CS3 and CS4. The length of the pubertal growth peak is defined as the age difference between these two stages (Perinetti G, 2016)(Salazar-Lazo R,2014).

Instead of identifying patients with low BMD, MCW exhibits a higher accuracy in excluding the existence of low BMD (specificity). Some research (Muramatsu et al. 2013; Roberts et al. 2013) employed partially or entirely computer-driven methodologies since manual measurement of MCW may induce operator bias. However, in the major OSTEODENT multicenter investigation (Devlin et al. 2007; Karayianni et al. 2007), the technique used (manual vs. semiautomatic computer method) did not significantly affect the accuracy of MCW 3 mm in identifying osteoporosis at either the spine or femur.

Our study also showed statistical differences in terms of the correlation between cortical bone thickness and type of dentition, namely between mixed dentition and permanent dentition. We conclude that in mixed dentition an even and sharp endosteal margin of the cortex (C1) predominates and in permanent dentition decreases and increases the endosteal margin which shows semilunar defects (C2). This is expected because as age increases, changes in occlusion may alter the distribution and magnitude of forces applied to the mandible during chewing and biting. In general, the development of the muscles of the craniofacial complex increases both the chewing capacity and the corresponding forces. Moreover, with age, the balance between bone resorption and formation may be disrupted. Osteoclast activity may outpace osteoblast activity, resulting in a net loss of bone mass and decreased quality of the mandible.

A non-statistically significant difference was shown in the correlation between cortical bone thickness and dental characteristics such as extensive caries,

composites, missing teeth and SSC. The lack of a connection between caries and bone thickness is consistent with earlier research, such as the study by Gunacar DN et al. (2022), which found no connection between trabeculation of the jawbone and dental decay in children aged 8 to 13 years. A study in the pediatric population indicates the connection between extensive proximal caries and alveolar bone loss in the primary dentition but on the grounds that it facilitates plaque retention (Bimstein E.,1992). Regarding missing teeth, our study did not find a correlation, however, similar studies in adults have found a statistically significant correlation. When a tooth is lost, the underlying bone that once supported the tooth is no longer stimulated by the forces of chewing and biting. This lack of stimulation can lead to a process called bone resorption, where the bone gradually diminishes in volume and density. The lack of correlation in children in our study probably has to do with age and the fact that the teeth have been missing for some time. Regarding stainless steel crowns, no correlation was found that is consistent with the existing literature (Guelman M, 1983). Studies have shown alveolar bone loss only in cases where crowns are judged radiographically as non-satisfactory (Aly A. Sharaf et al., 2004) (Bimstein E et al., 1996).

The clinical significance of our study consists of the early detection and adequate treatment of low BMD. It should be essential for the prevention of osteoporosis and fractures in the elderly. Poor bone formation has been linked to a variety of medical disorders and treatments. Children's bone growth may be negatively impacted by primary bone abnormalities including osteogenesis imperfecta, as well as illnesses that cause chronic inflammation, malabsorption, immobilization, hematological disorders, delayed sexual maturity, or gonadal insufficiency. Acute lymphocytic leukemia, Crohn's diseases, cystic fibrosis, cerebral palsy, thalassemia, cerebral palsy, and anorexia nervosa are a few examples of these. The development of new bones is also in danger from medical treatments like glucocorticoids. Paediatric reference data are essential for diagnosing and treating children with chronic illnesses who have poor bone acquisition.

This is also crucial in orthodontic treatment because bone density affects tooth movement. Dental movement is more difficult in individuals with dense bone

structures (Yasa Y et al., 2020). According to research by Von Bremen et al. (2016), a higher BMI was linked to more oral health issues and longer orthodontic treatment times. Those with a thinner mandibular cortex have a higher prevalence of developing dental relapse after receiving orthodontic treatment, according to research by Rothe et al. (2006).

Since dentists are the front-line members of the healthcare team, they provide a way to spot young patients who may have BMD impairments, which would improve patient health. To begin treatment early enough to prevent osteoporosis and other bone-related issues, oral healthcare professionals can become more involved in recognizing changes in BMD. The dentist might play a significant role in the early identification of individuals at risk for bone issues and serve as a source for early patient referral for care if bone alterations observed in panoramic radiographs could be equivalent to changes in QCT scans.

Dentistry students may be taught to examine panoramic radiographs and spot osteoporosis-related alterations (Shintaku WH et al.,2013. As a result, trained dentists could play a crucial role not only in screening for such changes but also in educating parents and cancer survivors about the need of maintaining a bone-healthy lifestyle by increasing weight-bearing exercise and getting enough calcium and vitamin D. Direct methods of preventing and treating BMD can also be achieved by properly referring individuals to address endocrinopathies. (Nathan PC et al.,2009).

Limitations of the study

Apart from the limitations in the design of retrospective studies, limitations common to linear measurements made on panoramic radiographs are mostly due to geometric distortion and unequal magnification. However, the same machine was used and this effect was minimal.

The fact that the sample is derived from the database of a specific institution limits the applicability of the results to the specific population because the present sample was recruited from an urban population. Finally, reporting bias was introduced by the subjective evaluation of the orthopantomograms by the researcher. However, this

was limited and was less influential since intra-examiner reliability was assessed before initiation.

Future Considerations

Prospective studies are necessary to verify whether DPRs may be considered as an auxiliary tool for other conditions related to low BMD, and also for previewing treatment outcomes in such populations. In addition, similar studies in healthy populations of other ethnicities should be conducted since it has been shown that ethnicity affects the bone due to differences in climate, nutrition, physical activities etc.

Furthermore, in adult studies, it has been suggested to combine the radiomorphometric indices with clinical indices (i.e.weight, height) to improve their accuracy because none of them has perfect sensitivity and specificity for identifying osteopenia or osteoporosis. This has not been studied in children yet. In the multicenter OSTEODENT research, MCW was paired with the osteoporosis index of risk (OSIRIS) clinical test (Sedrine et al. 2002), which considers age, weight, usage of hormone replacement medication, and history of fracture. The outcome was an improvement in the total area under the ROC curve, and in particular, the combination of OSIRIS with a panoramic index boosted the specificity, resulting in a decrease in the number of healthy patients who were referred for DXA (Horner et al. 2007) (Karayianni et al. 2007).

3.6. Conclusions

Within the limitations of this study, it can be concluded that:

- A statistically significant difference was found between gender and bone morphology according to MCI Index. The endosteal margin of the cortex is even and sharp more frequent in girls compared to boys and shows seminular defects more frequent in boys than girls.
- The developmental stage of dentition was statistically significant correlated with the cortical bone thickness, i.e. cortical bone thickness was significantly higher in permanent dentition compared to early or late mixed dentition.
- There is no correlation between cortical bone thickness or bone morphology and factors such as the existence of extensive caries, composites, stainless steel crowns and missing teeth.
- More broad and well-designed studies are required to support the correlations between age/gender and bone morphology or thickness.
- The results of this study can be an important guide for the clinical dentist, who may check the cortical bone thickness in panoramic radiograph and refer the patient for further examination.

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