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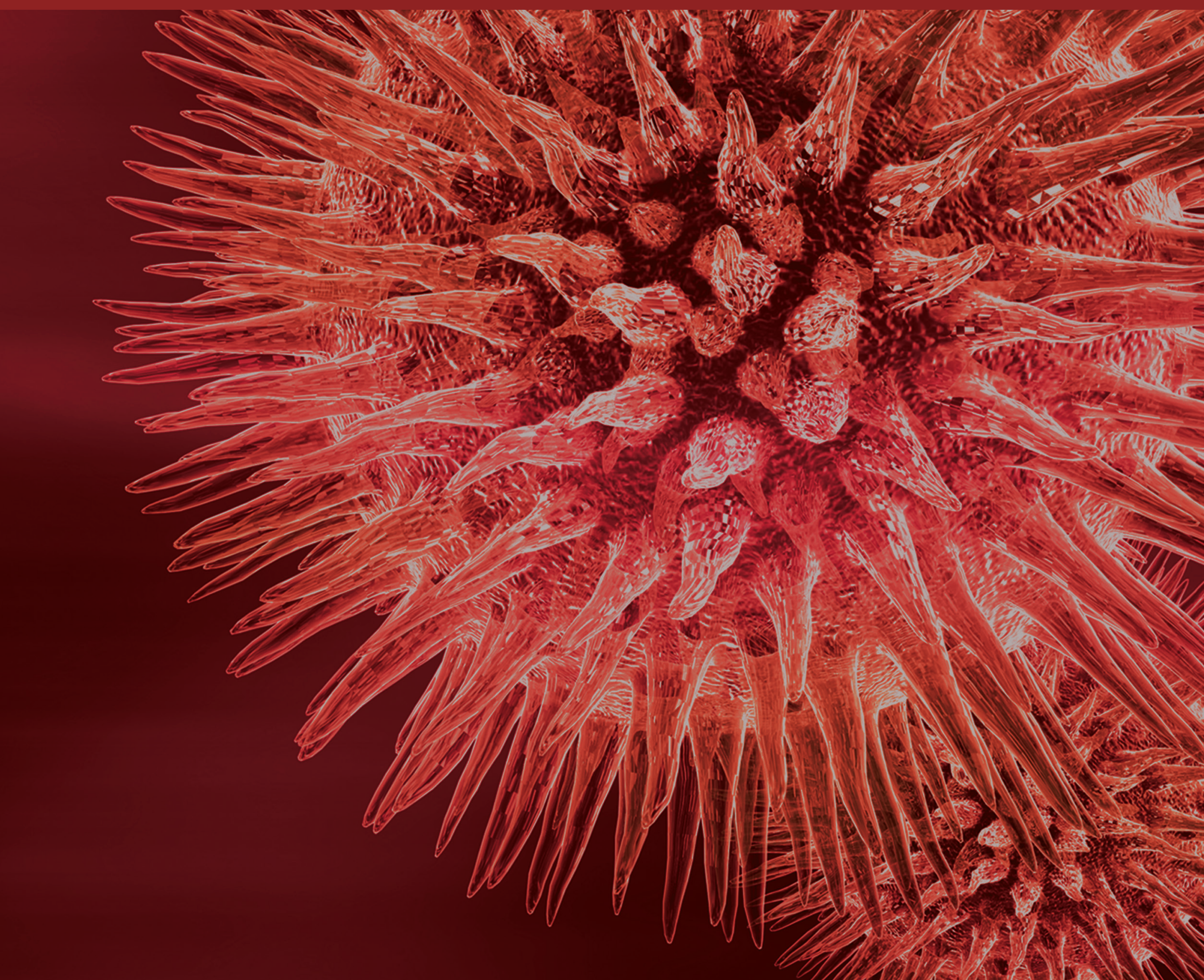
Guest Editors: Simona Tecco, Alberto Baldini, Enita Nakaš, and Jasmina Primozic



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Editorial

Interceptive Orthodontics and Temporomandibular Joint Adaptations: Such Evidences?

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The research of the anatomy of the temporomandibular joint (TMJ) and its development during the growing period is far beyond the classical approach. TMJ area has been thought to be a reactive growth site, which makes it more interesting for research. During the period of mixed dentition, TMJ area is affected by a considerable amount of growth and adaptation, which can alter the jaws relationships. Also, a variable adaptation can occur during an interceptive functional orthodontic treatment. Nowadays, TMJ studies comprise various fields of medicine, starting from clinical investigations, up to the in vitro models, which are useful in studies of the anatomy and disorders of the two jaws. This is the reason why we have gathered researches that are closely related to TMJ. The *leitmotif* of the special issue is the anatomy of the jaws and their adaptions during the growth and development of individuals and the interceptive orthodontic treatments.

G. Perinetti and L. Contardo, on the basis of a literature review, explain the current evidence and controversies on the efficiency of interceptive orthodontics and conclude that more favorable response is seen when subjects are treated during their pubertal growth spurt, mostly in skeletal Class II patients (even though high individual responsiveness remains). They also clarify that no growth indicator may be considered to have a full diagnostic reliability to assess the pubertal growth spurt of a patient. Nevertheless, their use may still be recommended for increasing efficiency of interceptive orthodontics, in particular for skeletal Class II malocclusion.

Another paper by G. Perinetti et al. is more specifically dealing with a growth indicator of the timing of circumpubertal skeletal maturation (circumpubertal cervical vertebral maturation, CVM) to assess its relationship with the sagittal and vertical mandibular development. This is a cross-sectional study aimed at evaluating whether sagittal and vertical craniofacial growth has an association with the timing of circumpubertal skeletal maturation. A total of 320 subjects (160 females and 160 males) are included in the study (mean age, 12.3 ± 1.7 years; range, 7.6–16.7 years). These subjects were equally distributed in the circumpubertal cervical vertebral maturation (CVM) stages 2 to 5. Significant associations were seen only for Stage 3, where the mandibular to cranial base angle (i.e., the mandibular divergence with cranial base) results negatively when associated with age (β coefficient, −0.7), suggesting that the mandibular divergence (linked to TMJ development) may have an anticipated and delayed attainment of the pubertal CVM Stage 3. The clinical conclusion is that this association remains of a small entity, and it becomes clinically relevant only in extreme cases.

M. C. Sobral de Aguiar et al. present a review of studies performed to evaluate whether the gingival crevicular fluid (GCF) biomarkers in growing subjects reflect both the stages of individual skeletal maturation and the local tissue remodeling triggered by orthodontic force. However the conclusion is that, in spite of several investigations, the clinical applicability of the GCF method is still limited to further data needed to reach a full diagnostic utility of specific GCF biomarkers in interceptive orthodontics.

T. Lauc et al. investigated whether skeletal pattern of the growth can influence dental development and found that males with Class III skeletal pattern have faster dental development. Research results suggest that diversity of the skeletal pattern could be connected with the different timing of dental development.

J. Badrov et al. have found that changes in the development of permanent teeth during growth can occur in children with the congenitally missing permanent teeth (CMPT). They also reported that the dental age is significantly delayed in CMPT children compared to the nonaffected group; the mean differences are -0.57 ± 1.20 years and -0.61 ± 1.23 years in males and females, without difference between sexes.

A. H. Al-Ani et al. also declared that the tooth agenesis, especially in its severe forms, is often associated with various anomalies in other teeth, such as delays in development, ectopic eruption, reduction in tooth dimensions and morphology, shortened roots, taurodontism, and enamel hypoplasia. Also, the authors explained that the hypodontia patients tend to show with lower mandibular plane angles, associated with a smaller lower anterior face height and lip protrusion. Other features associated with hypodontia include shorter maxillary and mandibular lengths and a Class III skeletal relationship tendency.

In reference to interceptive functional orthodontic treatment, the following two papers are dealing with the efficacy of functional appliances in growing subjects.

A study of the comparison between the Activator-Headgear (AH) and the Twin Block (TB) treatments approaches in Class II division 1 malocclusion has been conducted by S. Spalj et al. Their results suggest that both AH and TB appliances contribute successfully to the correction of Class II division 1 malocclusion when compared to the untreated subjects with primarily dentoalveolar changes. The authors explained that the correction of malocclusion is made by retroclination of maxillary incisors and proclination of mandibular incisors, the latter being significantly more evident in the TB group, and with the increase of effective mandibular length that was also more evident in the TB group.

Another clinical study to appraise the factors affecting the wearing time and patient's behavior during a functional treatment with a newly designed reverse pull headgear is presented by N. Ozkalayci and O. Cicek. They found that patients wore the new reverse pull headgears mostly during the night, due to problems related to aesthetic appearance, and during the weekends.

Two interesting papers are dealing with the study of the morphology of TMJ on 3D-imaging.

Cone-Beam Computerized Tomography (CBCT) represents widely used diagnostic image system, and it is based on 3D visualization. The study by S. Caruso et al. analyzed the recent literature about TMJ visualization on CBCT imaging. Sources included PubMed from June 2008 to June 2016. Eleven articles were finally included in the qualitative synthesis. The main topics treated in the studies are the volume and surface of the mandibular condyle, the bone changes on the cortical surface, the morphological asymmetry between the two condyles, and the optimum position of the condyle in the glenoid fossa. In particular, the conclusion of this review is that CBCT 3D imaging allows the calculation of volume and surface of the mandibular condyle, the calculation of its linear dimensions (height and length), and the measurement of the intra-articular space to clarify the position of the condyle in the glenoid fossa.

S. Mummolo et al. presented data about the 3D Tele Motion Tracking (3D-TMT), as a useful tool for facial analysis. A group of 40 patients (20 males and 20 females; mean age, 12–18 years) was included in the study. The measurements obtained by the 3D-TMT and by a traditional 2D radiological analysis were compared for each subject. The 3D-TMT system values resulted slightly higher, statistically significant, than the values obtained on radiographs; nevertheless, their correlation resulted very high, and the Dahlberg errors resulted in being always lower than the mean difference between the 2D and 3D measurements. The authors suggest that a clinician should always use, during the clinical monitoring of a patient, the same method (2D or 3D), to avoid comparing different millimeter magnitudes in the dimensions of a face.

Overall, studies show that the maxillary and mandibular area are affected by significant morphological changes during the period of the circumpubertal spurt and, therefore, can undergo a significant remodeling during that time, also in response to orthodontic interceptive devices. Although there are several methods in the literature useful to predict the coming of the circumpubertal spurt, none of them is infallible, and future studies are needed to clarify this point. Also, the dental age is influenced by several variables, such as the agenesis of the permanent elements. The clinical monitoring of facial changes during the interceptive therapy seems possible using 3D imaging techniques, such as CBCT images, and also through noninvasive methods for the study of facial structures (as, e.g., the 3D Tele Motion Tracking).

All presented papers share the same interest related to the anatomy of stomatognathic system during the growth development.

All of the above presented papers along with the latest technologies have contributed to advancing knowledge of anatomical structures and their changes during growth and interceptive orthodontics treatment. Their role in the pathogenesis of diseases and disorders of different origin is going to be, even partially, clarified.

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Review Article

Hypodontia: An Update on Its Etiology, Classification, and Clinical Management

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Hypodontia, or tooth agenesis, is the most prevalent craniofacial malformation in humans. It may occur as part of a recognised genetic syndrome or as a nonsyndromic isolated trait. Excluding third molars, the reported prevalence of hypodontia ranges from 1.6 to 6.9%, depending on the population studied. Most affected individuals lack only one or two teeth, with permanent second premolars and upper lateral incisors the most likely to be missing. Both environmental and genetic factors are involved in the aetiology of hypodontia, with the latter playing a more significant role. Hypodontia individuals often present a significant clinical challenge for orthodontists because, in a number of cases, the treatment time is prolonged and the treatment outcome may be compromised. Hence, the identification of genetic and environmental factors may be particularly useful in the early prediction of this condition and the development of prevention strategies and novel treatments in the future.

1. Definitions and Classifications

Hypodontia is the most prevalent dentofacial malformation in humans [1]. It may occur as part of a recognised genetic syndrome or as a nonsyndromic isolated trait [2]. The condition refers to the developmental failure of six or fewer teeth [3]. Its phenotypic presentation is varied in terms of severity and, as a result, various terms have been used to describe it. These terms include "congenitally missing teeth," "tooth agenesis," "hypodontia," "oligodontia," and "anodontia." The term "congenitally missing teeth" is challenging because tooth development is completed after birth, so that the presence of most tooth germs can be proved only during childhood [4–6]. Tooth agenesis, on the other hand, refers directly to the developmental failure of a tooth. Other terms, such as hypodontia, are more suitable for classifying the type of tooth agenesis present and may be more appropriate in this context [7]. Oligodontia and anodontia are used to describe more severe forms of tooth agenesis, typically the absence of more than six teeth and the entire dentition [3], respectively. Tooth agenesis and hypodontia are the preferred terms in this work, with the latter term limited to missing teeth other than third molars.

2. Prevalence

2.1. Deciduous Dentition. Tooth agenesis is considered rare in the deciduous dentition and is not as common as in the permanent dentition. An association exists between hypodontia in the primary and permanent dentitions, with reports of children with primary teeth hypodontia showing absence of the corresponding successor teeth [8, 9]. A prevalence of less than 1% has been described in Caucasian populations [4], although it has been reported to be much higher in Japanese populations [10]. The prevalence of tooth agenesis in New Zealand appears to be consistent with that seen in Europe [11]. The deciduous maxillary lateral and mandibular central incisors account for 50% to 90% of affected deciduous teeth [4]. Most cases present as unilateral hypodontia, with mostly one or two teeth missing [8]. No significant sex difference in prevalence has been reported from any of the populations studied [8].

2.2. Permanent Dentition. The prevalence of hypodontia, which may be increasing with time, ranges from 1.6% to 36.5%, depending on the population studied [1]. At least 1 in 5 individuals lacks a third molar, while most individuals with hypodontia (80%) lack only one or two teeth [13, 14]. A meta-analysis investigated the prevalence of nonsyndromic tooth agenesis, included 33 studies from North America, Australia, and Europe, and found a higher prevalence in Europe (5.5%) and Australia (6.3%) than in North America [15]. Most individuals were missing only one or two permanent teeth, with very few missing more than six. Mandibular second premolars and the maxillary lateral incisors were reported to be the most likely to be missing [15, 16]. Notably, the prevalence of tooth agenesis in the last few decades has reportedly increased [17]. However, there is no empirical evidence to support whether this apparent increase is due to more advanced screening and diagnosis or other factors.

Hypodontia is typically associated with a number of classical features, including the site of agenesis and the size of the adjacent teeth. Tooth agenesis does not seem to affect the maxilla and the mandible differently [15], although there was one early study that found the mandible to be more frequently affected than the maxilla [18]. Comparing bilateral and unilateral agenesis, Polder et al. (2004) found that bilateral agenesis of maxillary lateral incisors occurred more often than unilateral agenesis. For the other teeth, such as the second mandibular premolar, unilateral agenesis was more common [15]. There appears to be no significant sex difference in missing primary teeth [19], although, in the permanent dentition, there seems to be a small albeit nonsignificant predilection of hypodontia in females [20]. One meta-analysis, however, found a significant difference in females, with the prevalence of hypodontia being 1.4 times higher in them than in males [15].

3. Features Associated with Hypodontia

Tooth agenesis is often nonsyndromic, but it can also be associated with oral clefts and several other syndromes [8]. For example, hypodontia is a common trait in cleft-lip and/or palate (CLP) patients [21]. The prevalence of hypodontia is higher in more severe clefting cases, most likely presenting with the agenesis of a maxillary lateral incisor (in either dentition) [4, 8]. In these patients, hypodontia in regions outside the cleft field is also more common than in the general population [22]. Other conditions that have hypodontia as one of their features include Down's Syndrome and ectodermal dysplasia. In these syndromes, there is a characteristic pattern of agenesis that is usually different from the overall population [4]. Moreover, recent data suggests that hypodontia shares some common pathways with particular kinds of cancer [23]

It is not known whether individuals with hypodontia have characteristic skeletal features and growth patterns, although some evidence suggests that hypodontia patients have significantly different craniofacial features from those with no missing teeth [24]. What is known is that tooth agenesis, especially in its severe forms, contributes to abnormal occlusion and is often associated with various anomalies in other teeth [4]. These include delays in development, ectopic eruption, reduction in tooth dimensions and morphology, shortened roots, taurodontia, and enamel hypoplasia [8].

3.1. Dental Features. Microdontia is a widely reported feature of hypodontia in case reports and case series [19]. This condition, which can affect one or more teeth, may be seen in either dentition [24, 25]. In addition, microdontia is genetic and presents in its severest form as ectodermal dysplasia [24]. It is also present in patients who have had chemotherapy or radiation of the jaws earlier in childhood [26]. Brook proposed that microdontia and hypodontia are linked genetically as a continuum of tooth size, where a tooth will fail to develop if the tooth germ does not reach a particular tooth size and tooth number "thresholds" [27].

Delays in tooth development are another common feature, whereby the absence of a permanent successor delays the normal resorption of the roots of the primary teeth. Indeed, the deciduous teeth may be retained for up to 40 or 50 years [28]. Meanwhile, approximately 46% of individuals with tooth agenesis also have short roots of other permanent teeth [8]. In addition, an association between taurodontism and hypodontia was found in a Dutch study, where taurodontism of the lower first molars was present in 29% of oligodontia patients but only 10% of controls [29].

Another common feature of hypodontia is the ectopic positioning of the permanent teeth. This is likely caused by the absence of neighbouring teeth available to guide them during eruption or by the lack of space for them to erupt into. Transposition of teeth is also seen more commonly in individuals with hypodontia [30]. Tooth agenesis is also associated with enamel hypoplasia, diminutive or peg maxillary lateral incisors, primary molar infraocclusion, and palatally inclined or impacted maxillary canines [31, 32]. Intraorally, retroclined and overerupted lower incisors contribute to a greater overbite [33]. Generalised spacing and rotations of teeth adjacent to missing mandibular second premolars are also commonly seen [31]. Some of these features are evident in Figure 1.

3.2. Skeletal Features. Hypodontia patients tend to present with lower mandibular plane angles, associated with a smaller lower anterior face height and lip protrusion [34]. Other features include smaller maxillary and mandibular lengths and a Class III skeletal relationship tendency [35]. The short face height, along with the large freeway space, which is typical of hypodontia patients, may make them appear overclosed [24]. It was initially reported that children with hypodontia present with a shorter and more retrusive upper arch with proclined upper incisors [18]. However, the children were reexamined in another study and the authors reported that there were no changes in the craniofacial structures from 9 to 16 years of age to children without hypodontia [36].

In general, dentofacial changes are prominent in individuals with oligodontia, and these are related more to dental

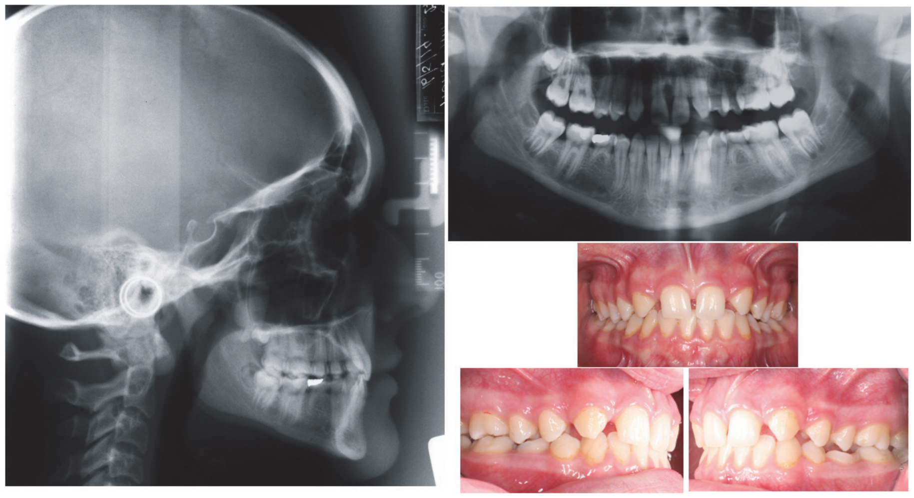

Figure 1: A female patient presenting with several common features of hypodontia. Note the agenesis of the maxillary lateral incisors and the second premolars, the retained primary mandibular molars, the generalised spacing, and the deep bite.

and functional compensation and not to a specific underlying pattern of growth [24, 35].

4. Aetiology

Numerous concepts about the aetiology of hypodontia have been proposed in the literature. The multiplicity of tooth agenesis theories suggests a multifactorial aetiology that involves genetic regulation and environmental factors. As such, the multifactorial nature of tooth agenesis entails a brief overview of tooth development and its genetic regulation. This will be followed by an outline of the theories surrounding hypodontia and a more detailed discussion of the specific factors, both genetic and environmental, that have been connected with this condition.

4.1. Tooth Development. Dental development is a complex process which involves mutual interactions between the oral epithelium and ectomesenchyme derived from the neural crest. During the initiation stage, thickening of the epithelium occurs, as it invaginates into the mesenchyme, creating a tooth bud [37]. Within the tooth bud, there is a collection of cells, the primary enamel knot, and these cells manage this process via signalling proteins. The mesenchyme surrounds the epithelium producing a cap stage, followed by a bell stage. Neighbouring mesenchymal cells differentiate into odontoblasts, and these secrete an organic dentine matrix [24]. Into this matrix, hydroxyapatite crystals are deposited [24]. At this stage, epithelial cells near to the dentine differentiate into ameloblasts, and these secrete an enamel matrix while controlling enamel mineralisation and maturation [37]. Secondary enamel knots control cusp formation in premolars and molars [38].

The region of the crown then undergoes histodifferentiation which is continued in the root. In terms of root development, apical extension of the odontogenic epithelium forms Hertwig's root sheath, which controls radicular dentine formation. This subsequently degenerates leading to cementoblast development. Following this, the cementoblasts produce cementum on the root [39]. Meanwhile, osteoblasts and fibroblasts, which aid in periodontal ligament formation, are produced from the differentiation of cells present in the dental follicle [40].

A series of genetically controlled successive molecular interactions are involved in the development of teeth [41, 42]. Numerous factors, such as those from the fibroblast growth factor (Fgf), wingless related integration site (Wnt), bone morphogenic protein (Bmp), and hedgehog (Hh) families, take part in the signalling of epithelial-mesenchymal interactions in tooth development [40]. Alterations in one or more of the signalling pathways may affect dental development and may play a role in causing a condition such as hypodontia.

4.2. Tooth Agenesis Theories. Several theories exist to decipher the cause of hypodontia, and most have focused on either genetic or environmental factors, although the importance of both components in the agenesis of teeth is now well recognised. These theories can be considered as either *evolutional* or *anatomical* [42].

Earlier studies concentrated on the evolutional viewpoint, which attributed tooth agenesis to shortening of the intermaxillary complex and the reduction in tooth number due to shorter arches. For instance, in 1945, Dahlberg used Butler's Field Theory that focused on evolution and development of mammalian teeth into the human dentition in order to explain different patterns of agenesis. Four morphological fields (incisors, canines, premolars, and molars) were described in each jaw. The more mesial tooth in each field was proposed to be the more genetically stable and as a result was seldom absent [24], while the teeth at the end of each field were less genetically stable. A later theory hypothesised that the last of each "class" were "vestigial bodies" that became obsolete during the evolution process [43]. Most currently, there is a theory that evolutionary

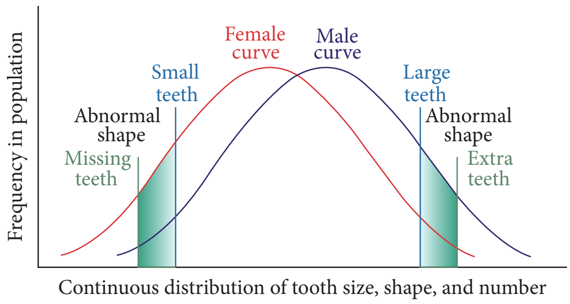

Figure 2: Model showing continuous distribution of tooth size, shape, and number adapted from [12].

change is working to reduce the human dentition by the loss of an incisor, premolar, and molar in each quadrant. According to Vastardis (2000), as humans evolve, the size of the jaws and the numbers of teeth appear to be decreasing [13].

Other theories focused on an anatomical principle, based on the hypothesis that specific areas of the dental lamina are prone to environmental effects throughout tooth maturation [42]. In support of this hypothesis, Svinhufvud et al. (1988) related the agenesis of the maxillary lateral incisors, the mandibular second premolars, and central incisors to the fact that they develop in areas of initial fusion of the jaw [44]. For example, maxillary lateral incisors develop in the region where the lateral maxillae and medial nasal bone processes fuse, while the mandibular second premolars originate in another delicate region [44]. Instead, Kjaer et al. (1994) argued that the region where development of innervation is last is the most sensitive one [45].

The proposed effects of both polygenetic and environmental factors on hypodontia represented a paradigm shift in thinking with respect to the aetiology of tooth agenesis. Grahnén was first to count hypodontia as a hereditary anomaly and deemed that the transmission is determined by a dominant autosome, with incomplete penetrance and variable expressivity [46]. Later, Brook's theory claimed a significant association between tooth agenesis and microdontia, with sex differences in tooth size and number [27]. According to Brook, each anomaly occurred more frequently in first-degree relatives than in the population sample, and this suggested that the more severe the hypodontia was, the more likely the relatives were to also have hypodontia. Additionally, females were more likely to have hypodontia and microdontia, whereas males were more likely to have megadontia and supernumerary teeth and the model was later revised to clarify that both tooth size and shape are involved [12]. Figure 2 shows the aetiological model incorporating all of the multifactorial influences proposed.

Nowadays, most tooth agenesis theories recognise the complex nature of the genetic and environmental interactions involved in hypodontia. In fact, identification and gene sequencing in tooth morphogenesis are now possible due to genetic research advances, while understanding of the molecular mechanisms leading to tooth agenesis has also increased [5]. The following discussion will therefore focus on the specific genetic and environmental factors that have so far been linked to hypodontia.

4.3. Genetic Factors. Most craniofacial traits result from a complex interactions between genetic and environmental factors. Heritability can be expressed as a ratio that estimates the extent to which genetic characteristics affect the variation of a trait in a specific population at a point in time, and it is often investigated in twin studies [47]. It can range from 1 (complete genetic control) to zero (complete environmental control [47]) but can exceed theoretical thresholds if dominant gene effects and acquired environmental effects are included [48]. Many studies have demonstrated a strong genetic influence in hypodontia. Twin and family studies have determined that agenesis of lateral incisors and premolars is inherited via an autosomal dominant gene, with incomplete penetrance and variable expressivity [7, 8, 13, 32, 49–52]. There is no consensus, however, on whether hypodontia is a result of a polygenetic or single gene defect [53], although the former appears to be largely supported in the literature [13, 27].

Since tooth development is under some degree of genetic control, it follows that hypodontia is also under genetic influence. For this reason, recent efforts have focused on identifying the specific genes that are involved in regulating tooth development. Past research has mainly relied on family studies to identify these genetic variants. Studies of mutant mice and cultured tissue explants have examined the expression of numerous genes involved in tooth development and provided insight into inductive signalling and hierarchies of downstream transcription factors necessary for tooth development [54]. Over 300 genes are expressed and involved in tooth morphogenesis, including *MSX1, PAX9, AXIN2, EDA, SPRY2, TGFA, SPRY4, WNT10A, FGF3, FGF10, FGFR2,* and *BMP4* [23, 55, 56]. Among these genes, *PAX9* (paired box gene 9), *MSX1* (muscle segment homeobox 1), *AXIN2* (axis inhibition protein 2), and *EDA* (ectodysplasin A) are the most frequently reported genes associated with nonsyndromic hypodontia [6, 57–60]. These all have roles in both signalling pathways and in mediating the signal transduction cascades [56].

PAX9 is a transcription factor expressed in the tooth mesenchyme during tooth morphogenesis [60], with mutations in this gene being implicated in arresting tooth development at the bud stage. Heterozygous mutations in *PAX9*, in humans, have been associated with nonsyndromic tooth agenesis [2]. Most recently, a case-control study of 306 unrelated Portuguese individuals found that single nucleotide polymorphisms in the *PAX9* gene were associated with a high risk of maxillary lateral incisor agenesis [56].

MSX1 is a member of the homeobox genes and it is expressed in regions of condensing ectomesenchyme in the tooth germ [61]. *MSX1* gene mutations have been associated with premature termination of tooth development in animals [2, 21] and severe forms of hypodontia in humans. Recently, however, a frameshift mutation in *MSX1* has been identified in a family missing all second premolars and mandibular central incisors [62].

The *AXIN2* gene is involved in cell growth, proliferation, and differentiation. It is a negative regulator of the *Wnt* signalling pathway, and this has been associated with lower incisor agenesis [23, 63]. In fact, these genes are involved in several forms of hypodontia, including syndromes in which this condition is a common feature [4].

More recently, *EDA* was found to be involved in isolated hypodontia. Mutations in this gene cause X-linked hypohidrotic ectodermal dysplasia (*HED*), which is characterised by sparse hair, fewer and smaller teeth, and a lack of sweat glands [42]. The *EDA* gene encodes a protein that is part of the tumour necrosis factor (*TNF*) family of ligands. Several studies have reported sporadic hypodontia in families affected by mutations in *EDA* and *EDA* receptor genes [64]. *EDA* has also been shown to be involved in missing maxillary lateral incisor cases [56].

4.4. Environmental Factors. Craniofacial bones, cartilage, nerves, and connective tissue all originate from neural crest cells. Specific developmental cascades are therefore common to the morphogenesis of both teeth and some craniofacial structures [1]. Indeed, several syndromes involving hypodontia often exhibit various dysplasias and clefts. Environmental factors have long been known to be associated with a higher risk of some of these craniofacial anomalies. Factors such as trauma, infection, and toxins have been implicated [65].

Several studies have suggested that intrauterine conditions could be involved in the aetiology of hypodontia, such as with thalidomide. It was reported that hypodontia was more common in children with thalidomide embryopathy (7.7%) than in normal children (0.4%) [65, 66]. Chemotherapy and radiotherapy treatment in early infancy have also been implicated in the development of hypodontia [5, 67]. According to some research, rubella infection during pregnancy can cause hypodontia in the developing child [68]. Interestingly, however, maternal health during pregnancy was found to be unrelated to the expression of hypodontia [69]. Trauma, such as fracture of the alveolar process, may also contribute to hypodontia, though disruption of tooth germ development, although evidence supporting this is weak in the literature.

Neural crest cells are extremely sensitive to high levels of oxidative stress that can arise due to both genetic and environmental factors. It is generally accepted that oxidative stress in the form of smoking, for example [70], plays a central role in the development of neural crest cells and the aetiology of craniofacial anomalies. In fact, maternal smoking has been associated repeatedly with a higher risk of CLP [71]. Exposure to alcohol has also been suggested as a risk factor, and, although the evidence has been more inconsistent, some studies have reported that "binge" drinking patterns during pregnancy increase the risk for CLP [72]. Given that hypodontia shares similar molecular pathways with some craniofacial anomalies, it would be useful to investigate whether there is an association between environmental factors and hypodontia. Unfortunately, no study to date has investigated smoking and alcohol as risk factors for hypodontia. Indeed, the identification of environmental risks (particularly if they can be combined with genetic covariates) provides the best opportunity for prevention.

5. Psychosocial and Functional Impact

Oral-health-related quality of life (OHRQoL) measures are often used to assess the impact of malocclusion on health and well-being. They aim to assess the functional, psychological, and social implications of the condition on an affected individual. Although numerous studies in the literature report on the prevalence, aetiology, and treatment of hypodontia, only few have investigated OHRQoL in individuals with hypodontia [73]. The few studies that have been carried out provide some evidence that hypodontia may have an adverse impact on quality of life.

In a retrospective study of 451 patients with hypodontia, the most common patient complaints included spacing between the teeth, poor aesthetics, and awareness of missing teeth [19]. The authors suggested that delayed referral of the patient is likely to have a negative impact on the social and educational development of these patients. Locker and coworkers reported similar findings, although the affected children had oligodontia [74]. Interestingly, Laing and colleagues found that the extent of the patients' complaints was associated with the severity of the condition and the number of missing permanent teeth. Those who had no complaints at the time of presentation had retained primary teeth that masked the problem [75].

Functionally, individuals with hypodontia tend to have deeper bites and spaces. Missing posterior teeth may not only result in further deepening of the bite, but the condition may also lead to nonworking interferences, poor gingival contours, and overeruption of the opposing teeth. Moreover, patients with hypodontia have been found to experience more difficulty in chewing due to a smaller occlusal table. In a recent cross-sectional study, it was found that hypodontia patients have more chewing difficulties if the deciduous teeth associated with the missing permanent teeth had been exfoliated [75]. It is therefore plausible that hypodontia may pose functional limitations that affect an individual's general well-being and quality of life in the process, although there is currently limited evidence to support this.

Ultimately, hypodontia carries an aesthetic, functional, psychosocial, and financial burden for affected individuals [3]. For these patients, hypodontia is a lifetime problem, which requires careful treatment planning in order to ensure best treatment outcomes. Treatment plans also involve long-term maintenance [24] and family counselling. Meanwhile, treatment of hypodontia patients often takes a number of years, from their initial visit through to completion of treatment.

Most important is the assessment of the complaints of the patients and the parents. Treatment plans needed to manage the missing teeth of hypodontia patients are complex and require an interdisciplinary approach, which usually comes at a financial cost to both the patient and their family [24]. Because of this, an experienced team of dental specialists should be involved in the treatment process [5, 29].

6. Timely Management of Hypodontia

The restoration of spacing that results from the agenesis of missing teeth is frequently complicated by the remaining present teeth, which are in unfavourable positions. Nevertheless, orthodontic treatment can facilitate any restorative treatment that may be required. Common issues faced in treating hypodontia patients include space management, uprighting and aligning teeth, management of the deep overbite, and retention [33]. Space issues within the dental arch are multifactorial in origin. The amount of spacing is influenced by the presence of microdontia, retention of the primary teeth, and the abnormal eruptive paths and drifting of the successional teeth [24]. The decision on whether the treatment plan involves space closure or opening of the spaces of the missing mandibular second premolar depends on factors such as age of the patient; degree of inherent crowding; state of the deciduous teeth; type of malocclusion; and the circumstances of the patient (finances, attitude towards treatment, etc.).

In hypodontia patients, dental development is often delayed, as is orthodontic treatment [76, 77]. In young patients with mild crowding, extractions of specific primary teeth in the early mixed dentition may be useful to permit some favourable movement of adjacent teeth. However, evidence shows that space closure and alignment, in missing premolar cases for example, are often incomplete following such an interceptive measure, and further intervention may be necessary [24, 78]. This is supported by an earlier study, which reported that there was a residual space of 2 mm in the mandible after extraction of the primary second molars [79]. Conversely, it has been shown that extracting primary second molars at a suitable time, for example, before or close to the pubertal growth spurt peak, can lead to relief of anterior crowding and spontaneous closure of the missing permanent second premolar space [80]. It was concluded that space closure occurred by mesial/rotational movements and tipping of the first molars as well as distal movement of the first premolars [80]. It was also suggested that extractions did not impact the overjet, overbite, or incisor inclination [80]. The study lacked a sufficient sample size, with only 11 subjects studied; and inclusion criteria involved only subjects with normal occlusion.

The best time for orthodontic treatment of patients with agenesis of mandibular second premolars is usually early adolescence. This is when most of the remaining developing permanent teeth are erupting and most of the facial growth has happened [33]. Notably, more adults are seeking orthodontic treatment. The management of adults missing mandibular second premolars is often complicated by caries and periodontal disease as well as the lack of facial growth potential, which reduces their adaptation to occlusal disturbances [33].

7. Summary

Hypodontia is the most common craniofacial malformation in humans, as it may occur as part of a recognised genetic syndrome or as a nonsyndromic isolated trait. The most commonly missing teeth are the mandibular second premolars and the maxillary lateral incisors. While it is not known whether individuals with hypodontia have characteristic skeletal features and growth patterns, several clinical features are commonly seen, including microdontia, transposition of permanent teeth, ectopic permanent teeth, and infraocclusion of primary molar teeth [81]. Recent research suggests that both genetic regulation and environmental factors are involved in the aetiology of this condition, with the former playing a more important role [81]. Finally, it is also likely that specific hypodontia pathways have some effect on the function and psychosocial well-being of an individual, given the aesthetic, functional, and financial burden for affected individuals [81].

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Research Article

Dental Age in Orthodontic Patients with Different Skeletal Patterns

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Objective. To evaluate the difference between chronological and dental age, calculated by Willems and Cameriere methods, in various skeletal patterns according to Steiner's ANB Classification. *Methods*. This retrospective cross-sectional study comprised the sample of 776 participants aged between 7 and 15 years (368 males and 408 females). For each participant, panoramic images (OPT) and laterolateral cephalograms (LC) were collected from the medical database. On LC ANB angle was measured; on OPT dental age (DA) was calculated while chronological age (CA) and sex were recorded. The sample was divided into three subgroups (Class I, Class II, and Class III) with similar distribution based on the chronological age and ANB angle. CA was calculated as the difference between the date of OPT imaging and the date of birth, while DA was evaluated using Willems and Cameriere methods. ANB angle was measured on LC by two independent investigators using the cephalometric software. Differences between sexes and the difference between dental and chronological age were tested by independent and paired samples t-test, respectively; one-way ANOVA was used to test differences among ANB classes with Tukey post hoc test to compare specific pairs of ANB classes. *Results*. The significant difference was found between Class III and other two skeletal classes in males using both dental age estimation methods. In Class III males dental age was ahead averagely by 0.41 years when using Willems method, while Cameriere method overestimated CA for 0.22 years. *Conclusion*. In males with Class III skeletal pattern, dental development is faster than in Classes I and II skeletal pattern. This faster development is not present in females.

1. Introduction

Dental development is a multilevel process, and it entails molecular and cellular interactions, which have macroscopic and clinical phenotypic outcomes. The process of dental development is multidimensional, requiring developments in the three spatial dimensions with the fourth dimension of time. It is progressive, occurring over an extended period, yet at critical stages of development [1, 2]. In the same time of intensive changes, growth and development of different bones constituting the facial skeleton do not exhibit the same rate of growth [3]. As the teeth grow in the bone substratum, under the similar growth factors, it can be expected that the growth factors can have similar influence onto dental and bone growth intensity in the same jaws.

It is well known that the growth is an important aspect in dentofacial orthopedics, as treatment outcomes and stability may be influenced by the maturational status of the patient [4]. Correlation and possible Influence of facial pattern of the growth and dental development have been intensively studied earlier [5–9]. All previous studies investigated the correlation between vertical growth pattern and dental development. At the same time, there is a limited amount of research that investigated horizontal skeletal growth pattern and dental development; even some studies showed that the rate of growth is different depending on the pattern of the sagittal skeletal growth [10, 11].

Many biological indicators can be used for determination of the growth and development such as body weight, body height, dental development, or skeletal development. The X-ray images are recognized as a reliable method for the exact determination of skeletal pattern, as well as for the dental development stage. Sagittal skeletal relationships can be determined from LC, with widely used Steiner's [12] sagittal analysis where the analysis of ANB angle indicates the magnitude of skeletal jaw discrepancy [13–15].

Different age estimation methods on developing teeth were presented over last 70 years [16, 17]. Most of the methods on developing teeth evaluate mandibular teeth from one side while some of them use all or just specific set of teeth from single or both jaws [18–22]. Demirjian method, scoring system introduced in 1973, is one of the most widely used methods for estimating dental developing stage [23]. It is based on an assessment of mineralization of seven teeth from one side of mandible where development from crypt formation until mature was divided into eight stages, marked with alphabet letters from A to H [19]. This method was used in many populations, including studies in Bosnia and Herzegovina [24, 25]. A meta-analysis by Yan et al. [26], based on 26 studies, showed that Demirjian's method overestimated dental age by 4.2 months in males and 4.68 months in females. Comparative studies of different dental methods have shown that another Willems method exhibited smaller error rate when compared to the real age [16, 20, 27, 28]. The other recent method developed by Cameriere et al. [29] introduced a different approach on the same set of seven teeth, analyzing a teeth maturation as the proportion of open apices and heights of the roots. Additional variables in the regression model were sex, the number of teeth with closed apices, and the sum of the proportion of all teeth in development while ethnicity was not a significant factor [29]. Willems and Cameriere's methods were found to be reliable and accurate in many populations and also confirmed as the appropriate method for evaluating dental development stage in Bosnia and Herzegovina population [16].

Most of the previous studies estimated dental age in general population without taking account of the possible effect of skeletal pattern on the dental development stage [16, 25, 30, 31]. However, one study by Celikoglu et al. [30] evaluated Demirjian dental age in patients with and without skeletal malocclusions. This study showed that girls with skeletal Class III according to the ANB angle classification by Steiner (ANB) have significantly earlier dental development than other Class I or Class II participants in the study [12]. Their result is in concordance with our hypothesis that the increase in skeletal growth, as the consequence of growth factors in the bone can influence the increase of the dental development.

Therefore, the purpose of this study was to investigate if patients with Class II patterns (ANB > 4 degrees) or Class III patterns (ANB 0 degrees or negative) have different timing of dental development. If so, that difference should be taken in calculation when age estimation analyses in dental forensics are provided, or in the planning of functional orthodontic treatment where the skeletal and dental age can be different from the chronological age of the patient.

2. Materials and Methods

This is a retrospective cross-sectional study of dental age estimation in orthodontic patients from the University of Sarajevo School of Dental Medicine Orthodontic Department. Ethical approval for the study was obtained from the School of Dental Medicine Ethical Committee, and the study was performed according to World Medical Association Declaration of Helsinki for ethical principles for medical research involving human subjects [32].

The sample consisted of 776 participants aged between 7 and 15 years (368 males and 408 females). The first inclusion criterion for each participant was that the panoramic image (OPT) and lateral cephalogram (LC) from the medical records were gathered at the same time, before any orthodontic treatment. The sample was divided into three subgroups (Stainer's skeletal Class I, Class II, and Class III according to ANB angle) with the similar distribution based on the chronological age.

All OPT and LC were recorded on the same X-ray scanner (KODAK 8000C Digital Panoramic and Cephalometric System, Carestream, France). Chronological age (CA) was calculated as the difference between the date of OPT scanning and the date of birth from the medical record.

Skeletal class was evaluated on each LC according to Steiner's A point-Nasion-B point angle (ANB angle) [12] by two independent investigators. No interexaminer difference was found for ANB angle calculation. Briefly, for ANB angle, A point presents the most concave point of the anterior maxillar base; Nasion (N) presents the most anterior point of the frontonasal suture, while B point presents the most concave point of the anterior contour of mandibular symphysis. Steiner's classification recognizes different skeletal patterns according to ANB angle, Class I ranges from 0 to 4 degrees, Class II presents angle of over 4 degrees, and Class III is ANB angle of negative value or 0 degrees.

Dental age was calculated according to Willems and Cameriere dental age estimation method, which shows the smallest error of age estimation [16, 27]. Willems' method is based on the assessment of Demirjian stages on seven mandibular teeth [19]. OPTs of French-Canadian children have been evaluated and seven permanent teeth from the left side of the mandible, excluding third molars, have been rated [19]. Demirjian stages are derived from evaluation of eight mineralization stages, alphabetically marked from A to H. The first stage A represents a beginning of calcification, seen at the superior level of the dental crypt, without fusion of this calcification, while the last stage H represents finished calcification of the tooth with apical ends of the roots completely closed [19]. For each stage, Demirjian presented specific self-weighted score and summed score on all seven teeth present a dental maturity score which can be converted to dental age [19]. Willems et al. [33] in 2001 revisited the original Demirjian method in a Belgian population and adopted the original Demirjian's scoring system by using a weighted ANOVA. The ANOVA model was used with all seven teeth as covariates for boys and girls separately. Specific tables for each sex with corresponding age scores expressed directly in years of each stage for each of the seven left mandibular teeth for age calculation were presented [33].

Cameriere's method was based on regression analysis of age as dependent variable and proportions of measurements of open apices and heights of the same seven mandibular teeth on the OPT, where sex (g) and number of teeth with finished maturation of root apex (N_0) are important dependent variables in calculating DA [29, 34]. Briefly, all teeth without complete root development or with open apices were examined and the distance (A_i, $i = 1, \ldots, 5$) between the inner side of the open apex was measured. For teeth with two roots, (A_i, $i = 6, 7$), the sum of the distances between the inner sides of the two open apices was calculated. Distances were normalized by dividing by the tooth length (L_i, $i = 1, \ldots, 7$) to minimize the effect of differences among X-rays in magnification and angulation [34]. Dental age was calculated according to the European formula: Age = $8.387 + 0.282g - 1.692x_5 + 0.835N_0 - 0.116s - 0.139s * N_0$, where g is a variable, with $g = 1$ for boys and $g = 0$ for girls, s is the sum of the normalized open apices of the seven left permanent developing mandibular teeth ($x_i = A_i/L_i$, $i = 1, \ldots, 7$), and x_5 is the normalized measurement of the second premolar [29].

The results were tested for each sex separately. A Shapiro-Wilk test and normal Q-Q Plots showed normal distribution of the differences between estimated and chronological age or residuals for both methods [35]. Differences between dental and chronological age for both methods were evaluated with paired samples t-test; one-way ANOVA was used to test the effect of ANB classes on differences between estimated and chronological age, with Tukey as the post hoc test [35]. Cohen Kappa was used to verify intraobserver and interobserver agreement in Demirjian staging and in a number of teeth with closed apices as evaluated by Cameriere's method between the two independent observers, as well as for two measurements by the same observer [36]. Intraclass correlation coefficient (ICC) was used to test calculated a dental age for the intraobserver and interobserver agreements [36]. SPSS Statistics 16.0 for Windows (SPSS Inc., Chicago, IL) was used for statistical analysis, and statistical significance was set at 0.05.

3. Results

In all participants involved in this study dental age estimation using both methods and classification into specific ANB angle skeletal class was possible to evaluate. Distribution of sample according to sex, ANB skeletal class, and age was presented in Table 1.

Cohen Kappa scores, for intraobserver and interobserver agreement between the same and two different observers, were 0.81 (95% CI, 0.72 to 0.90) and 0.72 (95% CI, 0.57 to 0.86), respectively, for scoring Demirjian staging system. Cohen Kappa for scoring the number of teeth with closed apices on Cameriere's method was 1.00. ICC for calculated dental age for the intraobserver and interobserver agreements were 0.98 (95% CI, 0.97 to 0.99) and 0.97 (0.95%, 0.95 to 0.98), respectively, for Willems method and 0.98 (95% CI, 0.97 to 0.99) and 0.97 (95% CI, 0.96 to 0.98), respectively, for Cameriere method. One-way between-groups ANOVA, to test difference of mean chronological ages among different ANB skeletal classes, showed no statistically significant difference in males, $F(2, 365) = 0.71$, $p = 0.49$ and females, $F(2, 405) = 0.54$, $p = 0.58$. Figure 1 shows a finding of the chronological age among ANB skeletal Classes I to III.

Dental age, calculated by the Willems method, showed a statistically significant overestimation of DA when compared to CA, $p < 0.001$. Average overestimation was 0.57 years with 95% confidence interval (95% CI, 0.46 to 0.68 years) in males and 0.48 years (95% CI, 0.38 to 0.59 years) in

Table 1: Distribution of sample according to sex, Steiner's skeletal classes of ANB angle and age.

Age	ANB angle Class I		ANB angle Class II		ANB angle Class III	
	M	F	M	F	M	F
7		4			2	
8	12	8	9	9	18	14
9	22	16	16	16	10	14
10	22	22	16	10	14	8
11	12	18	15	17	14	12
12	22	26	13	26	18	32
13	28	26	16	23	18	34
14	16	24	15	17	34	28
15	2	4			4	
Total	136	148	100	118	132	142

M = males; F = females.

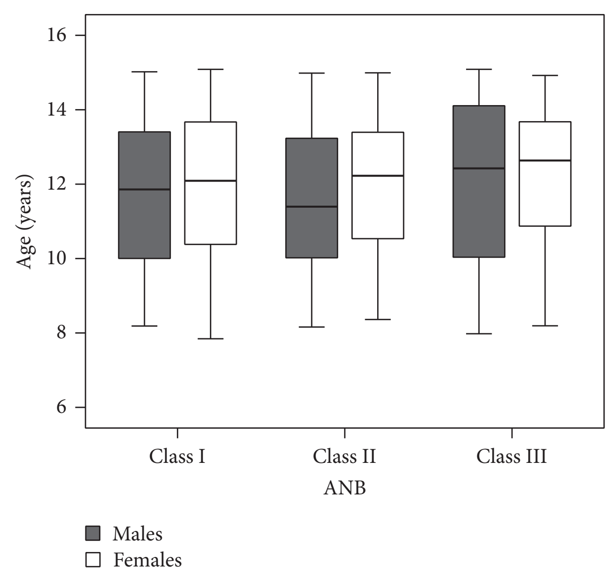

Figure 1: Distribution of the chronological age among ANB skeletal classes.

Table 2: Comparison of chronological age and dental age calculated by Willems and Cameriere methods in different ANB skeletal classes.

Method	Sex	Class	N	Chronological age (CA)		Dental age (DA)		DA-CA		Paired-samples t-test	
				Mean	SD	Mean	SD	Mean	SD	t(df)	p
Willems	Males	I	136	11.71	1.94	12.11	2.54	0.40	1.13	4.1 (135)	<0.001
		II	100	11.67	2.00	12.11	2.54	0.44	1.03	4.3 (99)	<0.001
		III	132	11.96	2.17	12.79	2.65	0.83	0.97	9.8 (131)	<0.001
		Total	368	11.79	2.04	12.36	2.65	0.57	1.06	10.2 (367)	<0.001
	Females	I	148	12.00	2.01	12.52	2.50	0.53	1.12	5.8 (147)	<0.001
		II	118	11.96	1.86	12.38	2.53	0.43	1.17	3.9 (117)	<0.001
		III	142	12.19	1.96	12.68	2.57	0.49	1.07	5.5 (141)	<0.001
		Total	408	12.05	1.95	12.54	2.53	0.48	1.12	8.8 (407)	<0.001
Cameriere	Males	I	136	11.71	1.94	11.44	2.04	−0.26	0.72	−4.36 (135)	<0.001
		II	100	11.67	2.00	11.44	1.90	−0.23	0.76	−3.06 (99)	0.003
		III	132	11.96	2.17	11.93	1.99	−0.02	0.73	−0.47 (131)	0.642
		Total	368	11.79	2.04	11.62	2.00	−0.19	0.80	−4.48 (367)	<0.001
	Females	I	148	12.00	2.01	11.86	1.70	−0.14	0.91	−1.88 (147)	0.063
		II	118	11.96	1.86	11.75	1.72	−0.20	0.73	−3.01 (117)	0.003
		III	142	12.19	1.96	11.94	1.74	−0.24	0.73	−4.02 (141)	<0.001
		Total	408	12.05	1.95	11.86	1.72	−0.17	0.74	−4.92 (407)	<0.001

females (Table 2). One-way between-groups ANOVA showed statistically significant difference in overestimation among classes in males, $F(2, 365) = 6.60$, $p = 0.002$, but not in females (Table 3). Post hoc comparison showed that the mean overestimation in males for Class III, 0.83 years (95% CI, 0.66 to 1.00 years), was statistically significantly different from Class I, 0.40 years (95% CI, 0.21 to 0.59 years) ($p = 0.0008$), and Class II, 0.44 years (95% CI, 0.24 to 0.65 years) ($p = 0.0056$). Classes I and II did not differ significantly (Figure 2).

Dental age calculated by the Cameriere method showed an underestimation of CA, which was not statistically significant only in males for Class III, $t\,(131) = -0.47$, $p = 0.642$ and in females for Class I, $t\,(147) = 1.88$, $p = 0.063$. Average underestimation was −0.19 years (95% CI, −0.27 to −0.18 years) in males and −0.17 years (95% CI, −0.24 to −0.09 years) in females (Table 2). One-way between-groups ANOVA showed statistically significant difference in underestimation only in males, $F(2, 365) = 3.99$, $p = 0.019$ (Table 3). Post hoc comparison showed that the mean underestimation in males for Class III, −0.02 years (95% CI, −0.16 to 0.10 years), was significantly different from Class I, −0.26 years (95% CI, −0.39 to −0.15 years) ($p = 0.008$), and Class II, −0.23 years (95% CI, −0.38 to −0.08 years) ($p = 0.037$). Classes I and II did not differ significantly, which is presented in Figure 3.

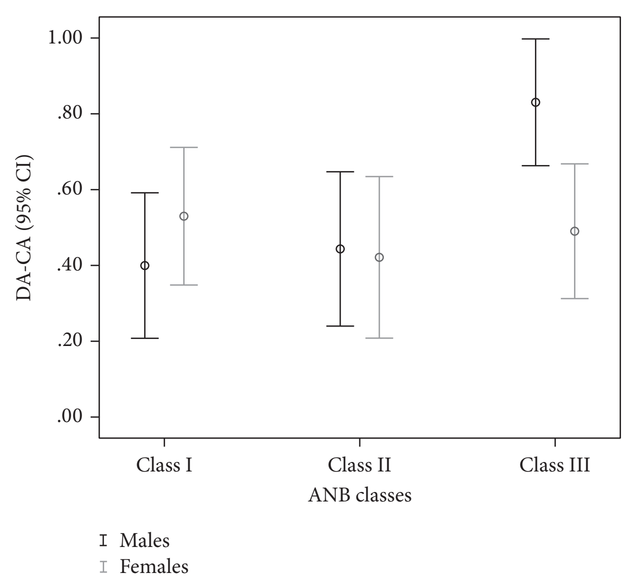

Figure 2: Differences between dental age calculated by the Willems method and chronological age (DA-CA) in years among ANB skeletal classes.

4. Discussion

Relevant studies reporting correlations between dental development and skeletal patterns are limited in the recent literature. The influence of skeletal pattern to dental development is still not fully understood, but if different dental development occurs in a various skeletal pattern then the diagnosis of the specific pattern may help to estimate the dental development in forensic dentistry properly and can have the clinical relevance in the planning of orthodontic treatment time.

In this study, we analyzed dental development stage using two dental age evaluation methods and compared the dental development with the pattern of skeletal growth. For the assessment of dental development, we used Willems and Cameriere methods that showed the smallest error between dental and chronological age as published in the recent literature [16]. The sample evaluated in our study was

Table 3: Summary ANOVA tables to test the differences in DA-CA among ANB skeletal classes for Willems and Cameriere methods.

Method	Sex		Sum of squares	df	Mean square	F	p
Willems	Males	Between groups	14.49	2	7.24	6.60	0.002
		Within groups	400.67	365	1.10		
		Total	415.16	367			
	Females	Between groups	0.78	2	0.39	0.31	0.732
		Within groups	505.26	405	1.25		
		Total	506.04	407			
Cameriere	Males	Between groups	4.31	2	2.15	3.99	0.019
		Within groups	196.84	365	0.54		
		Total	201.14	367			
	Females	Between groups	0.80	2	0.40	0.62	0.536
		Within groups	259.14	405	0.64		
		Total	259.93	407			

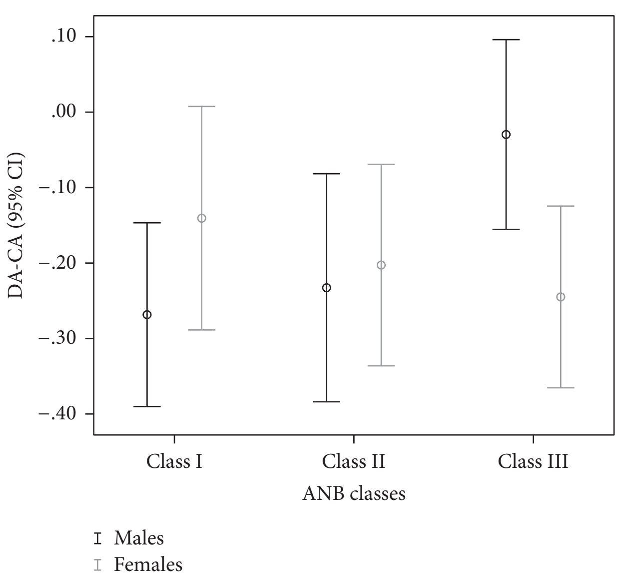

Figure 3: Differences between dental age calculated by the Cameriere method and chronological age (DA-CA) among ANB skeletal classes.

similarly distributed in all ANB classes and across the age range. Upper age of the sample was limited to only those OPTs with evidence of unfinished maturation of the second molars. Older subjects were not qualified for the evaluated methods.

Willems method of dental age evaluation in this sample overestimated the chronological age in all ANB classes and both sexes. This means that the error of Willems method is distributed among the all skeletal patterns and in both sexes. An overestimation was the same among all ANB classes in females, which means that in females dental development is equal among all skeletal patterns. However, in male examinees, dental age in ANB class III was overestimated almost twofold when compared to ANB Class I and/or Class II. This suggests that in Class III males dental development starts earlier than in Class I and/or Class II.

Cameriere method showed a smaller error in the estimation of chronological age when compared to Willems method, and that was negative, which means that Cameriere method of dental age evaluation underestimates chronological age. The mean underestimation was −0.19 years for males and −0.17 years for females. In males, ANB Class III was statistically different when compared to Class I or Class II. Cameriere method underestimated chronological age using evaluation of dental age in males with ANB Class III for only 0.02 years. These findings are in concordance with the explanations using Willems method and also suggest that in males with Class III ANB angle dental development starts earlier than in other skeletal patterns.

Previous study by Celikoglu et al. [30], who used Demirjian method for age estimation, showed that ANB Classes II and III patients were dentally advanced compared to Class I. Principally, they showed that the difference was the highest for their patients with mandibular prognathism or Class III for both sexes, which was statistically significant only in females. Differences in patterns between sexes in our study and study by Celikoglu et al. [30] indicate sex differences using different age estimation method, but the pattern of Class III earlier dental development is consistent between samples.

A similar pattern in the difference of the dental age in males with skeletal Class III or advanced dental maturation, when compared to other two classes, indicates a possible association between this skeletal anomaly and advanced dental maturation. Except for one study [30], there are no investigations that evaluate dental age evaluation in specific malocclusion groups. Jamroz et al. [8] demonstrated that subjects with short anterior facial height presented a slight tendency toward a more advanced dental age than those with long anterior facial height. Uysal et al. [37] found the difference in dental age between examinees with posterior cross-bite and control groups, where subjects with a posterior cross bite had a tendency for a prolonged dental maturation compared to the control individuals with the clinical relevance. No significant side differences in either group were detected.

It is important to stress that the dental age evaluation was calculated according to methods that use lower mandibular teeth from the left side of the mandible. If the mandibular growth is accelerated or started earlier, as it is usual in most Class III, we can expect that growth factors in mandible also influence the dental development of mandibular teeth, as they are only analysed in dental age evaluation methods. If this is the explanation of the difference in dental age in different skeletal pattern, we have to evaluate carefully different skeletal patterns with other age estimation methods in order to give the exact answer: does the skeletal pattern influence the dental development or are the dental age estimation methods dependable of the intensity of growth in the jaw where the teeth for estimation method are located?

5. Conclusions

Dental age calculated by Willems method overestimated, while by Cameriere method underestimated the chronological age in all ANB Classes. Both age estimation methods showed the same pattern in males with ANB Class III when compared to other two classes. Dental development in males with Class III was ahead by 0.4 years for Willems method and by 0.2 years for Cameriere method. The results of this investigation suggest that diversity of the skeletal pattern could be connected with the different time of dental development. If so, this should be involved in age estimation methods in dental forensics with the involving skeletal pattern in the process of age estimation or, in orthodontic clinical practice, to have in mind that the intensifying of skeletal growth can increase the dental development in surrounding jaw.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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Research Article

When Do Skeletal Class III Patients Wear Their Reverse Pull Headgears?

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Objective. The aim of this study is to evaluate the factors that affect wearing time and patient behavior during reverse pull headgear therapy with a newly designed reverse pull headgear. *Methods*. In clinical practice, new reverse pull headgears were applied to fifteen patients. The patients were monitored during reverse pull headgear therapy and the data were evaluated. Statistical analysis was made. *Results*. During the study, patients were monitored successfully and the evaluations showed that patients wear the new reverse pull headgears mostly at night. There are differences between days of week and hours of day. Weekends are more popular than weekdays for wearing reverse pull headgear. *Conclusions*. This new type of reverse pull headgears can be used successfully in clinical practice and can help the clinician. Study showed that the most important factor that affects the cooperation of reverse pull headgear patient is aesthetic appearance.

1. Introduction

Maxillary deficiency, mandibular prognathism, or both can lead to skeletal class III malocclusion. Different orthodontic approaches used to treat maxillary deficiency include early orthopedic correction, fixed treatment, or a combination of fixed mechanics and surgery. Early orthopedic correction can be done at the proper ages using extraoral appliances like reverse pull headgear [1]. Reverse pull headgear therapy is the gold standard for correcting maxillary deficiency and achieving maxillary protraction, but its effectiveness depends on the amount of time and regularity that patients wear reverse pull headgear [2, 3]. Objective and strict observation of reverse pull headgear therapy is needed and may help improve the level of treatment success.

Some studies have been done on patient compliance during different orthodontic protocols such as intraoral appliance therapy [4, 5]. Only a few devices are available to quantify extraoral appliance wearing time and usage regularity [6, 7].

Aim of this study is to present the objective evaluation of the wearing time of a reverse pull headgear during therapy.

2. Materials and Methods

A total of 15 patients (8 Males, 7 Females; mean age 11.9 ± 0.9 years; age range 11–13 years) with maxillary deficiency and skeletal class III were included in the study. Pretreatment orthodontic records were taken from all patients and evaluated. An expert orthodontist evaluated hand wrist radiographs and clinical signs of patients.

Inclusion criteria of the study were active growth period, true class III skeletal relationships due to maxillary deficiencies, a negative ANB angle due to lowered SNA angle, posteriorly positioned A point due to maxillary deficiency according to McNamara analysis, and concave profile.

All of the patients were appropriate for early orthopedic correction according to their age and hand wrist radiographies and evaluations of an expert orthodontist.

Ethical approval was obtained from the Ethical Commission of the University. All patients were informed about the treatment method and reverse pull headgear therapy. Patients also were informed about the iButtons placed on the forehead part of the newly designed reverse pull headgear.

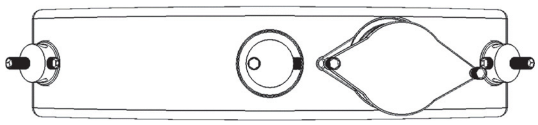

Figure 1: The new forehead design.

Figure 2: Sensor and programming process of sensor.

Informed consent was obtained from both the patients and their parents.

The newly designed headgear has a sensor slot in forehead part (Figure 1). The sensor of system (iButton) is a sophisticated digital thermometer (Figure 2).

The main function of the sensor is to measure the temperature and store the value of it in its memory [8].

Study models with bands were taken from all patients for hooked hyrax device production. Four banded hooked hyrax device and extraoral elastics were used to provide adequate orthopedic force loading (Figure 3).

At the first treatment visit, hyraxes were placed in the patients' mouths and the reverse pull headgear was applied. Hyraxes were activated at the beginning of the reverse pull headgear therapy. Orthopedic force level (around 450 gr per side) was loaded with elastics and patients were asked to wear them for 13–16 hours per day, especially during the evening and night. Patients were given information about the increased release of growth hormone and other growth-promoting endocrine factors, which has been observed to be higher during the evening and night than during the day. However, patients could decide for themselves what time of the day they wore the headgear. Both patients and their parents were also informed about possible damage caused by facial trauma during daily activities such as sports. Patients and parents were asked to explain the therapy to their friends and teachers in order to prevent demotivational factors like teasing at school.

During study, 15 programmed sensors were placed on the newly designed forehead part of the reverse pull headgear. At the second treatment visit (4 weeks after first treatment visit), new reverse pull headgears were given to 15 patients (Figure 3). Patients were seen for 4-5 weeks. Data of new reverse pull headgear were collected and stored.

Figure 3: Application of force.

Clinical examinations of patients were made and all the orthodontic mechanics were checked carefully.

At the end of study, stored data of new reverse pull headgears were evaluated and statistical analyses were made. Different days of week factor, different hours of day factor, and sex factor were analyzed by using Chi-squared test and ANOVA with an associate post hoc analysis (Tukey) was also used in more detailed statistical evaluation.

3. Results

During the study, any damage was detected on new reverse pull headgears, sensor, and hooked hyrax devices. All the new reverse pull headgears worked well and provided data. Temperature values were approximately 16–28°C (mean 24 ± 3.1°C) while the reverse pull headgear was not worn and approximately 31–39°C (mean 36.3 ± 2.9°C) temperature values while being worn by patients. The new reverse pull headgears measured the temperature and stored the values at planned intervals.

The data analysis showed the following results.

(i) The reverse pull headgear usage during night is significantly higher than daytime ($p < 0.05$) (Table 1) (Figure 4).

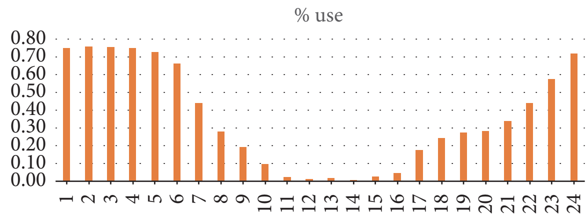

Figure 4: Graphics of all patients' usage percent during day (24 hours).

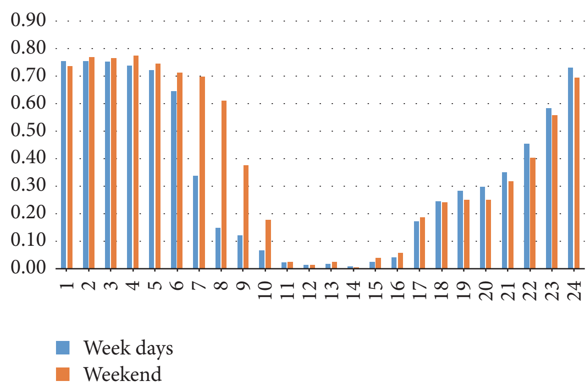

Figure 5: Graphics of comparison of usage percent between week days and weekends.

(ii) The reverse pull headgear usage during evening is significantly higher than daytime ($p < 0.05$) (Table 1) (Figure 4).

(iii) The reverse pull headgear usage during night is significantly higher than evening ($p < 0.05$) (Table 1) (Figure 4).

(iv) Usage increases over weekend ($p < 0.05$) (Tables 2 and 3) (Figure 5).

(v) The usage habits of boys and girls are not alike at different hours of day ($p < 0.05$) (Tables 4 and 5) (Figure 6).

Table 1: Comparison of usage time according to different hours of day and sex (two-way ANOVA).

	Df	Sum Sq	Mean Sq	p value
Hour factor	23	1386.7	60.7	* * *
Sex factor	1	68.9	68.91	* * *

* * * means $p < 0.05$.

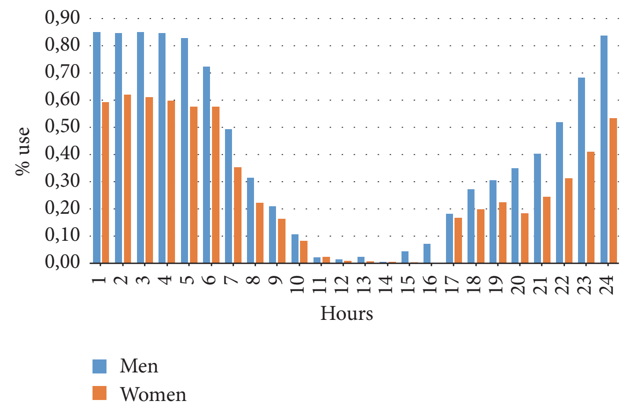

Figure 6: Reverse pull headgear usage percent according to hours of day and sex.

4. Discussion

The total wearing time and regularity of usage of reverse pull headgear therapy directly affects the success of these devices. An objective determination of the effect of reverse pull headgear can only be possible if the clinician obtains accurate information about headgear wear. Therefore, it is necessary to know the objective of reverse pull headgear usage when planning the treatment process. If the patient does not use the reverse pull headgear, clinicians can try repeatedly to motivate the patient. However, if the patient insists on resisting the suggestions, treatment can be delayed or other treatment alternatives can be considered. Thus, loss of money and time can be prevented.

Different techniques such as usage charts and talking with the patient and their parents, teachers, or school friends can provide information about compliance while undergoing reverse pull headgear therapy, but all provide subjective results. Obviously, there is a need for devices that provide objective measurements [9].

In modern orthodontics, reverse pull headgear was designed and made only for their mechanical requirements. They are produced to provide enough anchorage to generate the required protraction forces. A few studies used built-in electronic timing devices in removable appliances [10, 11]. In one study, DS1921G was used to measure patience compliance during cervical headgear therapy. Other studies investigated different devices such as a headgear timing device [12–14] and small quartz calendar [15]. These systems are not suitable to the aims of this study.

Reverse pull headgear therapy is indicated for patients with maxillary deficiency. The new reverse pull headgear was used for the same indication as the conventional one. Therefore, the evaluation of effectiveness of new reverse pull headgear can be achieved properly.

A hooked hyrax device and extraoral elastics were used to provide adequate orthopedic force loading. Orthopedic force level was loaded with elastics and 13–16-hour wearing time per day was required similar to that of routine reverse pull headgear therapy. The first month of treatment is the adaptation phase for patients and parents. Moreover, an evaluation of patients' behavior at this phase cannot provide sound results. So, at the second treatment visit, 15 patients

Table 2: Comparison of days (p values).

Tukey multiple comparisons of means (95% family-wise confidence level)							
	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Monday		0.6115052	0.7447838	0.9955896	0.9999974	**0.0054993**	**0.0014632**
Tuesday			0.0236437	0.2217987	0.4879183	**0.0000024**	**0.0000004**
Wednesday				0.9769117	0.8384991	0.3473935	0.1787557
Thursday					0.9992788	**0.0437167**	**0.0148834**
Friday						**0.0099470**	**0.0028086**
Saturday							0.9998783
Sunday							

Table 3: Comparison of usage time according to different hours of day, different days of week, and sex (ANOVA).

	Df	Sum Sq	Mean Sq	p value
Hour factor	23	1386.7	60.29	* * *
Week days/weekend factor	1	8.1	8.07	* * *
Sex factor	1	69.0	68.97	* * *

* * * means $p < 0.05$.

Table 4: Comparison of male and female patients.

	Week days	Weekend
No		
Male	4771	1714
Female	3585	1318
Wear		
Male	3080	1358
Female	1296	603

Chi-square test of independence, number of cases in table: 17725, number of factors: 3, and test for independence of all factors: Chisq = 332.5, df = 4, p value = $1.066e - 70$.

began to use the new reverse pull headgear. The new reverse pull headgear could be used to track the patient' personal headgear wearing time. Sensors (iButton) have been used in different types of studies such as sleep evaluation or the body temperature measurement of mammals. The type of iButton used in the present study was coded H, meaning human. So the characteristics of this type of iButton are appropriate for human studies.

All patients and parents were aware that the new reverse pull headgear could identify and store the wearing times. Sound and objective communication between the family and clinician is one of the bullet benefits of new reverse pull headgear. Because this factor improves the truth of patient and parents reports about wearing reverse pull headgear, patients cannot claim that they have put on reverse pull headgears as recommended by clinician although they have not. This good, accurate, and true communication between family and clinician can possibly improve the quality of treatment.

New reverse pull headgear's data is provided to understand the patient's behavior. By the way, patients can be given a chance to explain their feelings about therapy and reasons of their behavior. All of the patients reported that they are not beautiful or handsome with reverse pull headgear. As a result, they did not want to wear appliances while they are among people like school times or social activities like birthday party. So results of the study such as popularity of use at weekend and night can be explained by poor aesthetics of reverse pull headgear. Patients prefer to use headgears at bed time or evening at home. All of these findings are expected results. Because many patients on daily practice of reverse pull headgear therapy also complain about aesthetic appearance of reverse pull headgear. This objective measurement of patient compliance is very important for clinicians on the way of the treatment, because clinician can delay or stop the treatment or apply other treatment options. Clinicians also can explain the benefits of treatment like good facial aesthetics and prevention from future surgery procedures to motivate the patients. All of these opportunities can be beneficial for family, clinician, and economy [16–18].

5. Conclusions

(i) Patients usually wear more often the reverse pull headgears at night and weekends, probably because of the poor aesthetic appearance of the appliance.

(ii) Objective measurement of patient compliance can help clinicians with this challenging treatment.

(iii) Although not a hypertechnological appliance, the new reverse pull headgear can be used successfully to monitor patient compliance.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Table 5: Comparison of male and female patients.

		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Non	Male	987	1035	887	941	921	840	874
	Female	690	685	707	732	771	682	636
Wear	Male	602	532	652	637	657	696	662
	Female	270	275	253	266	232	279	324

Chi-square test of independence, number of cases in table: 17725, number of factors: 3, and test for independence of all factors: Chisq = 380.1, df = 19, p value = $5.953e - 69$.

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Research Article

Dental Age and Tooth Development in Orthodontic Patients with Agenesis of Permanent Teeth

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Objective. To compare the development of permanent teeth in a group of children with the congenitally missing permanent teeth (CMPT) and corresponding nonaffected group. *Methods*. The formation stages of all developing permanent teeth were determined on 345 panoramic radiographs (OPTs) by the method of Haavikko (1970), and dental age was calculated. The paired samples t-test was used to compare the differences between dental age (DA) and chronological age (CA) in those with CMPT and those not affected. Spearman test was used to evaluate the correlation between DA-CA and the number of missing teeth. The Wilcoxon signed rank test was used to compare the development of the teeth adjacent to the place of the agenesis with matched pair in corresponding nonaffected group. *Results*. Dental age was significantly delayed in CMPT children compared to the nonaffected group ($p < 0.001$). The mean differences were -0.57 ± 1.20 years and -0.61 ± 1.23 years in males and females, without difference between sexes ($p = 0.763$). The number of missing teeth affected the delay only in females ($p = 0.024$). Only mesial teeth in females were significantly delayed in development when compared to the nonaffected group ($p = 0.007$). *Conclusion*. Our findings show that the development of the permanent teeth is delayed when compared to the nonaffected group of the same sex and age.

1. Introduction

Congenitally missing permanent teeth (CMPT) or hypodontia is the most common anomaly of the permanent dentition [1, 2]. It is a failure of initial formation of tooth germ, causing permanent missing of the teeth. It could be associated with tens of different syndromes and craniofacial anomalies [3]. An etiology of familiar or nonsyndromic CMPT is not fully explained, and multifactorial inheritance including mutations of specific genes, *AXIN2*, *MSX1*, *PAX9*, and *WNT10A*, was reported [4–6]. The most common CMPT is nonsyndromic and affects a small number of teeth. A recent meta-analysis of the prevalence of CMPT demonstrated variability when comparing results for different continents, from 13.4% in Africa to 4.4% in Latin America and the Caribbean [7]. The most frequently CMPT are lower second premolars and upper lateral incisors, following upper second premolars and lower central incisors [7]. The development of permanent dentition, except third molars, can last up to 15 years of age, so it is important to recognize this pattern for timely treatment and particularly for the management of severe cases [8]. Dental methods for age calculation on developing teeth are important in the estimation of chronological age in cases of unknown date of birth, adoption of children, asylum seeking procedures, unaccompanied children, or estimating age from skeletal remains [9, 10]. Garn et al. [11] first reported a pattern of delayed dental development in children with CMPT. Some previous studies reported a significant delay of dentition development in children with CMPT when compared with their case-control pairs, while other showed no significant difference [12–17]. Odagami et al. [17] reported a significant association between severity of CMPT and delay of dental development while Uslenghi et al. [13], besides an association of the number of the missing teeth and dental delay, additionally showed a significant delay of both mesial and distal teeth adjacent to the missing tooth. Different age

Table 1: Distribution of participants with congenitally missing permanent teeth (CMPT), control sample of nonaffected children (control), and evaluated sample across different age groups.

Age group (years)	Males				Females				Total			
	N_{CMPT}	N	%	$N_{CONTROL}$	N_{CMPT}	N	%	$N_{CONTROL}$	N_{CMPT}	N	%	$N_{CONTROL}$
6.0–6.9	4	46	8.7	4	3	54	5.6	3	7	100	7.0	7
7.0–7.9	13	168	7.7	13	18	72	25.0	18	31	240	12.9	31
8.0–8.9	27	150	18.0	27	26	149	17.4	26	53	299	17.7	53
9.0–9.9	15	315	4.8	15	32	167	19.2	32	47	482	9.8	47
10.0–10.9	21	390	5.4	21	35	328	10.7	35	56	718	7.8	56
11.0–11.9	26	286	9.1	26	33	408	8.1	35	59	694	8.5	59
12.0–12.0	21	200	10.5	21	22	400	5.5	22	43	600	7.2	43
13.0–13.9	12	588	2.0	12	16	268	6.0	16	28	856	3.3	28
14.0–14.0	8	117	6.8	8	7	216	3.2	7	15	333	4.5	15
15.0–15.9	2	40	5.0	2	4	68	5.9	4	6	108	5.6	6
Total	149	2300	6.5	149	196	2130	9.2	196	345	4430	7.8	345

N_{CMPT}, a number of participants with CMPT; $N_{CONTROL}$, a number of nonaffected participants; N, a total number of participants.

estimation methods were used to study dental development in children with CMPT, and most studies applied Haavikko staging system [15, 18].

Reported results of delay in dental development, from three months to two years, varied in sample size and cohort, staging system and statistical significance [15, 19]. A significant delay in dental development, especially in cases with severe CMPT, can provide valuable information for the beginning of orthodontic treatment. Tooth development in orthodontic patients with CMPT was not previously evaluated in Southern Croatia on a cross-sectional sample. The aims of this study were to examine the radiographic development of permanent teeth in orthodontic patients with CMPT, excluding third molars, to test the association of the number of the missing teeth to the dental development and how it affects the development of the teeth mesial and distal to the space of agenesis of the tooth.

2. Materials and Methods

This retrospective cross-sectional study was based on the evaluation of pretreatment orthopantomogram (OPT) of the orthodontic patients with CMPT. Digital OPTs were recorded during the period between 2008 and mid-2015 from six different orthodontic practices in Southern Croatia. The evaluated sample consisted of 4430 OPTs, while the sample with CMPT consisted of 345 OPTs of the children aged from 6 to 15 years, 149 males (6.5%) and 196 females (9.2%), Table 1. In total, 287 and 384 missing teeth were in 149 males and 196 females. Prevalence of 1 or 2 missing permanent teeth in evaluated sample was 66 (44.3%) and 56 (37.6%) in males and 83 (42.3%) and 75 (38.3%) in females. The mandibular teeth were significantly more affected than maxillary, 191 versus 96 and 246 versus 138 while left and right sides were similarly affected, 141 versus 146 and 200 versus 184 in males and females, respectively. The occurrence of bilateral CMPT of lower second premolars and upper second incisors was more common than unilateral CMPT.

The mean ages were 10.65 ± 2.15 years and 10.58 ± 2.03 in males and females, respectively ($p = 0.780$). For each participant with CMPT, OPT of the child not affected with CMPT of the same age and sex (control sample) was matched with the whole sample evaluated in this study. The detailed prevalence and teeth distribution of the children with CMPT in Southern Croatia will be separately published. The data for analysis of the sample included the date of birth and OPT, sex, the specific type, and a total number of missing permanent teeth in each participant with CMPT. We excluded all those with cleft lip and palate, congenital syndromes, and conditions related to CMPT from further analysis. A final sample consisted of 690 OPTs, half with CMPT and half not affected (Table 1).

The development of the permanent teeth in the final sample, except third molars, was evaluated by the Haavikko stages and median ages of the teeth from the upper and lower jaw [18]. Specifically, Haavikko [18] published a method, based on the evaluation of the development of six stages of the crown and six stages of the root and published median ages with 90% confidence intervals (CI) for each permanent tooth from upper and lower jaw. We used this data of age by Haavikko to calculate dental age as the mean age of all existing permanent teeth in the sample with CMPT while dental age not affected was calculated with an exclusion of those missing teeth in CMPT matching pair. All teeth with apex closure or stage "Ac" were excluded from the calculation of dental age. The difference between dental (DA) and chronological age (CA) or DA-CA was compared with paired samples t-test in both sexes. Additionally, the effect of severity of CMPT on DA-CA was evaluated by Spearman correlation coefficients. To investigate affection of the teeth adjacent to the missing ones, we analyzed OPTs with a single tooth missing in one quadrant and not more than missing two permanent teeth, excluding the first incisors and second molars [13]. For this purpose, we compared the stages of corresponding mesial and distal tooth of the place of agenesis to the same teeth of nonaffected participant. Wilcoxon singed-rank test was

Table 2: Underestimation of dental and chronological age (DA-CA) in the children with congenitally missing permanent teeth (CMPT) and nonaffected children (control).

Sex	N	CA (years)	DA (years)	DA-CA (years)	t (df)	p
$\text{Males}_{\text{CMPT}}$	149	10.65 ± 2.15	9.85 ± 2.17	−0.80 ± 0.97	−10.11 (148)	<0.001
$\text{Males}_{\text{CONTROL}}$		10.65 ± 2.15	10.42 ± 1.96	−0.23 ± 0.90	−3.10 (148)	0.002
$\text{Females}_{\text{CMPT}}$	196	10.59 ± 2.04	9.70 ± 1.92	−0.88 ± 1.14	−10.81 (195)	<0.001
$\text{Females}_{\text{CONTROL}}$		10.58 ± 2.03	10.31 ± 1.83	−0.27 ± 0.89	−4.25 (195)	<0.001
$\text{Total}_{\text{CMPT}}$	345	10.61 ± 2.08	9.77 ± 2.02	−0.85 ± 1.07	−14.71 (344)	<0.001
$\text{Total}_{\text{CONTROL}}$		10.61 ± 2.08	10.36 ± 1.88	−0.25 ± 0.89	−5.24 (344)	<0.001

N, a number of participants; CA, chronological age; DA, dental age; DA-CA, difference between DA and CA; t, paired samples t-test; df, degrees of freedom.

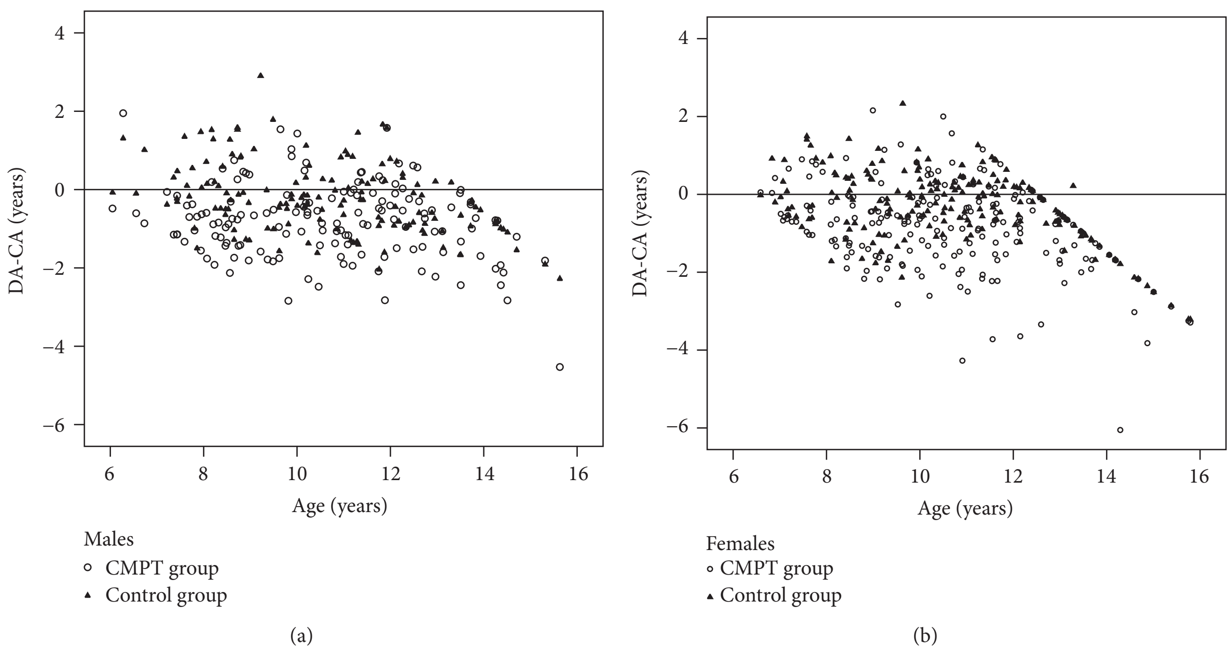

Figure 1: Scatterplot of difference between dental and chronological age (DA-CA) and chronological age (age) for the congenitally missing permanent teeth (CMPT) group and nonaffected group (control group).

used to compare developmental stages. Kappa scores were used to examine intraobserver agreement of Haavikko stages on randomly selected 30 OPGs by the first author after four weeks without knowledge of age and sex.

3. Results

There was no difference between mean chronological age in CMPT and nonaffected groups for males ($p = 0.603$) and females ($p = 0.393$). Dental age, calculated by using the Haavikko standards, was underestimated in both CMPT and nonaffected samples.

Principally, dental age in both sexes was underestimated more in CMPT group, which is statistically significant, Table 2 and Figure 1. Dental development was more delayed in the CMPT children than in nonaffected CMPT (<0.001); the main difference was -0.57 ± 1.20 years and -0.61 ± 1.23 years in males and females without significant difference between sexes ($p = 0.763$).

Figure 2 shows the differences between dental and chronological age and a total number of missing teeth. The majority of the children have one or two missing teeth. The delay in dental development was significantly correlated with the severity of CMPT in females ($p = 0.024$) while in males was not significant ($p = 0.451$).

Adjacent teeth to the place of missing showed a different pattern in sexes. In males, there were no significant delays in neither mesial ($Z = -1.39$, $p = 0.166$) nor distal teeth ($Z = -0.28$, $p = 0.978$). In females mesial teeth are significantly delayed ($Z = -2.72$, $p = 0.007$) while distally teeth were without significant difference ($Z = -0.60$, $p = 0.547$). The greatest difference was at one stage, up to four stages of delay, Figure 3.

The Kappa scores of intraobserver agreement varied between 0.51 for the tooth number 35 and 0.91 for the tooth number 36, with a mean value of 0.68 for maxillary and 0.70 for mandibular teeth which are substantial agreements according to Landis and Koch, Table 3 [20].

Table 3: Kappa scores for intraobserver agreement of the evaluated teeth on the randomly selected 30 orthopantomograms.

Maxillary teeth	*17*	*16*	*15*	*14*	*13*	*12*	*11*	*21*	*22*	*23*	*24*	*25*	*26*	*27*
Kappa score	0.68	0.76	0.65	0.74	0.68	0.55	0.76	0.81	0.61	0.68	0.79	0.56	0.71	0.57
Mandibular teeth	*47*	*46*	*45*	*44*	*43*	*42*	*41*	*31*	*32*	*33*	*34*	*35*	*36*	*37*
Kappa score	0.72	0.81	0.61	0.77	0.68	0.75	0.66	0.65	0.69	0.76	0.73	0.51	0.91	0.60

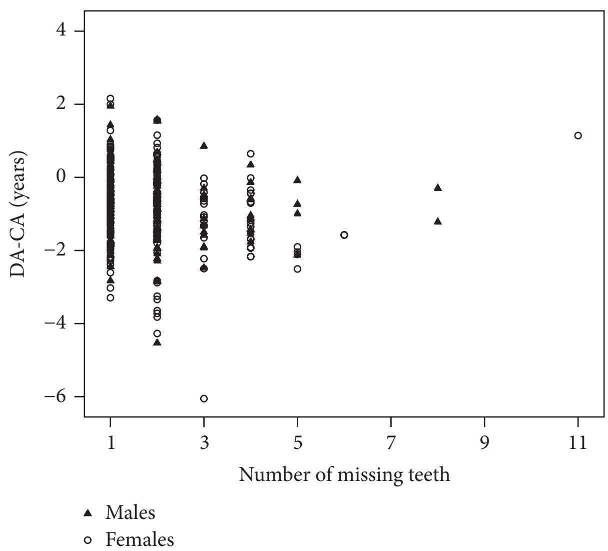

Figure 2: Scatterplot of difference between dental and chronological age (DA-CA) and a number of the congenitally missing permanent teeth in males and females.

4. Discussion

We found a delay in dental development of −0.57 years and −0.61 years in the CMPT group when compared to nonaffected group in males and females, respectively. We also found the similar affection between the left and right sides of the jaws and greater affection of the lower permanent teeth versus the upper. Delayed dental development in orthodontic patients with CMPT may influence the beginning of clinical treatment, treatment plan, and the duration of therapy. Delayed dental age was also reported in males with constitutional delay of growth and puberty [21]. Kan et al. [19] hypothesized that dental delay in children with nonsyndromic CMPT indicates that CMPT may be an expression of disturbance of dental development. Clinical cases with severe hypodontia require both orthodontic correction and implant placement after ending of delayed dental and maxillofacial development [19]. It is still not clear what is the minimal clinically important and biologically relevant difference in a dental age that could affect orthodontic treatment plan and the results of dental age estimation in children with CMPT [22]. However, given the age range of observed children in this study, the difference in dental age of 0.6 years between the CMPT and control groups corresponds to 6% of the observed age range. A difference which is higher than 5% of a range size has been defined as the minimal clinically important differences in other clinical studies as well [23]. Age estimation method in living or dead based on an assessment of mineralization of permanent teeth may not be implemented in case of subjects with CMPT. Most of the methods use lower permanent teeth, and these are the teeth most likely to be affected with agenesis.

The delay was smaller than that in other studies which used the Haavikko method. Uslenghi et al. [13] reported the delay of −1.53 years for the total sample and Rune and Sarnäs [12] reported −1.8 years for males and −2.0 years for females. Ruiz-Mealin et al. [24] used Haavikko and Demirjian stages and reported also underestimated dental age when compared to nonaffected group. Principally, dental age was underestimated by −0.88 years in males and −0.60 years in females for Haavikko method and by −0.84 years for males and −0.87 years for females for Demirjian method [24]. Tunç et al. [25] applied Demirjian standards and also found the delay in the children with hypodontia when compared to nonaffected group; the mean delay did not exceed 0.3 years in either sex. Odagami et al. [17], in their study on 77 males and 100 females using Moorrees radiographic stages, also showed the delay of dental development which was not statistically significant. Lozada Riascos and Infante Contreras [16] also reported the insignificant delay in dental development of 0.7 years for males and 1.0 years for females. The most recent Danish study also reported −0.37 to −0.50 years in dental development when compared to nonaffected dentition [14].

A significant association between severity of agenesis and delay in development was found in females in our study while Uslenghi et al. [13] also reported a significant association, without an evidence of the difference for the specific sex. Odagami et al. [17] also reported a significant association, while the study of Lozada Riascos and Infante Contreras [16] found no significant association between development and sex or the number of missing teeth. Tunç et al. [25] found no correlation between the differences in dental and chronologic age and the severity of CMPT.

Our study showed a different pattern in delay of the teeth adjacent to the place of the agenesis. Only females demonstrated a statistically significant delay in the distal adjacent teeth. Uslenghi et al. [13] revealed that the teeth adjacent to the position of the agenesis, both mesial and distal, were significantly delayed compared to the corresponding teeth in the matched group. Daugaard et al. [26] evaluated dental maturity in the mandibular canine, premolar, and molar innervation fields in children with agenesis of the mandibular second premolars, by using Haavikko's approach. A development of canines was delayed in those with unilateral CMPT, with a larger delay in females, while the second molar was not delayed in males but was in females [26].

In orthodontic practice, it is important to understand normal dental development clearly and to recognize those

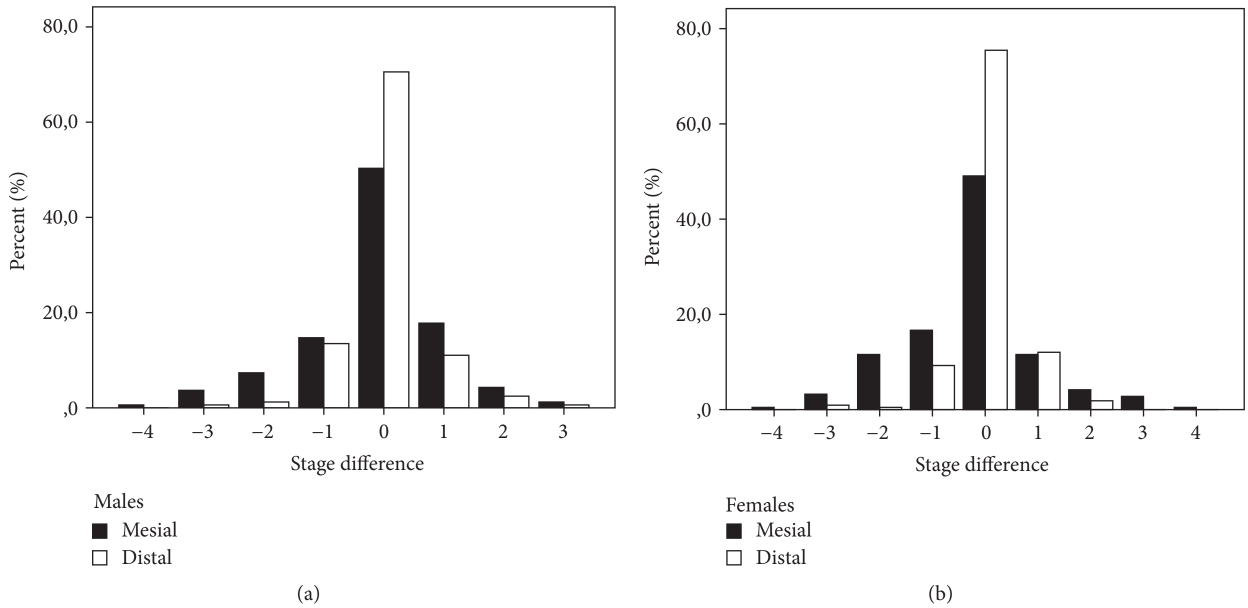

Figure 3: Distribution of stage differences of adjacent teeth in males and females.

patients with agenesis to plan orthodontic treatment in a proper manner, with right starting time and duration [15]. Population studies have investigated a large number of children who were orthodontic patients. Although the proportion of those with hypodontia was higher compared to the general population, data collected on this orthodontic population is considered to be reliable and was included in the meta-analysis of the prevalence of CMPT [7]. Evidence of difference in the dental development of the children with CMPT should be taken into account when calculating the dental age for different purposes because various dental methods have been recognized as a reliable approach for estimating biological maturity. Dental age can help estimate someone's age in forensic, civil, and archaeological investigations.

5. Conclusion

A delay of −0.57 years in females and −0.61 years in males in dental age was found in the children with CMPT compared to nonaffected group ($p < 0.001$). A delay was noticed in females in the mesial teeth adjacent to the location of CMPT compared to the teeth from the control group ($p = 0.024$). Only females showed a significant correlation between the number of missing teeth and severity of delay of development ($p = 0.007$). These findings should be taken into account because they can impact the orthodontic treatment plan and the results of dental age estimation in children with CMPT.

Competing Interests

The authors declare that they have no competing interests.

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Review Article

Temporomandibular Joint Anatomy Assessed by CBCT Images

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Aim. Since cone beam computed tomography (CBCT) has been used for the study of craniofacial morphology, the attention of orthodontists has also focused on the mandibular condyle. The purpose of this brief review is to summarize the recent 3D CBCT images of mandibular condyle. *Material and Methods*. The eligibility criteria for the studies are (a) studies aimed at evaluating the anatomy of the temporomandibular joint; (b) studies performed with CBCT images; (c) studies on human subjects; (d) studies that were not clinical case-reports and clinical series; (e) studies reporting data on children, adolescents, or young adults (data from individuals with age ≤ 30 years). Sources included PubMed from June 2008 to June 2016. *Results*. 43 full-text articles were initially screened for eligibility. 13 full-text articles were assessed for eligibility. 11 articles were finally included in qualitative synthesis. The main topics treated in the studies are the volume and surface of the mandibular condyle, the bone changes on cortical surface, the facial asymmetry, and the optimum position of the condyle in the glenoid fossa. *Conclusion*. Additional studies will be necessary in the future, constructed with longitudinal methodology, especially in growing subjects. The limits of CBCT acquisitions are also highlighted.

1. Introduction

Radiological images are indispensable in orthodontic diagnosis, as they have increased the accuracy of diagnosis. Since three-dimensional (3D) diagnostic imaging has been diffused for the study of craniofacial morphology, the attention of orthodontists has also focused on the study of the anatomy of the mandibular condyle. As the condyle is the primary center of growing in the mandible and is a special cartilage (secondary cartilage), it answers the continuous stimuli through a remodeling process from childhood to adulthood [1]. The functional stimuli act through a remodeling of the subchondral bone volume, as assessed in rats and mice [2] (the most prevalent bony changes of the condyle are, for example, the flattening, the erosion, the sclerosis, the presence of osteophytes, and the resorption) [3]. Functional stimuli can be represented also by a disc displacement as shown in the rabbit joints [4] which was demonstrated to cause an enlargement of the condyle, which is in part caused by hyperplasia of the condylar cartilage and partly by an increase of the surface area of nonarticulating portion of the condyle.

The study of the condylar morphology is important to understand the complex mechanism of interdependence between form and function during the growing process.

Cone Beam Computed Tomography (CBCT) has been introduced as CBCT scanner in 1982 at Mayo clinic; it began to be marketed during 1990s [5]. Initially, the CBCT scanners had been extensively used in the field of medical clinical imaging [6]. Since then, the CBCT scanner systems have evolved a lot. Today, they are used in various sectors of diagnostic imaging in medicine [6]. The CBCT images are considered very useful in joint visualization of the temporomandibular joint (TMJ), among all the other methods [7]: (a) the *panoramic radiograph* does not show very well the condylar anatomy, its variation, and its adaption to the functional stimuli; it is a simple exam to obtain; so it is very easy to be obtained but not always useful [8]. (b) The *lateral radiographs* of the skull present too much overlapping images of other anatomical structures; in addition they do not

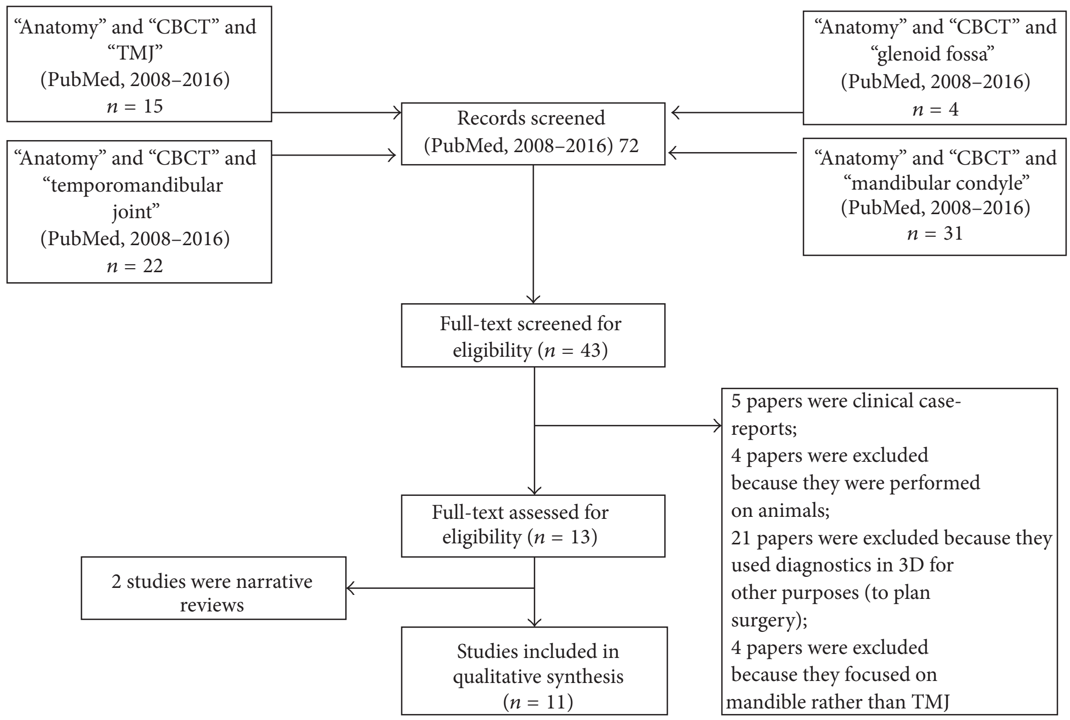

Figure 1: Flow chart of the study.

visualize soft tissues. (c) The *correct axial tomography* gives a well view of the erosions and osteophytes on the surface of condyle [9], but their visualization and interpretation are not easy, as the other structures are often not represented to reduce overlap; so it is not easy to study the whole anatomy of the condyle [7]. (d) The *computed tomography* (CT) is valid, in both clinics and research, for the visualization the mandible [10] but the device has a high cost, so it was finally confined in public hospital structures because it requests infrastructure [5].

The CBCT images are considered to evidence very well the temporomandibular joint (TMJ). The purpose of this brief review is to summarize the recent 3D CBCT images of mandibular condyle.

2. Material and Methods

The eligibility criteria for the studies are as follows: (a) studies aimed at evaluating the anatomy of the temporomandibular joint; (b) studies performed with CBCT images; (c) studies on human subjects; (d) studies that were not clinical case-reports and clinical series; (e) studies reporting data on children, adolescents, or young adults (data from individuals with age ≤ 30 years). No language restriction was applied. Sources included PubMed from June, 2008 to June, 2016. A search strategy using three different keywords was developed, including "anatomy," "CBCT," and "mandibular condyle" (this latter term has also been flanked with "temporomandibular joint," "glenoid fossa," "temporomandibular joint disc," and "TMJ"). The terms were combined together using the Boolean conjunction "and." Additionally, hand searching was applied to the reference list of retrieved articles.

2.1. Data Extraction. Data were extracted from the studies about the sample size, both the number of individuals and the number of TMJs observed, because both the right and left TMJs were observed in the majority of the studies, and the results are reported with particular reference to the differences between left and right TMJs (to investigate the symmetry). The data were extracted relative to the gender distribution and range of age in the samples. Furthermore, the methodological structure of the same research has been extracted for each study. Finally, for each study, data about the results were reported (Table 1). The quality of the studies is established by the assignment of scores to each full-text article included in the qualitative analysis. The quality of each study, with a maximum possible score of 11, was considered as follows: low: total score ≤ 4; medium: 5 ≤ score ≤ 8; high: score ≥ 9 (Table 2).

3. Results

The results of the searches are summarized in a flow chart of Figure 1.

43 full-text articles were initially screened for eligibility. Then the following papers were excluded: 5 papers were clinical case-reports; 4 papers were excluded because they were performed on animals; 21 papers were excluded because they used diagnostics in 3D for other purposes (to plan surgery); 4 papers were excluded because they focused on mandible rather than TMJ. Finally, 13 full-text articles were

Table 1: Data from the studies.

Authors	Year	Type of study	Number of TMJs	Sample	Title
Saccucci et al. [11]	2012	Observational study	188 TMJs	94 patients (46 females and 48 males; 15–30 years old)	Resultant rendering reconstructions of the left and right temporal mandibular joints (TMJs) were obtained. Subjects were then classified on the basis of ANB angle in three classes (I, II, III). The data of the different classes were compared.
Saccucci et al. [12]	2012	Observational study	400 TMJs	200 patients (15–30 years old, 95 males and 105 females)	The condylar volume, the area, and the morphological index (MI) were compared among class I, class II, and class III young adult subjects.
Huntjens et al. [13]	2008	Observational study	40 TMJs	20 patients (14 girls and six boys; mean age 11.21 ± 3.54 years)	Condylar asymmetry and a wide variety of condylar destruction patterns were observed in children with juvenile idiopathic arthritis assessed by cone-beam computed tomography.
Zhang et al. [16]	2014	Cross-sectional study	42 TMJs	42 TMJs evaluated by 7 dentists	42 temporomandibular joints were scanned, respectively, with the CBCT units ProMax® 3D (Planmeca Oy, Helsinki, Finland) and DCT PRO (Vatech, Co., Ltd., Yongin-Si, Republic of Korea) at normal and high resolutions. Seven dentists evaluated all the test images.
Barghan et al.	2012	Review	/	/	Application of cone beam computed tomography for assessment of the temporomandibular joints.
Dos Anjos Pontual et al. [17]	2012	Observational study	638 TMJs	319 patients (250 women and 69 men, range 10–89 years old) *Data from adult subjects were excluded*	The differences in percentage of bone changes among the categories of mobility were compared (ipo, iper, normo, and based on mouth opening) and the right and left sides.
Alexiou et al. [3]	2009	Observational study	142 TMJs	71 patients (60 females and 11 males) (20–75 years old) *Data from adult subjects were excluded*	Evaluation of the severity of temporomandibular joint osteoarthritic changes related to age using cone beam computed tomography.
Farronato et al. [14]	2010	Observational study	60 TMJs	30 children (8–13 years old)	The mandible was isolated from other craniofacial structures; the whole mandibular volume and its components' volumes (condyle, ramus, hemibody, and hemisymphysis on right side and on left side) were calculated.
L. Palomo and J.M. Palomo [18]	2009	Review	/	/	Cone beam CT for diagnosis and treatment planning in trauma cases.
Schlueter et al. [19]	2008	Cross-sectional study	50 condyles	/	Three linear three-dimensional measurements were made on each of the 50 condyles at 8 different Hounsfield unit (HU) windows. These measurements were compared with the anatomic truth.

Table 1: Continued.

Authors	Year	Type of study	Number of TMJs	Sample	Title
Zhang et al. [20]	2016	Case-control study	20 TMJs	5 patients with facial asymmetry and 5 asymptomatic subjects, mean age, 26 ± 1.2 years	The TMJ spaces and condylar and ramus angles were assessed and compared between the groups.
Illipronti-Filho et al. [21]	2015	Observational study	40 TMJs	9 males (mean 7.9 years) and 11 females (mean 8.2 years)	Dimensional measurements of the condyles between the right and left sides and crossed and noncrossed sides in sagittal and coronal view were made.
Ikeda et al. [22]	2011	Observational study	24 TMJs	10 males, 12 females; range 12–25 years old	Joint-space distances between the condyle and glenoid fossa were measured at the medial, central, and lateral positions in the coronal plane and medial and lateral positions in the axial plane.

assessed for eligibility. Two articles were review, and 11 articles are finally included in the qualitative synthesis. One study is with case-control construction; two studies with cross-sectional structure. All the other studies are observational analyses. More data about the studies are reported in Table 1.

The quality level of the studies was judged to be medium for ten studies and low for one study (Table 2). Thus, the overall level of the studies on this topic is judged to be merely adequate. The level of quality is mainly affected by the lack, actually in literature, of prospective longitudinal reports that could really clarify what happens inside the TMJs during the long period of craniofacial growth and development.

4. Discussion

The purpose of this brief review is to summarize data on the study of TMJ through CBCT images during the period of craniofacial growth development (data derived from samples of children, adolescents, and young adults, i.e., individuals aged ≤ 30 years). A great body of literature concerning the TMJ visualization in CBCT images dates back to recent years. Contrary to what one might consider, CBCT images are not widely used to study the pure anatomy of the joints.

The findings of the studies included in this review can be divided into the following broad topics: (a) the evaluation of the volume and surface of the mandibular condyle; (b) the visualization of the bone changes on the cortical surface; (c) the comparison between the two condyles in cases of facial asymmetry; (d) the linear dimensions of the condyle; and (e) the optimum position of the condyle in the glenoid fossa.

4.1. CBCT 3D Imaging Allows the Calculation of Volume and Surface of the Mandibular Condyle. CBCT three-dimensional reconstructions allow the calculation of volume and surface of the mandibular condyle. Saccucci et al. (2012) [11] report that, in Caucasian young adults and adolescents (data from a sample of individuals with a range of 15–29 years, mean age 19.2 years), with varied malocclusions, free of pain or dysfunction of TMJs, the condylar volume is 691.26 ± 54.52 mm^3 in males and 669.65 ± 58.80 mm^3 in females and significantly higher in the males compared to females. The same is observed for the condylar surface, although without statistical significance (406.02 ± 55.22 mm^2 in males, and 394.77 ± 60.73 mm^2 in females). The Morphometric Index (MI, the volume to surface ratio) is 1.72 ± 0.17 with no significant difference between males and females or the right and left sides.

The same authors report that, in Caucasian young adults and adolescents (15–30 years old) [12], subjects in skeletal class III have a significantly higher condylar volume, with respect to class I and class II subjects, while class II subjects show lower condylar volume, with respect to individuals with class I and class III skeletal relationship.

In Caucasian young adults and adolescents [11] mandibular condyle shows a significantly higher volume and surface in low angle subjects (individuals with low mandibular divergence), compared to the high and normal angles groups (individuals with high and normal mandibular divergence).

By the calculation of condylar volume and the index of asymmetry between the right and the left condylar volumes, CBCT three-dimensional reconstructions allow the diagnosis of early stages of juvenile idiopathic arthritis (JIA) in growing individuals (data derived from a sample of 14 girls and 6 boys with a mean age of 11.21 ± 3.54) [13]. Condylar head volume in growing individuals with JIA is about 844 mm^3 (median value), with a statistically significant asymmetry between the right and the left condyles of about 26% in their volume. In addition, the analysis of CBCT images allows the detection of early *qualitative* signs of JIA that range from small erosions within the cortex to almost complete deformation of the condylar head [13]. It has been stated that early stages of JIA can be detected by CBCT imaging even before this disease has yet caused damages to the individual's facial development during growth [14].

4.2. CBCT 3D Imaging Improves Qualitative Analysis of Condylar Surface and Allows Detecting Mandibular Condylar Shape. In Caucasian young adults and adolescents (data from

Table 2: Quality of the studies.

Authors	Type of study	Sample selection adequacy based on age range across the group/s	Sample selection adequacy based on gender across the group/s	Description of at least an error analysis method	Complete description of technical data about CBCT acquisition	Description of blinding procedure	Prior estimation of sample size or a posteriori power analysis	Points
	Longitudinal Construction: 2 Other methods: 1 Not defined: 0	Full: 2 points: properly and clearly detectable data according to age range (i.e., data derived from groups of children or adolescents, or young adults, or adults) Partial: 1 point Not: 0 point	Full: 2 points Balanced distribution of males and females and separate reports for males and female Partial: 1 point No: 0 point	Yes: 1 point No: 0 point	Complete: 2 Partial: 1 Insufficient: 0	Yes: 1 point No: 0 points	Yes: 1 point No: 0 points	
Saccucci et al. [11]	+ Observational study	+ 15–30 years old (adolescents and young adults)	++ 94 subjects: 46 females and 48 males;	+	+	0	+	7
Saccucci et al. [12]	+ Observational study	+ 15–30 years old (adolescents and young adults)	++ 200 subjects: 95 males and 105 females	+	+	0	+	7
Huntjens et al. [14]	+ Observational study of children with Juvenile idiopathic arthritis	+ Mean age 11.21 ± 3.54 (adolescents and children)	+ 20 patients: 6 males and 14 females	0	++	0	0	5
Zhang et al. [16]	+ Cross-sectional study	0 42 TMJs from 21 dry human skulls not identified for age	0 42 TMJs from 21 dry human skulls not identified for gender	+	++	0	0	4
Dos Anjos Pontual et al. [17]	+ Observational study	++ Range 10–89 years old (adolescents, young adults, and adults)	+ 319 subjects: 69 males and 250 females	+	+	0	0	5
Alexiou et al. [3]	+ Observational study	++ Range 20–75 years old (adolescents, young adults, and adults)	+ 71 subjects: 11 males and 60 females	+	+	0	0	6

Table 2: Continued.

Authors	Type of study	Sample selection adequacy based on age range across the group/s	Sample selection adequacy based on gender across the group/s	Description of at least an error analysis method	Complete description of technical data about CBCT acquisition	Description of blinding procedure	Prior estimation of sample size or a posteriori power analysis	Points
Farronato et al. [14]	+ Observational study of children with Juvenile idiopathic arthritis	++ 30 subjects range 8–13 years old	+	+	+	0	+	7
Schlueter et al. [19]	+ Cross-sectional study	0 50 TMJs from 25 dry human skulls not identified for age	0 50 TMJs from 25 dry human skulls not identified for gender	0	++	0	0	3
Zhang et al. [20]	+ Case-control study	++ 10 subjects (5 cases and 5 controls) mean age, 24.8 ± 2.9 among cases and 26 ± 1.2 years among controls (young adults)	++ 10 subjects (2 males and 3 females as cases and 2 males and 3 females as controls)	+	+	0	0	7
Illipronti-Filho et al. [21]	+ Observational study	++ 9 males (mean 7.9 years) and 11 females (mean 8.2 years) (children)	++ 20 subjects: 9 males and 11 females	+	+	0	+	8
Ikeda et al. [22]	+ Observational study	+ 10 males and 12 females range 12–26 years old (adolescents and young adults)	++ 22 subjects: 10 males and 12 females	+	+	0	0	6

a sample with mean age 19.2 years; range: 15–29; 74 males and 76 females), CBCT three-dimensional reconstructions allowed establishing that the shape of the condylar head is more frequently *round*, compared to *oval*, followed by a *flattened* form, and, at last, a *spiked* form [15]. In addition, it has been established that CBCT images allow well evidence of signs of adaption (*qualitative analyses*) on the condylar surface [16], whatever the age of the individual is (data derived from a sample of 42 TMJs obtained from 21 dry human skulls, not identified by age, sex, or ethnicity and with no demographic data available). Consequently, the qualitative view of the condylar head surface, looking for signs of adaption, is one of the most common clinical applications of the CBCT images, as also pointed out in a recent review of the literature [17]. Degenerative changes of the mandibular condyle are undeniably more common in individuals over 40 years old [3], because the prevalence of bone changes increases with age [17], but about 40% of young individuals aged 10–29 years seem to show bone changes in their TMJs, and these bone changes are well detectable using CBCT images (data extrapolated from 52 individuals ranged 10–29 years old, adolescent and young adult subjects, included in a greater sample, aged between 10 and 89 years) [17]. Among the bone changes, the small *erosions* of the surface are the more common among adolescents and young adults and can be effectively detected with CBCT images using a FOV (field of view) of 6 inch. The *flattening* and the *osteophytes* are instead more frequent in adults and old subjects and well detected by CBCT images [17]. CBCT is additionally intended to be the superior method to acquire adequate information on the extent, the nature, and precise location of TMJ fractures, in growing individuals who have suffered severe maxilla-facial trauma, with the involvement of the TMJ [18]. CBCT images are not suitable to view inflammatory reactions (e.g., marrow oedema) or to view synovia or cartilage or changes in the deeper zones of the condylar head (e.g., cysts), because the segmentation of the structures, based on the thresholding, is restricted to the delineation of the cortical region in those cases where the cortex had not yet reached its final maturity and density, as it happens in growing individuals [13]. Therefore, in these cases, the segmentation is restricted to delineating only the cortical region, without taking possible changes in the deeper zones into account.

4.3. CBCT 3D Imaging Improves the Accuracy of Linear Measurements of Mandibular Condyle (Width, Length, and Height). The most recent literature states that CBCT images are reliable to evaluate the linear measurements of the condyle: the condylar length (linear distance between anterior point of mandibular condyle and posterior point of mandibular condyle), the condylar width (linear distance between the lateral point and the medial point of mandibular condyle), and the condylar height (linear distance between superior point of mandibular condyle and mandibular lingula), as ascertained by data obtained from a sample of 25 dry skulls, for which the age and gender distribution were not known [19]. One of the latest recommendations, on this topic, is that the linear measurements of the condyle appear more accurate when they are measured through images at density levels below those recommended for osseous examination, which extend into the soft tissue range. These lower density levels may compromise the clinician's capacity to view the bone topography of the whole condylar structure. Consequently, when the aim is to perform the linear measurements of the condyle, it will be not appropriate to perform a global analysis on its shape and volume by the same images and vice versa.

4.4. CBCT 3D Imaging Clarifies That, in Cases of Facial Asymmetry, Mandibular Condyles Are Often Symmetric, While Joint Space Can Change between the Two Sides. One of the principal clinical situations associated with the study of the condylar morphology is that of facial asymmetry, mostly in groups of children, adolescents, or young adults.

The CBCT images have contributed to clarifying that in spite of the facial asymmetry, the size of the condyles does not seem to differ between the two sides of the face, in young adult subjects, while what seems to suffer from facial asymmetry is mostly the vastness of the intra-articular spaces. In other words, during the craniofacial growth period, it is witnessing a continuous shift of the condyles in the articular fossae, and this may result in differential growth phenomena between the two sides, but it seems that these differences should not necessarily lead to anatomical asymmetry of the mandibular condyles, while what seems to suffer of facial asymmetry is mostly the vastness of the intra-articular spaces. The TMJ intra-articular spaces are well detectable by CBCT images [20], as showed by a small case-control study which recruited 5 patients diagnosed with facial asymmetry (the cases, 3 females and 2 males with mean age: 24.8 ± 2.9 years) and 5 asymptomatic subjects (the controls, 3 females and 2 males, with mean age, 26 ± 1.2 years) [20]. While no difference in the size of condyle (the coronal condylar width) in either group was observed between the two sides or between the study and the control subjects, some differences were detected in joint space. The superior space of the joint became significantly smaller, compared to control individuals, in both nondeviation and deviation side. Because of the small sample (5 cases and 5 controls), however, it should be emphasized that the data from this study have at least a doubtful reliability.

In addition, in young adults with facial asymmetry, the coronal condylar angle appears significantly different between the two sides and also remarkably larger with respect to asymptomatic subjects [20]. In individuals with facial asymmetry the angle measures 19.18 degrees. In addition, the horizontal condylar angle in young adults with facial asymmetry also is significantly larger than in the asymptomatic subjects, no matter on the nondeviation or the deviation side. This increase of the condylar angles may probably cause the rise of the condylar ridge, and then it may lead to the aggravation of the squeezing in the disc and other soft tissues in the TMJ [20]. In individuals with facial asymmetry, the medial and the anterior joint spaces are different between the left and right sides [16], because the spaces of the nondeviation side are significantly smaller than those on the deviation side. Meanwhile, the medial space in the patients group is significantly smaller than that in the control group on both sides. The lateral and the superior joint space of patients with facial asymmetry appear observably larger than for asymptomatic subjects.

The authors indicate that the decrease of the joint space for the patients with facial asymmetry may lead to the articular disc suffering severe squeezing. This severe squeezing may lead to the joint pain, disc perforation, or other TMJ dysfunctions, which are the common symptoms of the TMJ dysfunction. Data detected from children with occlusal asymmetry (from a sample of 20 Brazilian children, aged 7–10 years: 9 males, mean age 7.9, and 11 females, mean age 8.2 years, affected by unilateral posterior cross-bytes, without premature contacts or functional mandibular shift but with transverse maxillary deficiency, i.e., not functional cross-byte, but anatomical!), by CBCT images, allow confirming the absence of differences in condylar size between the crossed and noncrossed sides [21]. In children, mandibular condylar width results in about 14.1 ± 1.78 mm in the crossed side and 14.56 ± 1.79 mm in the control side, while condylar length is 6.58 ± 0.85 mm in the crossed side and 6.63 ± 0.66 mm in the control side [21].

4.5. CBCT 3D Imaging Clarifies the Position of the Condyle in the Glenoid Fossa. The condylar position in the glenoid fossa is well defined by CBCT images.

In young adults, (data derived from 24 TMJ from a Japanese sample of 22 asymptomatic patients with optimal joints function, ranged 12–26 years, mean age 18 years, 10 males and 12 females) the following optimal joint spaces are reported [22].

The optimum mean joint spaces in the coronal view, that is, the coronal lateral space, the coronal central space, and the coronal medial space, are, respectively, 1.8 ± 0.4 mm, 2.6 ± 0.4 mm, and 2.3 ± 0.4 mm, in males, and 1.8 ± 0.4 mm, 2.7±0.6 mm, and 2.4±0.7 mm in females, respectively, with no significant sex differences in these measurements. The mean spaces from the axial view, that is, medial axial space and lateral axial space, are 2.1 ± 0.6 mm and 2.2 ± 0.7 mm, in males, respectively, and 2.2 ± 0.6 mm and 2.4 ± 0.6 mm, in females, respectively, with no significant sex differences in these measurements [22].

These data clarify that in young individuals joint space is smaller laterally than centrally or medially in the coronal view. In the axial view, instead, data indicate that the condyle is nearly centred within the fossa, when observed axially, in a normal joint. The ratio among lateral, central, and medial spaces in the coronal view is 1 to 1.5 to 1.3, while the ratio between lateral and medial spaces in the axial view is 58% to 52% [22].

Summary. One of the most important benefits achieved through the CBCT images is the ability to calculate volume and surface of the condyle, potentially useful to study the TMJ development during growing period [11, 15].

In addition, CBCT images have helped to clarify that, in cases of facial asymmetry, mandibular condyles are symmetric in volume and size (although the condyle is the main growth center of the mandible), while differences are detectable only in the amplitude of mandibular joint spaces.

In addition, thanks to CBCT images, it has been possible to establish the extent of the optimum joint space on coronal and axial planes in the glenoid fossa in young individuals.

The starting point of all these studies is the condition that the mandibular condyle holds remodeling abilities that persist throughout one's life. It is histologically characterized by the presence of a layer of undifferentiated germinative mesenchyme cells, a layer of cartilage, and the presence of islands of chondrocytes in the subchondral trabecular bone. This adaptable structure allows answering different force vector against the condyle during mastication [23].

Although the CBCT images have clarified form, volume, surface, location, and symmetry of the condyles, there is still a need to develop longitudinal research protocols to clarify the normal growing process of the TMJ. Owing to ethical constraints, it is known that is not possible to schedule successive radiographic procedures over time in health subjects, and for this, longitudinal studies are rendered more difficult, although CBCT provides low radiation dose. The lack, actually in literature, of prospective longitudinal reports depends primarily on ethical and overall health reasons, which preclude the possibility of performing repeated acquisitions on healthy individuals.

The segmentation of the mandibular condyle is based on 2D Digital Imaging and Communications in Medicine (DICOM), created with CT data set. Software as the Mimics™ software 9.0 (Materialise NV Technologielaan, Leuven, Belgium) can be used. Each condyle must be visualized in the recommended bone density range (range of gray scale from 1350 to 1650) and then graphically isolated prior to the 3D measurements. Frankfort horizontal (FH) plane can be constructed by creating a plane from the inferior orbital rim to the superior border of the external auditory meatus. The initial segmentation can be made parallel to the FH plane just above the superior aspect of the condyle [11]. Then, the area of TMJ can be graphically enlarged, and the remaining surrounding structures can be progressively removed using various graphical sculpting tools for the upper, the lower, and the side condylar walls.

The upper limit of the condyle was defined where the first radiopaque area was viewed in the area of synovia; then, for each of the lower sections, the condyle was isolated through the visualization of cortical bone. The lower limit of condyle was traced when the section left the ellipsoidal shape (due to the presence of the anterior crest) and became circular suggesting the level of the condylar neck. Once the computer isolations were made, three-dimensional multiplan reconstructions were produced for each condyle.

Volumetric measurements were made for each condyle with the Mimics automatic function.

Another limitation of the studies available in the current literature is that sometimes, accurately and unequivocally, all the parameters useful to understand how the acquisitions and the image processing have been performed are not indicated. This aspect can affect the reliability about the repeatability of procedures. Moreover, there is still a considerable difficulty by dentists to set and standardize the acquisition parameters of their device, as many studies published in the literature do not report acquisition parameters clearly. In this review, for example, only 3 studies over 11 report accurate and unequivocally complete data about CBCT acquisition. Although, in any case, it can be emphasized that most of the studies report their error analyses method, as observed in 9 out of 11 studies included in this review.

In general, in all the studies, there is a unanimous conclusion in promoting CBCT as a useful aid for displaying the TMJ, although there are still some technical problems, highlighted by several authors.

5. Limitations of the CBCT Acquisition

The issue of the artifacts associated with the patient's accidental movements during the acquisition is not yet resolved, which can be a problem in the pediatric population, especially in case of no compliance. In addition, a further technical problem is the Hounsfield Units (HU) distortion, so that CBCT cannot be used to estimate bone density (bone density is estimated using micro-CT). A further limitation is that the decrease of the radiation dose is accompanied by a proportional decrease in image quality, especially with regard to the contrast resolution, so the soft tissues are not displayed well, especially if internally positioned, near to bone structures [24], such as, the TMJ articular disc. Finally, in growing individuals, CBCT imaging has some limitations when it tries to highlight the changes in the deeper structures of the condylar head (e.g., cysts) that are not well detectable with CBCT images if the cortex of condylar head has not yet reached its final maturity and density. This seems to happen because the segmentation of the CBCT images is based on the thresholding and, when the cortex is not mature, is consequently restricted to delineate the cortical region, without taking possible changes in the deeper zones into account.

This brief review represents only an initial classification of recently published data.

Although CBCT helped to clarify some aspects of the morphology of the mandibular condyle (form, volume, surface, location, and symmetry of the condyles) additional studies will be necessary in future, constructed with longitudinal methodology, especially in growing subjects.

Competing Interests

The authors declare that they have no competing interests.

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Review Article

The Gingival Crevicular Fluid as a Source of Biomarkers to Enhance Efficiency of Orthodontic and Functional Treatment of Growing Patients

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Gingival crevicular fluid (GCF) is a biological exudate and quantification of its constituents is a current method to identify specific biomarkers with reasonable sensitivity for several biological events. Studies are being performed to evaluate whether the GCF biomarkers in growing subjects reflect both the stages of individual skeletal maturation and the local tissue remodeling triggered by orthodontic force. Present evidence is still little regarding whether and which GCF biomarkers are correlated with the growth phase (mainly pubertal growth spurt), while huge investigations have been reported on several GCF biomarkers (for inflammation, tissue damage, bone deposition and resorption, and other biological processes) in relation to the orthodontic tooth movement. In spite of these investigations, the clinical applicability of the method is still limited with further data needed to reach a full diagnostic utility of specific GCF biomarkers in orthodontics. Future studies are warranted to elucidate the role of main GCF biomarkers and how they can be used to enhance functional treatment, optimize orthodontic force intensity, or prevent major tissue damage consequent to orthodontic treatment.

1. Introduction

Gingival crevicular fluid (GCF) (Figure 1) is a biological exudate and quantification of its constituents is a current method to identify specific biomarkers with reasonable sensitivity [1]. Its formation was first defined by Alfano [2]. At sites in the absence of inflammation and subgingival plaque, the production of GCF is mediated by passive diffusion of the extracellular fluid by an osmotic gradient. In this situation, the GCF is considered as a transudate. When an inflammatory response is provoked by compounds of microbial origin, the permeability of the epithelial barrier and the underlying vasculature increases and the GCF protein concentration is now modulated by extent of plasma protein exudation. Subsequently, the GCF is considered an inflammatory exudate.

The GCF is a mixture of substances derived from serum, host inflammatory cells, structural cell of the periodontium, and oral bacteria [3, 4]. The molecules isolated from the sulcular fluid include electrolyte, small organic molecules, proteins, cytokines, specific antibodies, bacterial antigens, and enzymes of both host and bacterial origin [5, 6]. The host-derived substances in the GCF include antibodies, cytokines, enzymes, and tissue degradation products [7, 8].

The analysis of GCF is a very useful diagnostic instrument to both periodontology and orthodontics. The correlations between the levels of many host GCF biomarkers and periodontal diseases have been extensively studied and the predictive values for the biomarkers as summarized in Table 1 [9–12]. In orthodontics, biomarkers related to bone deposition (bone alkaline phosphatase and osteoprotegerin) represent new possibilities for the understanding of bone growth and remodeling [13]. The possibility of identifying the bone turnover in children and juvenile subjects can help orthodontists to decide when to intercept a malocclusion. The biomarkers found in GCF also permit the monitoring of

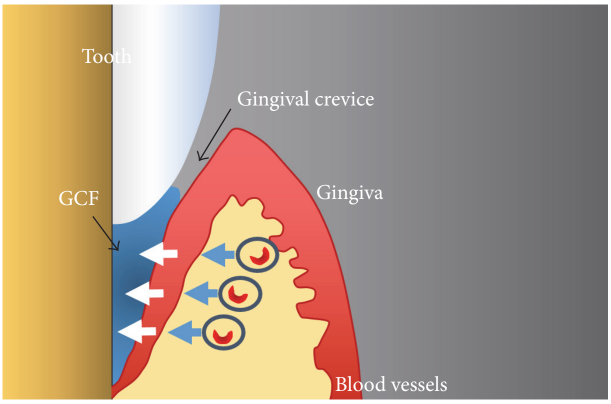

Figure 1: The gingival crevicular fluid (GCF) formation. The GCF flow is an interstitial fluid which appears in the crevice as a result of an osmotic gradient.

Table 1: Main GCF host biomarkers according to biological significance.

Bone deposition and mineralization
Bone alkaline phosphatase
Osteoprotegerin
Bone resorption
Osteonectin
Bone phosphoprotein
Osteocalcin
Cross-linked carboxyterminal telopeptide of type I collagen
Receptor activator of nuclear factor kappa-B and its ligand
Inflammation
Cytokines (interleukins, tumor necrosis factors, interferons, growth factors, and colony-stimulating factors)
Arachidonic acid derivates (prostaglandins, leukotrienes)
Neutrophil alkaline phosphatase
Hydroxyproline
Collagen cross-linking peptides
Others
Cell death or tissue damage
Aspartate aminotransferase
Lactate dehydrogenase
Hydroxyproline
Collagen cross-linking peptides
Glycosaminoglycans
Metalloproteases (proteolytic enzyme)
Cathepsin B (proteolytic enzyme)
Antibodies

the orthodontic movement and consequences of the forces applied through its level's variations.

The biomarkers found in GCF are interleukins, tumor necrosis factor-alfa prostaglandin E2, osteocalcin, RANK, OPG, RANKL, TGF-β1, matrix metalloproteinases, acid and alkaline phosphatase (ALP), aspartate aminotransferase (AST), IL-1RA, interferon-gamma, and others [14]. These biomarkers can be divided into six categories: biomarkers of cell death, tissue damage, inflammation, bone resorption, bone deposition and mineralization, and other biomarkers [14].

There are three methods to collect the gingival crevicular fluid. The gingival washing technique consists of perfusing the GCF with an isotonic solution, as Hank's balanced solution, with fixed volume. The fluid collected represents a dilution of crevicular fluid, containing cells and soluble constituents, as plasma proteins. Another method is inserting capillary tubes, with specific diameter, into the entrance of the gingival crevice and the fluid migrates into the tube by capillary action [15]. However, the most used method for GCF collection is made with specifically designed absorbent filter paper as endodontic paper points or periopapers (Figure 2). The paper strips are inserted into the gingival crevice and left in situ for 5 to 60 seconds to allow the GCF to be adsorbed by the paper [16].

The purpose of this review is to identify the biochemical markers present in the gingival crevicular fluid and their relevance to identify the growth phase and as well analyze the expression of the biomarkers during the orthodontic movement in children and young subjects.

2. Identification of Growth Phase

The decision to intercept orthopedically on a growing patient depends primarily on the identification of his skeletal maturation phase. The most desirable time for treatment is different in various malocclusions [17–19].

Different established methods are used to identify the growth phase. The analysis of cervical vertebra maturation (CVM) is a method based on assessing the shape of the cervical bodies, as seen in lateral cephalograms. The CVM method shows great reliability, according to Baccetti et al. [20], Franchi et al. [21], and Rainey et al. [22]. Another radiographic method is the hand-wrist analysis that calculates the mean age for the appearance of each of the various centers of ossification or the epiphyseal closure and variations in these ages [23, 24].

Alternative methods to identify the growth phase are analysis of dentition [25], chronological age [26, 27], and dental maturation [28, 29]. These methods are mainly morphological and recent studies affirm that those are not reliable assessments of growth phases [30, 31]. New possibilities might be offered by the biochemical markers. Collection of gingival crevicular fluid avoids radiographic exposure and the biomarkers represent agents that are directly involved in bone growth and remodeling [1].

The alkaline phosphatase (ALP) has been investigated as reliable biologic indicator of skeletal maturation in different studies, where the ALP levels are compared with other methods to identify the skeletal maturation in growing patients [32, 33]. The bone alkaline phosphatase is synthesized by the osteoblasts and is presumed to be involved in the calcification of bone matrix. It is considered to be a highly specific marker of the bone-forming activity of osteoblasts.

(a)

(b)

Figure 2: The gingival crevicular fluid collection with endodontic paper points (a) or periopapers (b).

Perinetti et al. [33] compared the relation between the cervical vertebra maturation and the level of ALP in the gingival crevicular fluid in patients with age range 7.8–17.7 years. The enzyme activity greater level was detected in CS3 and CS4 phases that are correspondent to the peak in the mandibular growth in the CVM analysis. As reported by Szulc et al. [34], serum ALP activity, which is the most used biochemical marker for bone turnover, increases at puberty and decreases in adulthood. Neither dentition phase or chronological age show significant correlations with the skeletal maturation phases, as monitored through the GCF ALP activity, according to Perinetti and contardo [35]. The authors have concluded that the treatment of dentofacial disharmonies in individual patients should not rely on the clinical parameters of dentition and chronological age. This conclusion is the opposite of a recent Indian study, which affirms that there is a positive correlation between chronological age and cervical vertebrae skeletal maturation [36].

3. Monitoring of Orthodontic Tooth Movement

The orthodontic tooth movement is possible by the application of a controlled mechanical force and it results in biologic reactions that alter the surrounding dental and periodontal tissues [37]. These alterations include a cascade of events—in the mineralized (alveolar bone) and non-mineralized (periodontium) tissues—that allow the tooth movement. Biochemical markers representing these biological modifications are expressed during specific phenomena, that is, simile-inflammatory process, bone resorption and formation, periodontal ligament changes, and vascular and neural responses [38].

Monitoring the levels of biochemical markers during orthodontic movement might be a useful procedure for clinicians to analyze the degree of bone remodeling. Gingival crevicular fluid reflects the immune reactions, interactions host-parasite [39], and reactions to biochemical stress [40].

Interleukins are particularly important for consequent tooth movement, because these cytokines stimulate osteoclast formation and bone resorption promoted by preformed osteoclasts. Interleukins can be classified as proinflammatory or anti-inflammatory. Proinflammatory interleukins are interleukin-1 β (IL-1β), interleukin-2, interleukin-6, and interleukin-8 and the anti-inflammatory are interleukin-1, receptor antagonist (IL-1RA), interleukin-4, interleukin-10, and interleukin-13. Interleukin-1 β (IL-1 β) is a cytokine that stimulates the bone resorption [41] and its concentration 24 hours after the beginning of tooth movement increases, according to Uematsu et al. [42]. These authors also demonstrated an increase in the levels of other proinflammatory cytokines, as IL-6 and tumor necrosis factor-alpha. IL-6 is a cytokine originated from macrophages and T-cells. When children and adult subjects, undergoing orthodontic treatment, had their GCF compared, children showed a higher mean concentration of IL-6 than the adults 24 hours after the beginning of the movement [42].

Tooth movement also requires the binding of receptor activator of nuclear factor kappa β ligand (RANKL) to receptor activator of nuclear factor kappa (RANK), a cell membrane protein found on osteoclast precursor cells [43]. RANK is a cell membrane protein found on osteoclast precursor cells while the RANKL is a protein produced by the osteoblasts. During the orthodontic movement, RANKL is responsible for the generation and maintenance of osteoclasts by binding RANK [3]. On the other hand, osteoprotegerin (OPG) acts as a decoy receptor that binds to RANKL and blocks osteoclastogenesis [43].

The RANK-RANKL-OPG system is of primary importance to osteoclast differentiation during orthodontic movement. The levels of RANKL in GCF during the movement have increased, while the levels of OPG decreased, especially in the first 24 hours after the application of orthodontic force, which suggests bone resorption [43, 44]. A study compared the effects of aging on RANKL and OPG levels in gingival crevicular fluid during orthodontic tooth movement and as a result, it was found that juvenile patients had a higher amount of tooth movement when compared with that of adults, after 168 h of the beginning of treatment. That difference could be related to a lower RANKL/OPG ratio in GCF in adult patients during the early stages of orthodontic movement and suggests that is the reason the movement is faster in young patients [44].

When an orthodontic force is applied to a tooth, it creates areas of tension and compression in the periodontal ligament (PDL). The mechanical stress changes the vascularity and blood flow within the PDL, which allow the remodeling of the PDL.

Bone-forming cells have been shown to have alkaline phosphatase (ALP) activity and changes in this enzyme in serum and bone have been used as markers for bone metabolism in several diseases [45, 46]. During orthodontic treatment, acid and alkaline phosphatase in human GCF have been correlated with the total appliance duration. GCF ALP has a primary role in bone mineralization, because it hydrolyses inorganic pyrophosphate, which is an inhibitor of the mineralization process. The ALP has been shown to be sensitive to alveolar bone formation during orthodontic tooth movement [47, 48]. A split-mouth prospective study [49] in prepubertal subjects was made to monitor alveolar bone formation at the tension sites of the first molars undergoing rapid maxillary expansion (RME) treatment. In this study, the GCF ALP activity was used as a biomarker of tissue remodeling to determine the existence and duration of active alveolar bone formation during the retention phase. The authors have concluded that during the retention phase of RME, there is an increase in GCF ALP activity in the tensions sites, at both 3 and 6 months.

Perinetti et al. [48] investigated the ALP activity in GCF and analyzed if this enzyme can be a diagnostic method to assess the orthodontic movement. In this split-mouth study, the maxillary first molars under treatment served as a test in each patient, with one being retracted, and the contralateral molars were not subjected to distal forces. Thus, they showed that GCF ALP activity was greater in the distalized molars than that in the nonmoved contralateral molars. The ratio of the activity of the ALP was higher in tension sites, when compared with the compression sites. As a conclusion, they suggested that the ALP activity in GCF reflects the biologic activity in the periodontium during orthodontic movement. The GCF ALP was tested in other studies [50, 51], which also showed a higher level of ALP in the tension sites, after application of orthodontic force, and confirmed this enzyme as a biomarker of orthodontic movement.

Prostaglandin E2 (PGE2) is produced by the periodontal ligament cells and it is a proinflammatory mediator. PGE2 acts as biochemical mediator of bone resorption induced by the orthodontic movement, stimulating the osteoclastic activity. This biomarker is known to be a potent stimulator of bone resorption and its production is controlled in part by IL-1 [3]. Grieve III et al. [52] showed that PGE2 and IL-1β were significantly elevated after the initial tooth movement but returned to baseline levels after seven days. Ren et al. [7] showed that the concentrations were significantly elevated after 24 hours of activation in juvenile and adult patients but concluded that the mediator levels in juvenile subjects are more responsive than the levels in adults. In agreement with this conclusion, another study [53] showed that the levels of PGE2 were higher in young subjects than in the older patient group. This could be an explanation of why the speed of orthodontic treatment may be different in adults versus juveniles. The hypothesis is that, in juveniles, the inflammatory responses can react faster to local changes.

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine that can be derived from both monocyte and macrophage. TNF-α stimulates proteolytic enzyme synthesis and osteoclastic activity, so it is involved in bone resorption. It is also an apoptotic factor for osteocytes, which could be the signal for osteoclast recruitment to resorb bone in the side undergoing PDL pressure, while it simultaneously inhibits osteoblasts [3]. TNF-α also controls the appearance of osteoclasts at compression sites. In a study [54] with juveniles patients (16–19 years old) who need orthodontic treatment with molar distalization, the levels of TNF-α and IL-1β were assessed and there were increases in their concentrations and also an increase in GCF volume. Lowney et al. [55] also studied the expression of TNF-α and found an increase in its expression during orthodontic treatment.

The major noncollagenous components of bone in serum and a product of the osteoblast activity, osteocalcin, have been used as a marker of bone formation, but there are several factors that complicate interpretation of the results. Nevertheless, assays for intact osteocalcin have been shown to be related to growth velocity in children [56]. The ALP and osteocalcin levels were also investigated in a group of girls during puberty, with ages between 11.6 and 15.5 years and it showed that the increase in levels of bone specific alkaline phosphatase, osteocalcin, and urinary deoxypyridinoline suggests that these markers may be relatively more sensitive as indicators of skeletal health during puberty [57].

Osteoprotegerin (OPG) is a member of the tumor necrosis factor receptor family and a soluble decoy receptor against RANKL. It is produced by osteoblasts and other cells and a key factor in the inhibition of osteoclast differentiation and activation [58]. Nishijima et al. [59] analyzed the levels of RANKL and OPG in GCF during orthodontic movement in adolescent patients. They showed that RANKL levels increased during the treatment and in contrast, the OPG levels decreased. The changes in these cytokines may be involved in bone resorption as a response to compression force.

The soft tissue is also remodeled following orthodontic tooth movement. These tissues are metabolized by various enzymes, including matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs). Collagenases, MMP-1 and MMP-8, degrade collagen fibers, whereas gelatinases (MMP-2 and MMP-9) degrade denatured collagen, complementing collagenases [60]. In humans, GCF MMP-1 and MMP-8, MMP-2, and MMP-9 [61] and TIMP-1 [62] have all been shown to increase at sites of compression and tension. Therefore, crevicular MMP-9 may also serve as biomarker to monitor remodeling of the periodontal tissues during tooth movement [63].

4. Concluding Remarks

The GCF is a well-known source of biomarkers with potential applications in both periodontology and orthodontics. Its analysis permits the orthodontists to identify the consequences of orthodontic forces in paradental tissues (periodontal ligament and alveolar bone). The GCF biomarkers may be also helpful to assess the growth phase in children and juvenile patients. Main advantages of this method are that it can be done in private dentist offices, is quick, and avoids radiographic exposure. However, despite all the reported investigations, the clinical applicability of the method is still limited with further data needed to reach a full diagnostic utility of specific GCF biomarkers for orthodontics. Therefore, more studies are warranted to elucidate the role of main GCF biomarkers and how the quantification of which may be used to enhance functional treatment, optimize orthodontic force intensity, or prevent major tissue damage consequent to orthodontic treatment. In this view, biochemical monitoring related to orthodontic treatment represents a promising issue.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Comparison of Activator-Headgear and Twin Block Treatment Approaches in Class II Division 1 Malocclusion

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The purpose was to compare the treatment effects of functional appliances activator-headgear (AH) and Twin Block (TB) on skeletal, dental, and soft-tissue structures in class II division 1 malocclusion with normal growth changes in untreated subjects. The sample included 50 subjects (56% females) aged 8–13 years with class II division 1 malocclusion treated with either AH (n = 25) or TB (n = 25) appliances. Pre- and posttreatment lateral cephalograms were evaluated and compared to 50 untreated class II division 1 cases matched by age, gender, ANB angle, and skeletal maturity. A paired sample, independent samples tests and discriminant analysis were performed for intra- and intergroup analysis. Treatment with both appliances resulted in significant reduction of skeletal and soft-tissue facial convexity, the overjet, and the prominence of the upper lip in comparison to untreated individuals ($p < 0.001$). Retroclination of maxillary incisors and proclination of mandibular incisors were seen, the latter being significantly more evident in the TB group ($p < 0.05$). Increase of effective mandibular length was more pronounced in the TB group. In conclusion, both AH and TB appliances contributed successfully to the correction of class II division 1 malocclusion when compared to the untreated subjects with predominantly dentoalveolar changes.

1. Introduction

Early treatment of class II malocclusion aims to correct the sagittal relationship, modify the pattern of facial growth, and improve both hard- and soft-tissue profile [1–4]. The majority of the clinical studies recognize the useful effect of functional appliances in sagittal correction of the malocclusion but agree that the treatment is mainly restricted to dentoalveolar changes [5]. Favorable skeletal changes which can modify the growth pattern can also occur depending on individual growth potential [1, 6].

A class II malocclusion may result from mandibular deficiency, maxillary excess, or combination of both [7, 8]. Several varieties of functional appliances are currently in use aiming to correct the skeletal imbalances. The combination of an activator with headgear (AH) is used to provide greater cumulative skeletal changes than either appliance would provide alone [9]. They affect maxilla by decreasing forward and downward growth of the maxillary complex, while allowing the forward growth of the mandible to continue, thus influencing the profile more favorably [9, 10]. Twin Block (TB) appliance as well as most of other functional appliances is designed to encourage adaptive skeletal growth by maintaining the mandible in a corrected forward position for a sufficient period of time [1, 4, 11].

Many studies have investigated the effect of AH and TB appliance on the dental and skeletal variables. However, no studies have provided a direct comparison of the treatment changes between them. One study compared the effects of both appliances [3], but the evaluation was limited to the soft-tissue profile changes.

Therefore, the aims of this study were to explore skeletal and dentoalveolar changes in class II division 1 patients treated with TB and AH and to compare their treatment effect with normal growth changes of untreated controls (CTRL) with the same malocclusion. The hypotheses were as follows:

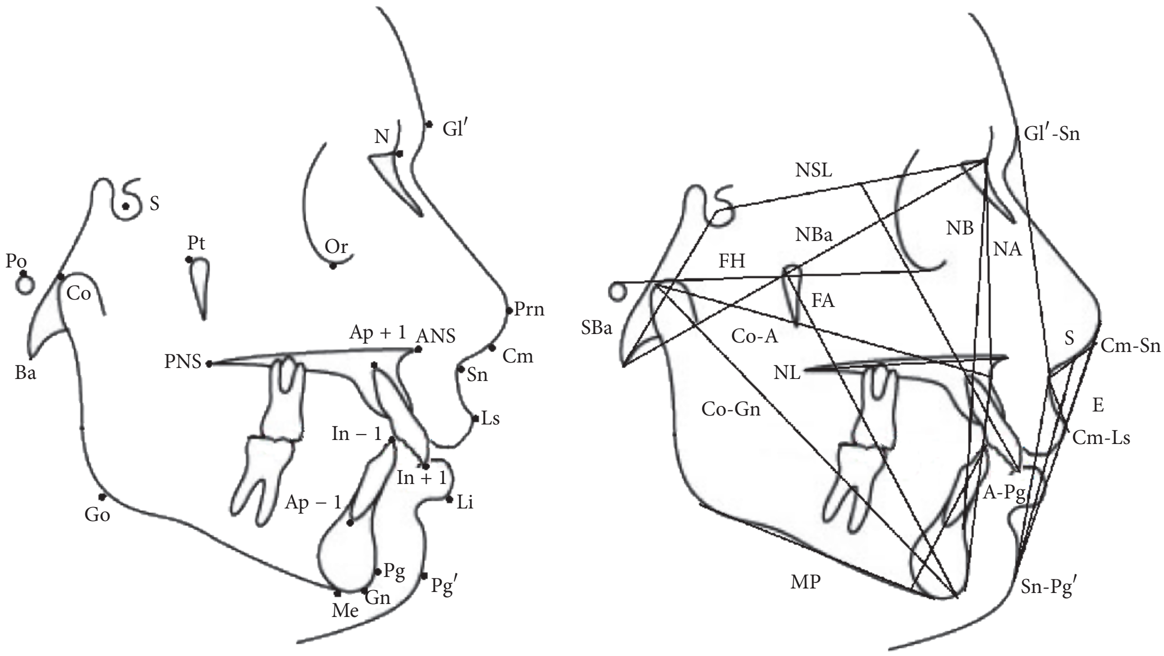

Figure 1: Points and plains used in cephalometric analysis: Gl′ (soft-tissue glabella), Prn (pronasale), Cm (columella), Sn (subnasale), Ls (labrale superius), Li (labrale inferius), Pg′ (soft-tissue pogonion), Pg (osseous pogonion), Gn (gnathion), Me (menton), Go (gonion), Ba (basion), Co (condylion), Po (porion), Pt (pterygoid point), S (sella), PNS (posterior nasal spine), ANS (anterior nasal spine), N (nasion), Or (orbitale), Ap + 1 (apicale superius), Ap − 1 (apicale inferius), In + 1 (incisale superius), In − 1 (incisale inferius), NSL (nasion-sella line), FA (facial axis), NL (nasal line), MP (mandibular plane), FH (Frankfort horizontal), E (Ricketts' Esthetic line), and S (Steiner's line).

(1) Both appliances have more pronounced dentoalveolar effect in the treated groups than growth itself in the untreated group.

(2) TB stimulates more skeletal growth of mandible than AH.

(3) AH has better control of vertical dimension than TB.

2. Materials and Methods

2.1. Study Population and Design. The sample included 50 subjects (56% females) aged 8–13 years (median 11) with class II division 1 malocclusion treated with either AH ($n = 25$) or TB ($n = 25$) appliances. The data were collected retrospectively among 151 subjects treated in the period of 2000–2015 at the Department of Orthodontics in Oslo, Norway, and the Department of Orthodontics in Rijeka, Croatia. Inclusion criteria were distal molar occlusion, overjet (OJ) >5 mm, and having pre- and posttreatment lateral cephalograms. According to the cervical vertebral maturation method [12], the included subjects were in the prepeak stages (CS1–CS3) of skeletal maturation before treatment and CS3–CS5 after treatment.

The AH appliance had all maxillary teeth covered with acrylic and included labial spring for the torque control of the incisors [13]. High pull headgear was always used simultaneously with the appliance. TB appliance [14] with addition of maxillary labial bow to aid the anterior retention and make the maxillary incisors retroclined was used in the other group. The expansion screw was incorporated in the maxillary plate and activated one quarter-turn each week for an average period of six months. Construction bite was the same in both appliances with the anterior positioning of mandible by 6 mm and vertical opening by 4 mm in the first molar area. The patients were recommended to use the appliances for 12–14 hours per day. Treatment was stopped when the patients achieved molar class I occlusion or slight hypercorrection.

Pretreatment (T1) and posttreatment (T2) lateral cephalograms were evaluated and compared to 50 untreated class II division 1 cases matched by age, gender, ANB angle, skeletal maturation of cervical vertebrae, and observation period. They were selected from American Association of Orthodontists Foundation Craniofacial Growth Legacy Collection. Cephalometric analysis (Table 1, Figure 1) was performed on calibrated pre- and posttreatment lateral cephalograms by two investigators (KMT and SS) using the cephalometric software Facad (Ilexis AB, Sweden) and AudaxCeph (Audax, Slovenia).

The study was in accordance with the Helsinki Declaration and the protocol was approved by the local ethical committees in Norway (02-09-2010) and in Croatia (2170-24-01-15-2).

2.2. Statistical Analysis. After inspection of histograms and quantile-quantile plots and testing the normality of the data with the Shapiro-Wilk test, a paired t-test was preformed to assess the statistical significance of changes occurring during the treatment with each appliance (intragroup analysis).

Table 1: Cephalometric variables used in the study.

Number	Variable	Unit	Description
1	NSBa	°	Cranial base angle expression of the flexion of the cranial base (nasion-sella-basion)
2	SNA	°	Angle of anterior part of cranial base (S-N) and point A (subspinale) on maxilla
3	SNB	°	Angle of anterior part of cranial base (S-N) and point B (supramentale) on mandible
4	ANB	°	Angle between point nasion and point on maxilla and mandible, basal sagittal relation between the jaws
5	A-NPg	mm	The shortest distance from A point to the facial plane (N-Pg), expression of the skeletal convexity of the face
6	NL/NSL	°	Angle between the nasal line (anterior to posterior nasal spine ANS-PNS) and the nasion-sella line, expression of the tilting of the maxilla relative to the anterior cranial base
7	MP/NSL	°	Angle of mandibular plane (Go-Me) relative to the anterior cranial base
8	MP/NL	°	Angle of mandibular plane (Go-Me) and nasal line
9	FA/NBa	°	Lower angle between the facial axis (pterygoid point-gnathion) and the nasion-basion line, expression of the growth direction of the chin and the relationship, facial height and depth
10	UFH	mm	Upper facial height (middle third of the face), distance from nasion point to spina nasalis anterior measured perpendicular to Frankfort horizontal (FH)
11	LFH	mm	Lower facial height (lower third of the face), distance from spina nasalis anterior to menton measured perpendicular to FH
12	UFH/LFH	%	Upper to lower facial height ratio
13	Co-A	mm	Distance from condylion to A point; measurement of the effective length of midface
14	Co-Gn	mm	Distance from condylion to gnathion; measurement of the effective length of mandible
15	Max Mand diff	mm	Maxillomandibular differential length, the difference between the effective mandibular length (Co-Gn) and the effective midface length (Co-A): gives an indication of the sagittal discrepancy between maxilla and mandible
16	−1/MP	°	Superoposterior angle of lower incisor long axis and mandibular plane
17	+1/NSL	°	Inferoposterior angle of upper incisor long axis and a nasion-sella line
18	−1/A-Pg angle	°	Angle between the long axis of the lower incisor and A-Pg line
19	+1/A-Pg angle	°	Angle between the long axis of the upper incisor and A-Pg line
20	−1/A-Pg distance	mm	Distance from the midpoint of the incisal edge of the most prominent mandibular incisor to A-Pg line, expression of the protrusion of the lower incisors
21	+1/A-Pg distance	mm	Distance from the midpoint of the incisal edge of the most prominent maxillary incisor to A-Pg line, expression of the protrusion of the upper incisors
22	Gl′-Sn-Pg′	°	Lower angle formed by the line from glabella to subnasale and the line from soft tissue pogonion to subnasale, expression of the convexity of the soft tissue profile
23	Cm-Sn-Ls	°	Nasolabial angle, expression of dentoalveolar protrusion
24	Li-E	mm	Distance from lower lip (labrale inferius) to Prn-Pg′ (Ricketts' Esthetic line)
25	Ls-E	mm	Distance from upper lip (labrale superius) to Prn-Pg′ (Ricketts' Esthetic line)
26	Li-S	mm	Distance from lower lip to Cm-Pg′ (Steiner's line)
27	Ls-S	mm	Distance from upper lip to Cm-Pg′ (Steiner's line)
28	OJ	mm	Distance between the incisal edges of the most prominent maxillary and mandibular incisors, measured parallel to the occlusal line

Table 2: Gender, age, and treatment duration of the Twin Block (TB), Activator headgear (AH) and untreated, control (CTRL) group.

	Treatment group TB	AH	CTRL	p
Female gender (N; percentage)	15 (60)	13 (52)	28 (56)	0.850*
Age before treatment (years)				
Median (interquartile range)	11 (10–12)	10 (9–11)	11 (10-11)	0.336**
Min–max	9–13	8–12	8–13	
Mean observation period (months)				
Mean ± std. deviation	14.2 ± 4.8	15.4 ± 5.5	14.9 ± 5.2	0.745***
Min–max	8–24	12–24	10–24	

*χ^2 test. **Kruskal-Wallis test. ***ANOVA.

Independent samples test was used for intergroup analysis (between appliances groups). For the differences in age between groups, the Kruskal-Wallis test was used and χ^2 for differences in gender. Analysis of variance with the Student-Newman-Keuls post hoc test was used to test the amount of changes between treated groups and controls. Effect size, that is, the magnitude of the relationship, was estimated by r and η^2. Discriminant function analysis, a multivariate technique, was used to explore which changes in cephalometric parameters discriminate treatment groups and untreated subjects the most, and how effective those parameters are in predicting treatment group membership.

Reliability, that is, consistency of measurements, was assessed on ten randomly selected cephalograms remeasured with a three-month interval. Intraclass correlation coefficient (ICC) and Dahlberg formula were used. Dahlberg formula for method error is ME $= \sum d^2/2n$, where "d" is the difference between two registrations and "n" is the number of double registrations [15]. IBM SPSS 22 (IBM Corp, Armonk, USA) software was used for data analysis.

3. Results

The reliability of measurements was good or excellent, with ICC ranging from 0.660 for upper-to-lower facial height ratio to 0.995 for inclination of mandibular plane relative to the anterior cranial base and ME from 0.3 for SNA to 6.6 for nasolabial angle. The error of the method was less than 10% of the biologic variation. Power calculation of this study showed the least detectable mean difference in diff ANB to be 1.1 degree (80% test power with 95% significance level). The present study was not suitable for statistical analysis of gender differences in treatment effects due to small samples.

At T1, the treatment groups had similar characteristics (Tables 2 and 3), and differences between genders in those variables were not significant. Untreated subjects had lower OJ at T1 (5.6 ± 2.1; $p < 0.001$), but higher OJ at T2 (5.9 ± 2.2; $p < 0.001$) compared to the treated groups.

Treatment with both appliances resulted in significant increase of the SNB angle, reduction of the ANB angle, retrusion and retroclination of the maxillary incisors, protrusion and proclination of the mandibular incisors, and reduction of the OJ (Table 3). Soft tissues demonstrated reduction of convexity and prominence of the upper lip and increased nasolabial angle.

The untreated group manifested significant increase in the SNB angle ($p = 0.005$), upper and lower facial height ($p \leq 0.001$), and increased maxillary and mandibular length ($p < 0.001$), with the mandible growing significantly more than the maxilla (Table 4).

Treatment with the TB appliance resulted in increased mandibular incisor proclination and protrusion compared to the AH appliance ($p < 0.05$; Table 5).

Treatment with both functional appliances resulted in significant reduction of the ANB angle when compared to the untreated population ($p < 0.001$; Table 5). It was mainly due to the increase in the SNB angle and maxillomandibular differential length (difference between effective mandibular length (Co-Gn) and the effective midface length (Co-A); $p < 0.001$). Both appliances significantly reduced the convexity of the hard and soft facial tissues in comparison to the untreated population ($p < 0.001$). Additionally, retroclination of the maxillary incisors was noticed in both treatment groups and was slightly but insignificantly more pronounced in the AH group. Proclination of the mandibular incisors was significantly more pronounced in the TB group ($p < 0.05$). As a consequence, OJ and the prominence of the upper lip were significantly reduced in comparison to the untreated subjects ($p < 0.001$).

In order to explore which variables mostly distinguish the three groups of subjects, discriminant analysis was applied. Changes in cephalometric variables during treatment and observation period were used as predictors. Variables that demonstrated most changes or differences were selected, with special attention in obtaining the lowest possible correlation between predictors. Two discriminant functions in this analysis could be estimated, both having significant discriminating power. Figure 2 demonstrates that functions clearly discriminate groups. First discriminant function, presented in horizontal direction of Figure 2, distinguishes treated from untreated subjects. Variables that comprise this first discriminant function are presented in Table 6 and their correlations with the first discriminant function are marked with asterisks in the first numeric column. More effect size was seen in the position of the incisors and soft tissues than in the skeletal changes. Changes in those features explained high proportion of variability of distinction between treated and untreated subjects (90.9%; $p < 0.001$).

Second discriminant function, presented in vertical direction of Figure 2 and marked in the last column of Table 6, mostly distinguishes the two treatment groups. More effect size was seen in inclination of incisors and mandibular growth than in the position of the lower lip. Changes in those features accounted for low variability of distinction between treatment groups (9.1%; $p = 0.041$). Discriminant

Table 3: Pretreatment (T1) and posttreatment (T2) values of the investigated variables in the Twin Block (TB) and activator-headgear (AH) groups.

	TB				AH			
	T1	T2	p^*	r^{**}	T1	T2	p^*	r^{**}
	Mean ± SD	Mean ± SD			Mean ± SD	Mean ± SD		
NSBa	131.0 ± 4.5	130.9 ± 4.6	0.752	0.065	128.3 ± 5.1	127.4 ± 5.0	**0.014**	0.476
SNA	80.1 ± 3.2	79.8 ± 3.6	0.118	0.315	81.8 ± 2.8	81.7 ± 2.7	0.432	0.161
SNB	74.2 ± 3.0	75.3 ± 3.3	<**0.001**	0.751	76.2 ± 2.5	77.4 ± 2.5	<**0.001**	0.835
ANB	5.9 ± 1.6	4.4 ± 1.7	<**0.001**	0.751	5.7 ± 1.7	4.2 ± 1.7	<**0.001**	0.899
A-NPg	4.9 ± 2.1	3.7 ± 2.3	<**0.001**	0.661	4.2 ± 2.2	2.9 ± 2.4	<**0.001**	0.831
NL/NSL	7.9 ± 2.9	7.6 ± 3.1	0.359	0.187	5.4 ± 2.5	5.2 ± 2.6	0.420	0.165
MP/NSL	35.2 ± 4.7	35.3 ± 5.2	0.925	0.019	33.3 ± 5.0	32.4 ± 4.7	**0.011**	0.488
MP/NL	27.3 ± 4.5	27.7 ± 4.8	0.431	0.162	27.9 ± 4.6	27.2 ± 4.6	0.086	0.343
FA/NBa	86.1 ± 3.4	86.3 ± 3.7	0.614	0.104	87.5 ± 3.7	87.8 ± 4.0	0.299	0.212
UFH	47.7 ± 3.0	49.3 ± 3.4	**0.001**	0.597	46.2 ± 4.8	46.7 ± 3.3	0.534	0.128
LFH	56.8 ± 4.5	59.9 ± 4.7	<**0.001**	0.784	57.3 ± 5.7	58.8 ± 4.4	0.154	0.288
UFH/LFH	84.4 ± 8.0	82.8 ± 7.2	**0.014**	0.474	80.7 ± 4.9	79.6 ± 5.3	0.157	0.286
Co-A	81.0 ± 5.3	83.0 ± 4.3	**0.016**	0.467	83.0 ± 8.2	82.6 ± 4.2	0.799	0.053
Co-Gn	99.9 ± 6.1	105.0 ± 6.3	<**0.001**	0.768	102.6 ± 10.4	105.1 ± 6.0	0.162	0.283
Max Mand diff	18.9 ± 3.1	22.0 ± 4.3	<**0.001**	0.743	19.6 ± 3.6	22.4 ± 3.5	<**0.001**	0.784
−1/MP	97.7 ± 7.4	100.7 ± 7.4	**0.002**	0.572	95.5 ± 7.6	96.1 ± 6.4	0.456	0.153
+1/NSL	107.6 ± 7.1	100.5 ± 6.4	<**0.001**	0.803	110.1 ± 6.7	102.7 ± 6.3	<**0.001**	0.772
−1/A-Pg angle	22.0 ± 5.8	27.5 ± 5.2	<**0.001**	0.765	21.0 ± 7.3	23.7 ± 5.1	**0.002**	0.583
+1/A-Pg angle	38.5 ± 5.5	28.9 ± 4.7	<**0.001**	0.893	37.9 ± 5.6	27.5 ± 5.2	<**0.001**	0.867
−1/A-Pg distance	0.3 ± 2.0	2.6 ± 1.7	<**0.001**	0.875	0.0 ± 2.3	1.4 ± 2.0	<**0.001**	0.775
+1/A-Pg distance	9.3 ± 1.9	6.4 ± 1.9	<**0.001**	0.915	9.2 ± 2.0	5.6 ± 2.0	<**0.001**	0.861
Gl′-Sn-Pg′	20.3 ± 5.3	18.2 ± 5.6	**0.002**	0.583	18.5 ± 5.8	16.4 ± 5.2	**0.002**	0.586
Cm-Sn-Ls	116.9 ± 11.9	118.1 ± 10.2	0.589	0.111	107.7 ± 8.5	113.8 ± 11.3	**0.005**	0.533
Li-E	0.1 ± 2.5	−0.5 ± 2.5	0.120	0.313	−0.6 ± 3.5	−1.5 ± 2.8	**0.020**	0.455
Ls-E	−0.5 ± 2.0	−2.2 ± 2.0	<**0.001**	0.701	−0.1 ± 2.2	−1.9 ± 2.4	<**0.001**	0.823
Li-S	1.1 ± 2.4	0.7 ± 2.3	0.327	0.200	0.7 ± 3.3	−0.1 ± 2.8	0.050	0.389
Ls-S	1.3 ± .7	−0.2 ± 1.6	<**0.001**	0.661	2.0 ± 2.0	0.1 ± 2.2	<**0.001**	0.861
OJ	9.0 ± 2.5	3.8 ± 1.8	<**0.001**	0.956	9.2 ± 2.3	4.3 ± 1.9	<**0.001**	0.888

*Paired samples t-test.
**Effect size calculated by using the formula $r = \sqrt{t^2/(t^2+df)}$. Cohen criteria for interpretation of effect size were used: $r = 0.1$–0.3 = small effect size, 0.3–0.5 = medium, and >0.5 = large.

analysis correctly classified 79% of the subjects. Correct group membership was retained in 96% untreated subjects, 72% of TB, and 52% of AH group.

4. Discussion

Both TB and AH functional appliances successfully reduced the severity of class II malocclusion by a combination of dental and skeletal changes. Overjet, SNB, and ANB angles were significantly improved in both groups. All of these changes were significantly different from the changes in the untreated, control group suggesting positive treatment effect with functional appliances. The only variables that exhibited significant differences between the two appliances after the treatment were the proclination and the protrusion of the mandibular incisors, which were more pronounced in the TB group.

The SNB angle significantly increased in both treatment groups, which is in agreement with other studies [8, 13, 16]. However, these changes, particularly in the TB group, were smaller than the previously reported and could be related to the concomitant increase in the lower anterior facial height, lower incisor proclination, and posterior displacement of point B [14].

Great variability in increase in effective mandibular length, that is, Co-Gn, is demonstrated, particularly in AH group. The effective mandibular length increased mostly in the TB group which is supported by numerous investigations [2, 5, 8]. The amount of mean increase in mandibular length in the AH group is similar to normal mandibular growth of untreated class II division 1 cases. Supplementary mandibular length growth of 2.5 mm in the TB subjects in comparison to untreated subjects in this study corresponds with the results reported in a recent meta-analysis [17]. One of the several systematic reviews on the treatment effect of removable functional appliances reported that short-term evidence suggested mainly dentoalveolar rather than skeletal effects; however, the skeletal changes were more pronounced with the TB appliance [5]. The most recent meta-analysis revealed more supplementary mandibular growth in pubertal

Table 4: Mean values of the investigated variables in the untreated, control group at the same pretreatment (T1) and posttreatment (T2) age as the treated groups.

	T1 Mean ± SD	T2 Mean ± SD	p^*	r^{**}
NSBa	130.9 ± 4.2	130.7 ± 4.7	0.514	0.093
SNA	82.1 ± 2.4	82.4 ± 2.5	0.174	0.193
SNB	75.8 ± 2.8	76.3 ± 2.6	**0.005**	0.384
ANB	6.3 ± 2.0	6.0 ± 1.9	0.204	0.181
A-NPg	5.2 ± 2.0	5.1 ± 2.1	0.479	0.101
NL/NSL	6.6 ± 3.3	6.7 ± 3.5	0.772	0.042
MP/NSL	35.0 ± 4.8	34.9 ± 5.0	0.625	0.070
MP/NL	28.4 ± 5.0	28.2 ± 5.3	0.526	0.091
FA/NBa	87.9 ± 4.3	88.2 ± 4.2	0.304	0.147
UFH	46.3 ± 3.1	47.6 ± 3.4	<**0.001**	0.581
LFH	56.5 ± 5.2	57.9 ± 6.0	**0.001**	0.463
UFH/LFH	82.3 ± 6.6	82.8 ± 7.3	0.535	0.089
Co-A	81.3 ± 4.9	82.7 ± 5.3	<**0.001**	0.512
Co-Gn	99.8 ± 5.9	102.4 ± 6.4	<**0.001**	0.761
Max Mand diff	18.5 ± 3.2	19.7 ± 4.0	**0.001**	0.461
−1/MP	97.8 ± 5.5	96.9 ± 5.5	0.105	0.230
+1/NSL	102.7 ± 7.2	103.1 ± 7.2	0.487	0.100
−1/A-Pg angle	22.7 ± 5.1	22.5 ± 5.2	0.708	0.054
+1/A-Pg angle	32.8 ± 6.7	32.4 ± 6.8	0.345	0.135
−1/A-Pg distance	1.3 ± 2.3	1.2 ± 2.4	0.749	0.046
+1/A-Pg distance	6.9 ± 2.2	7.1 ± 2.7	0.144	0.207
Gl′-Sn-Pg′	16.4 ± 4.4	16.8 ± 4.3	0.258	0.161
Cm-Sn-Ls	110.0 ± 13.9	112.9 ± 9.6	**0.037**	0.293
Li-E	1.4 ± 2.2	1.1 ± 2.3	0.270	0.157
Ls-E	0.4 ± 2.2	−0.1 ± 2.1	**0.017**	0.334
Li-S	2.3 ± 2.2	2.2 ± 2.3	0.783	0.039
Ls-S	2.1 ± 2.0	2.0 ± 2.2	0.829	0.031
OJ	5.6 ± 2.1	5.9 ± 2.2	0.068	0.258

*Paired samples t-test.
**Effect size.

Table 5: Comparison of the treatment changes (Δ) in the Twin Block (TB) and activator-headgear (AH) group and untreated controls (CTRL).

	ΔTB Mean ± SD	ΔAH Mean ± SD	ΔCTRL Mean ± SD	p^*	η^{2**}
NSBa	−0.1 ± 2.1	−0.9 ± 1.6	−0.2 ± 2.1	0.313	0.024
SNA	−0.4 ± 1.2	−0.2 ± 1.2	0.3 ± 1.5	0.087	0.049
SNB	1.1 ± 1.0	1.2 ± 0.8	0.6 ± 1.3	**0.036**	0.066
ANB	−1.5 ± 1.3^{a}	−1.4 ± 0.7^{a}	−0.3 ± 1.5^{b}	<**0.001**	0.179
A-NPg	−1.2 ± 1.3^{a}	−1.3 ± 0.9^{a}	−0.1 ± 1.4^{b}	<**0.001**	0.161
NL/NSL	−0.4 ± 1.9	−0.3 ± 1.6	0.1 ± 2.1	0.588	0.011
MP/NSL	−0.0 ± 1.7	−0.9 ± 1.7	−0.1 ± 2.1	0.138	0.040
MP/NL	0.4 ± 2.4	−0.7 ± 1.9	−0.2 ± 2.6	0.283	0.026
FA/NBa	0.2 ± 2.0	0.3 ± 1.5	0.3 ± 2.0	0.976	0.001
UFH	1.6 ± 2.2	0.5 ± 4.0	1.3 ± 1.9	0.295	0.025
LFH	3.0 ± 2.4	1.5 ± 5.1	1.4 ± 2.6	0.119	0.043
UFH/LFH	−1.7 ± 3.2	−1.1 ± 3.8	0.5 ± 5.8	0.134	0.041
Co-A	2.0 ± 3.9	−0.3 ± 6.7	1.4 ± 2.4	0.114	0.044
Co-Gn	5.1 ± 4.4	2.5 ± 8.6	2.6 ± 2.2	0.086	0.049
Max Mand diff	3.1 ± 2.9^{a}	2.8 ± 2.3^{a}	1.1 ± 2.2^{b}	**0.001**	0.126
−1/MP	3.0 ± 4.4^{a}	0.5 ± 3.6^{b}	−0.9 ± 3.8^{b}	<**0.001**	0.145
+1/NSL	−7.0 ± 5.3^{a}	−7.3 ± 6.2^{a}	0.4 ± 4.0^{b}	<**0.001**	0.378
−1/A-Pg angle	5.5 ± 4.8^{a}	2.7 ± 3.8^{b}	−0.2 ± 3.3^{c}	<**0.001**	0.283
+1/A-Pg angle	−9.6 ± 4.9^{a}	−10.4 ± 6.1^{a}	−0.5 ± 3.4^{b}	<**0.001**	0.528
−1/A-Pg distance	2.3 ± 1.3^{a}	1.3 ± 1.1^{b}	−0.1 ± 1.2^{c}	<**0.001**	0.416
+1/A-Pg distance	−2.9 ± 1.3^{a}	−3.6 ± 2.2^{a}	0.2 ± 1.1^{b}	<**0.001**	0.592
Gl′-Sn-Pg′	−2.1 ± 3.0^{a}	−2.0 ± 2.9^{a}	0.4 ± 2.3^{b}	<**0.001**	0.182
Cm-Sn-Ls	1.2 ± 11.0	6.1 ± 10.0	2.9 ± 9.5	0.207	0.032
Li-E	−0.6 ± 1.8	−0.9 ± 1.9	−0.3 ± 1.6	0.290	0.025
Ls-E	−1.8 ± 1.8^{a}	−1.8 ± 1.3^{a}	−0.4 ± 1.2^{b}	<**0.001**	0.205
Li-S	−0.4 ± 1.8	−0.8 ± 2.0	−0.1 ± 1.6	0.212	0.032
Ls-S	−1.5 ± 1.7^{a}	−1.9 ± 1.1^{a}	−0.0 ± 1.4^{b}	<**0.001**	0.261
OJ	−5.2 ± 1.6^{a}	−4.9 ± 2.6^{a}	0.3 ± 1.2^{b}	<**0.001**	0.712

*ANOVA with Student-Newman-Keuls post hoc tests. Groups in the same row that share the same superscript letter do not differ significantly.
**Effect size calculated according to formula: η^2 = between groups sum of squares/total sum of squares. Cohen criteria for interpretation of effect size were used: η^2 = 0.02–0.13 = small effect size, 0.13–0.26 = medium, and >0.26 = large.

than prepubertal class II malocclusion patients treated with functional appliances [18]. Therefore, treatment timing, as well as individual differences in treatment response, may give a plausible explanation for the reported discrepancies.

Both appliances in the current study had little, insignificant restraining effect on the maxilla. Several investigations have previously reported that forward growth of the maxilla may be inhibited during AH treatment [4, 9, 10, 16]. Others could not confirm this effect [13, 19]. Restricted forward growth of maxilla in patients treated with TB is found in most of the studies included in the systematic review by Ehsani et al. [17]. The labial bow used to increase retention and control the maxillary incisors in the TB appliance might have made the maxillary incisors retroclined, made the roots proclined, and affected the position of the A point [11]. Thus, it is possible that the restraining effect on maxilla was more pronounced but was underestimated due to a forward movement of the A point. The increased SNA angle in the control group is also in support of this notion.

The ANB angle showed higher decrease in both treatment groups in comparison to the untreated controls. The significant change in the TB group was mainly due to the significant skeletal mandibular effect concerning both angular and linear measurements. In the AH group, the nature of the ANB changes is controversial and could be a combination of dentoalveolar and skeletal changes in both jaws. Some studies indicate that reduction of the ANB angle is mainly due to a delayed forward growth of maxilla, while some report

Table 6: Structural matrix of canonical discriminant functions.

	Function	
	1	2
Δ+1/A-Pg distance	**−0.699***	−0.394
Δ−1/A-Pg distance	**0.476***	−0.453
Δ+1/NSL	**−0.458***	−0.108
ΔLs-E	**−0.298***	−0.076
ΔGl′-Sn-Pog′	**−0.277***	−0.025
ΔANB	**−0.275***	−0.008
ΔSNB	**0.153***	0.112
ΔSNA	**−0.131***	0.087
ΔUFH/LFH	**−0.120***	0.062
Δ−1/MP	0.210	**−0.387***
ΔCo-A	−0.034	**−0.383***
ΔMP/NSL	−0.045	**−0.351***
ΔCo-Gn	0.080	**−0.340***
ΔLi-E	−0.082	**−0.150***

*Largest absolute correlation between each variable and any discriminant function. Variables ordered by absolute size of correlation within function.

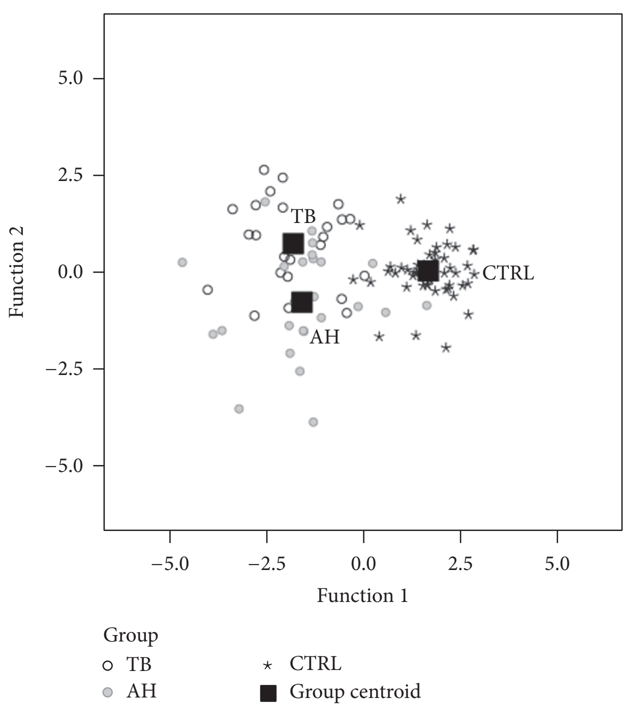

Figure 2: Canonical discriminant functions graph.

that reduced ANB angle is more dependent on increased mandibular growth [16]. Regardless of the treatment changes that lead to reduction in the ANB angle, the same effect could not be demonstrated in the control group. This finding further supports the fact that there is no self-correction of class II malocclusion and that functional treatment is beneficial for the patient.

Several authors underline the importance of keeping control of the vertical dimensions while correcting sagittal discrepancies [16, 20]. This is an imperative in patients with a tendency for posterior rotation of the mandible. Treatment with activator without a headgear showed effective condylar growth and change in chin position; however, these changes were not in the desired sagittal direction, rather in the vertical one [21]. In the present study, the effects of the two appliances on vertical measurements are similar; still, the AH appliance seemed to have some tendency to control the vertical dimension by promoting anterior rotation of the mandible and this is a consistent finding [7, 9, 19, 22]. Posttreatment changes in mandibular plane inclination were not observed in the TB group. This is in accordance with most studies; however, an increased mandibular plane inclination has also been reported [23, 24]. It should be emphasized that individual growth pattern varies and must be seen as an important factor contributing to the divergent treatment response.

Dentoalveolar changes played a dominant role in class II malocclusion correction in both groups, which is in agreement with other reports [11, 13]. Retroclination of maxillary incisors is a consistent finding in many other TB [2, 6, 8] and AH studies [9, 16, 19]. A more pronounced retrusion of the upper incisors was found in the AH group, which may reflect the additional headgear forces acting posteriorly on the maxillary apical base and alveolar structures. Retroclination and retrusion of prominent maxillary incisors may have a preventive effect since large overjet doubles the risk of dental trauma [25]. The most prominent dentoalveolar effect in the TB group was proclination and protrusion of the mandibular incisors compared to the AH group. Changes in the inclination of the lower incisors in functional appliances studies are contradictory and probably not sufficiently controlled by their capping with acrylic [8, 13, 18, 22].

At the end of the treatment, both treatment groups showed similar reduction of the profile convexity and retrusion of the upper lip. These results are in agreement with previous studies [9, 16, 24, 26, 27]. However, retrusion of the lip relative to the nose-chin line may reflect growth of the nose but also more forward chin position induced by functional treatment. It should also be noted that there is a large variation in treatment response for most of the soft-tissue parameters and sometimes the magnitude of the changes may not be perceived as clinically significant [28].

The discriminant analysis revealed that there was a greater difference between the control group and the two treated groups than that between the TB and AH group. The majority of the changes could be attributed to treatment with either of the two appliances, but the treatment effect was more dentoalveolar than skeletal compared to the controls.

5. Conclusions

Both AH and TB appliances contributed successfully to the correction of class II division 1 malocclusion when compared to the untreated growing class II subjects producing predominantly dentoalveolar effects. TB appliance leads to more pronounced protrusion and proclination of the mandibular incisors than the AH group. Treatment with TB results in some supplementary mandibular length growth while AH exerted some tendency to more control of the vertical dimension of the lower anterior facial height. Normal growth pattern in untreated class II subjects comprises forward and downward growth displacement of the maxilla and the mandible without major changes in basal sagittal relation between the jaws. Clinical relevance of these findings is that early treatment may correct or at least ameliorate class II division I malocclusion which is not self-corrective.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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Review Article

Reliability of Growth Indicators and Efficiency of Functional Treatment for Skeletal Class II Malocclusion: Current Evidence and Controversies

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Current evidence on the reliability of growth indicators in the identification of the pubertal growth spurt and efficiency of functional treatment for skeletal Class II malocclusion, the timing of which relies on such indicators, is highly controversial. Regarding growth indicators, the hand and wrist (including the sole middle phalanx of the third finger) maturation method and the standing height recording appear to be most reliable. Other methods are subjected to controversies or were showed to be unreliable. Main sources of controversies include use of single stages instead of ossification events and diagnostic reliability conjecturally based on correlation analyses. Regarding evidence on the efficiency of functional treatment, when treated during the pubertal growth spurt, more favorable response is seen in skeletal Class II patients even though large individual responsiveness remains. Main sources of controversies include design of clinical trials, definition of Class II malocclusion, and lack of inclusion of skeletal maturity among the prognostic factors. While no growth indicator may be considered to have a full diagnostic reliability in the identification of the pubertal growth spurt, their use may still be recommended for increasing efficiency of functional treatment for skeletal Class II malocclusion.

1. Background

It has been reported decades ago that the growth rate of the mandible is not constant throughout development [1–3] showing a peak during puberty [1, 2, 4, 5]. However, the intensity, onset, and duration of the pubertal growth peak (including mandibular growth peak) are subjected to noteworthy individual variations [1, 3–5]. A deficient mandibular growth on the sagittal plane is the most frequent diagnostic finding in skeletal (and dental) Class II malocclusion that occurs in up to one-third of the population [6, 7]. Thus, a therapy able to enhance mandibular growth is indicated in skeletal Class II patients [8]. In this regard, animal studies have shown that forward mandibular displacement enhances condylar growth resulting in significant mandible elongation [9, 10]. Consequently, a wide range of functional appliances (either removable or fixed) have been developed to stimulate mandibular growth by forward posturing of the mandible.

To date, the efficiency of functional treatment for skeletal Class II malocclusion is still controversial with reviews reporting very limited [11–13], partial [14–16], or relevant [17–19] effects of such treatment in terms of induced mandibular growth. Among the reasons for such inconsistencies is the timing, that is, skeletal maturity [18, 20, 21], during which treatment is performed. Clinical trials indicated that the functional treatment for skeletal Class II malocclusion is efficient when performed during the pubertal growth spurt [22–26] and without clinically relevant effects when performed before [27–29].

Therefore, over the last six decades, efforts have been carried out to find reliable and reproducible indicators of skeletal maturity in individual subjects [5, 20, 30–33]. These indicators have included radiographic hand and wrist maturational (HWM) methods [30, 34, 35], third finger middle phalanx (MPM) method [36–38], cervical vertebral maturational (CVM) methods [20, 33, 39], dental maturation

[31, 32, 40] and dental emergence [32, 41], chronological age [5, 41], and noninvasive biomarkers from serum [42, 43] or gingival crevicular fluid (GCF) [44, 45].

2. Common Issues related to the Investigation and Use of the Skeletal Maturity Indicators

Current evidence on the reliability of the different growth indicators and consequent definition of treatment timing is highly controversial. Contrasting results have been reported on the capability of the growth indicators (mainly the CVM method) in the identification of the mandibular growth peak [46–53] and on the efficiency of functional treatment for Class II malocclusion [13, 18]. The investigation on growth indicators has common sources of controversies for all the indicators and specific issues related to each indicator. Herein, common controversial issues to all indicators are listed, while specific issues and controversies on the functional treatment are reported below.

2.1. Stages versus Ossification Events. In using radiographical indicators of growth phase that are based on sequential discrete stages, an important distinction has to be made between stages and ossification events [54, 55]. The stages are specific periods in the development of a bone that have been described in that particular rating method, while an ossification event occurs when a given stage matures into the following one [54, 55]. Of particular clinical relevance, as ossification event is defined as the midpoint between two consecutive stages, a proper identification event requires serial radiographs. The main limitation raised by the use of single stages resides in the concept that these stages have variable duration [35, 47, 55, 56] as has been seen for the HWM [5, 55], MPM [37], and CVM [47, 56] methods, making the prediction of the imminent growth spurt less reliable. Therefore, the exact determination of the imminent growth spurt would require closer monitoring of the ossification event, that is, longitudinal recordings, rather than being based on a single stage. This aspect is of further relevance considering that fine transitional changes in the hand and wrist or cervical vertebral morphology may be responsible for determining a pubertal or nonpubertal stage. According to these concepts, longitudinal studies on the capabilities of the different indicators in the identification of the mandibular growth peak (or pubertal growth spurt) are to be preferred over cross-sectional ones. From a clinical standpoint, whenever possible, serial monitoring should be preferred over growth prediction based on single staging.

2.2. Correlation Analysis versus Diagnostic Reliability. In spite of the huge number of studies on growth indicators and pubertal growth spurt, the diagnostic reliability of any of the growth indicators in the identification of the peak in standing height or mandibular growth on an individual basis is yet undetermined. Of note, correlations between parameters do not necessarily imply diagnostic accuracy [57, 58].

One of the reasons underlying this noteworthy lack of data may reside in the difficulty of obtaining diagnostic parameters, such as sensitivity, specificity, and accuracy, from longitudinal data in a subset of selected subjects all with a predetermined condition (mandibular growth peak) or a diagnostic outcome (a given HWM/CVM stage). However, the identification of a mandibular growth peak requires longitudinal data, and it is defined as the greatest growth interval [21, 37].

To overcome such limitations, a recent study [21] using already published data on the CVM method [49] has introduced a simple procedure to derive data on diagnostic reliability in the case of longitudinal recordings of growth indicators and mandibular growth. In particular, individual CVM stages and increments in mandibular growth recorded longitudinally were analysed in a group of subjects according to the different predetermined annual (chronological) age intervals. Therefore, a full diagnostic reliability analysis, including sensitivity, specificity, positive and negative predictive values (PPVs and NPVs), and accuracy, of a given CVM stage in the identification of the mandibular growth peak could be carried out within each age interval group. To date only limited longitudinal studies reported on the diagnostic reliability of the CVM [21] and MPM [37] methods in the identification of the mandibular growth peak. Therefore, longitudinal studies reporting diagnostic reliability should be preferred over investigations using bivariate correlations [59, 60] or even multiple regression analyses [61, 62].

2.3. Definition of Total Mandibular Length. In several studies on the reliability of growth indicators [34, 35, 63–66] or on the efficiency of functional treatment for Class II malocclusion [17, 26, 67, 68] (see below), the landmark Articulare (Ar) was used instead of the landmark Condylion (Co) to assess the posterior end-point of the mandible. The Ar is defined as the point of intersection of the images of the posterior border of the ramal process of the mandible and the inferior border of the basilar part of the occipital bone [69]. The problem with Ar is that it is not an anatomical landmark that pertains to the mandible exclusively. On the other hand, the landmark Ar has the advantage of being more easily identified as compared to the Co. Even though a previous study [70] reported close correlation between the Ar-Pogonion (Pog) and Co-Pog distances on a sample of 60 cases; other evidence [71, 72] suggested the use of the point Co over Ar as being more reliable in terms of mandibular growth recording. In particular, the posture of the mandible might also affect the position of Ar [71]. Yet repeatability analysis on a cross-sectional sample [70] does not provide evidence that, in a longitudinal analysis, increments in mandibular length (as Ar-Gn and Co-Gn or Ar-Pog and Co-Pog) would yield overlapping patterns of mandibular growth peaks (which are mostly used to validate growth indicators). Therefore, future data are warranted to fully elucidate whether the different landmarks may be used indifferently.

3. Hand and Wrist Maturation Method

The use of the hand and wrist bones for the assessment of skeletal maturity has initially been reported by Todd [73]

Table 1: Description of the stages of the hand and wrist maturation (HWM) method according to Fishman [35].

Stage description	Attainment
SMI 1: third finger proximal phalanx, epiphysis as wide as metaphysis	Before the standing height and mandibular growth peaks (prepubertal)
SMI 2: third finger middle phalanx, epiphysis as wide as metaphysis	
SMI 3: fifth finger middle phalanx, epiphysis as wide as metaphysis	
SMI 4: thumb, appearance of adductor sesamoid	
SMI 5: third finger distal phalanx, epiphysis showing capping towards the metaphysis	Generally, at coincidence of the standing height and mandibular growth peaks (pubertal)
SMI 6: third finger middle phalanx, epiphysis showing capping towards the metaphysis	
SMI 7: fifth finger middle phalanx, epiphysis showing capping towards the metaphysis	
SMI 8: third finger distal phalanx, fusion of epiphysis and diaphysis	After the standing height and mandibular growth peaks (postpubertal)
SMI 9: third finger proximal phalanx, fusion of epiphysis and diaphysis	
SMI 10: third finger middle phalanx, fusion of epiphysis and diaphysis	
SMI 11: radius, fusion of epiphysis and diaphysis	

The method is also referred to as skeletal maturity assessment (SMA). SMI, skeletal maturity indicator.

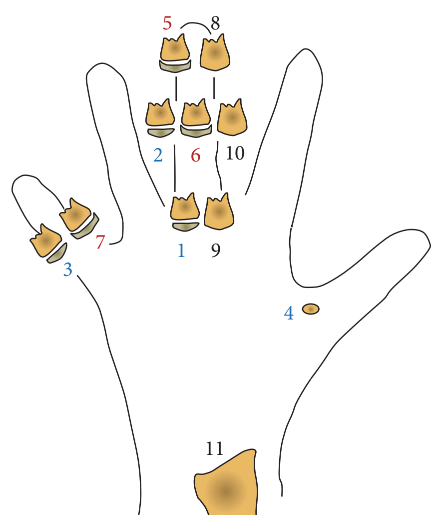

Figure 1: Diagram of the stages of the hand and wrist maturation (HWM) method according to Fishman [35]. The method is also referred to as skeletal maturity assessment (SMA). Blue, prepubertal stages; red, pubertal stages; black, postpubertal stages. See Table 1 for details. Modified from Fishman [35] with permission.

followed by others [30, 74, 75]. In particular, all of these methods were based on the assessment of a skeletal age (in years) according to specific ossification events of the hand and wrist. Subsequently, such individual skeletal age had to be compared with reported norms. For reasons listed below, stage-based procedure for the hand and wrist maturation has been added. Among the different stage-based HWM methods [32, 34, 35, 65], the most used nowadays both in research and clinical practice is likely to be that proposed by Fishman [35], also known as skeletal maturation assessment (SMA). Details of the 11-stage HWM method according to Fishman [20] are summarized in Table 1 and shown in Figure 1, while main longitudinal investigations in relation to mandibular growth in untreated subjects without major malocclusion are summarized in Table 2.

3.1. Current Evidence. All the published longitudinal studies on the HWM methods and mandibular growth peak included Caucasian [35, 53, 65] and Australian aborigine [34, 76] subjects, and none reported a specific diagnostic reliability analysis. Tofani [65] reported that onset of fusion of distal phalanges are good predictors of mandibular growth peak; however, this study included only females. The study by Grave [34] also reported moderate significant correlations of the hand and wrist maturation with mandibular growth peak for both females and males. A further study by Grave and Brown [76] on the same sample reported previously [34], investigating the HWM method with standing height, reported that peak height velocity would occur up to 3 and 6 months later, in males and females, respectively, of the attainment of the third finger middle phalanx (MP3) stage

Table 2: Main longitudinal studies on the hand and wrist maturation (HWM) method and mandibular growth peak in untreated subjects without major malocclusion.

Study	Sample origin and other information	Sample size and sex distribution/age range	Hand and wrist maturation assessment	Main mandibular parameter(s)	Statistical analysis	Main results	Clinical implications according to the authors
Tofani 1972 [65]	Broadbent-Bolton growth study	20 F/9–18 yrs	Onset of fusion of the first and third finger distal phalanges	Ar-Pog, Ar-Go, Go-Pog	Differences between pre- and postpubertal and correlation analyses	Age of onset of fusion of distal phalanges and that for mandibular growth peak were significantly correlated	Onset of fusion of distal phalanges are good predictors of mandibular growth peak
Grave 1973 [34]	Australian aborigines	36 F, 52 M/8–18 yrs	Custom method	Ar-Pog	Correlation analyses	Some moderate significant correlations were seen for females and males	The HWM method may be useful in clinical practice
Fishman 1982 [35]	Denver Child Research Study and own practice	206 F, 196 M/0–25 yrs	Eleven-stage method (SMIs) according to Fishman [35] (Figure 1)	Ar-Gn	Differences among stages	Maximum growth increments were seen during stages 5–7	The SMIs provide a key to identification of maturation level with important clinical applications
Mellion et al. 2013 [53]	Broadbent-Bolton growth study (a)	50 F, 50 M/8 and 10 yrs at least for females and males, respectively, with 6 to 11 annual recordings	Eleven-stage method (SMIs) according to Fishman [35] (Figure 1)	Co-Gn	Actual age at onset and peak in mandibular growth used as the gold standards against which key ages inferred from SMIs method was compared	The SMIs showed in males and females a moderately strong or weaker relationships, respectively, to the timing for the onset and peak in mandibular growth	The SMIs appear to offer the best indication that peak growth velocity has been reached

Studies using maturation method based on ossification events (stages) are represented. Ar, Articulare; Pog, Pogonion; Go, Gonion; Gn, Gnathion; Co, Condylion; SMIs, skeletal maturation indicators (according to Fishman [35]). *Note.* a: it may include some Class II subjects.

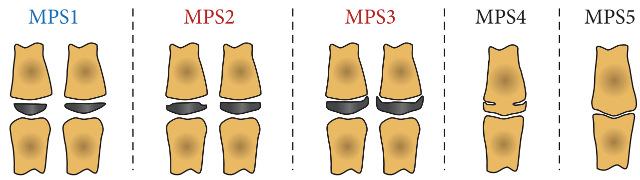

FIGURE 2: Diagram of the improved third finger middle phalanx maturation (MPM) method according to Perinetti et al. [37]. Blue, prepubertal stages; red, pubertal stages; black, postpubertal stages. See Table 3 for details. Modified from Perinetti et al. [37] with permission.

G (corresponding to the SMI6, See Table 1). In the HWM method according to Fishman [35], peak in mandibular growth (as Ar-Gn) would occur in stage 6 and 7 for females and males, respectively [35]. Further studies correlated this HWM method with standing height [32, 54, 76]. Similarly, the study by Mellion et al. [53] reported for the HWM according to Fishman [35] a moderately strong or weaker relationships in males and females, respectively. In particular, the HWM method assessments had consistently lower errors than either mean chronologic age or CVM method in the identification of both the peaks in standing height and mandibular length [53].

Of note, a previous longitudinal study [77] compared the skeletal age of the whole HWM method (according to Todd [73] and Greulich and Pyle [30]) with specific ossification events of the first, second, and third finger, referred to as the three-finger maturation assessment. As a result, the three-finger maturation assessments were shown to mature in slight advancement than the whole HWM assessments. However, this study [77] was based on correlation analyses and differences in skeletal age between methods, lacking a true diagnostic analysis [78] of concordance or measurement of agreement [79].

3.2. Current Controversies. The Greulich and Pyle method [30] and other similar methods [73–75] have been criticized in that it may be difficult to set a reference standard, because of the differential rate of maturation in different bones across individuals of the same population or across different population [54, 80]. For this reason, several standards, that is, norms, have been published for the hand and wrist maturation assessment according to the population of interest. For more detail, see Greulich and Pyle [30] and Todd [73] for white American subjects, Sutow and Ohwada [74] for Japanese subjects, and Tanner and Whitehouse [75] for British subjects. However, such norms are not always available for each population, while another important issue relates to the secular trends, with successive generations becoming taller and reaching puberty at earlier stages [81, 82]. Therefore, the staging of skeletal maturity by describing specific ossification events on the hand-wrist radiograph [32, 34, 35, 53, 65, 66, 83, 84] may be a valid tool as being more independent of differences among populations and secular trends and availability of published standards [80]. The methods based on ossification events [32, 34, 35] might thus be considered to have a wider clinical applicability.

3.3. Clinical Implication. Even though the number of studies correlating the HWM methods with mandibular growth peak is limited (Table 2), all of these investigations concluded that these methods may be useful in clinical practice. Therefore, the use of the HWM method may be recommended for planning treatment timing. In spite of this favorable evidence, the HWM method has a main disadvantage residing in the need of an additional film, with consequent increased radiation exposure of the whole hand and wrist. This aspect would prevent a serial recording to monitor closely the ossification events, limiting the diagnosis that has to rely on single stages.

4. Third Finger Middle Phalanx Maturation Method

Previous studies reported above on the HMW methods [34, 54, 76, 85] provided an indication of the possibility for the third finger middle phalanx maturation to the used alone as an indicator of skeletal maturity. Close concurrence of the attainment of MP3 stage G with the peak height velocity has been reported for both males and females [54, 85]. Similar results were seen when correlating the third finger middle phalanx maturation with mandibular growth peak [35, 76]. Therefore, the use of the sole third finger middle phalanx for a maturational method has been proposed [36, 38, 86–88]. This third finger middle phalanx maturation (MPM) method [37, 78] would thus have the advantage of an easy interpretation of the stages, without double contours or superimposition by other structures. Details of a 5-stage MPM method according to Perinetti et al. [37] are summarized in Table 3 and showed in Figure 2, while the only longitudinal investigation [37] in relation to mandibular growth in untreated subjects without major malocclusion is summarized in Table 4.

4.1. Current Evidence. All of previous investigations [36–38, 78, 86–88] suggested the use of the MPM method in clinical practice. The main advantage of the MPM method resides in the minimal radiation exposure that would allow close monitoring of the ossification events by longitudinal recordings. Therefore, ideal timing of treatment in individual patients may be identified more precisely as compared to when information comes from single recording, as for the case of the HWM and CVM methods. Finally, the MPM method is of easy execution and interpretation and may be performed in any clinical setting with minimal instrumentation. In spite of the potential clinical advantages offered by

Table 3: Description of the stages of the third finger middle phalanx maturation (MPM) method according to Perinetti et al. [37].

Stage description	Attainment
MPS1: epiphysis is narrower than the metaphysis, or epiphysis is as wide as metaphysis but with both tapered and rounded lateral borders. Epiphysis and metaphysis are not fused. Reported as MP3-F [32]	More than 1 year before the onset of the pubertal growth spurt [32] or mandibular growth peak [37]
MPS2: epiphysis is at least as wide as the metaphysis with sides increasing thickness and showing a clear line of demarcation at right angle, either with or without lateral steps on the upper contour. In case of asymmetry between the two sides, the more mature side is used to assign the stage. Reported as SMI2 [35] or as MP3-FG [32]	1 year before the pubertal growth spurt [32] or mandibular growth peak [37]
MPS3: epiphysis is either as wide as or wider than the metaphysis with lateral sides showing an initial capping towards the metaphysis. In case of asymmetry between the two sides, the more mature side is used to assign the stage. Epiphysis and metaphysis are not fused. Reported as SMI6 [35] or as MP3-G [32]	At coincidence of the pubertal growth spurt [32] or mandibular growth peak [37]
MPS4: epiphysis begins to fuse with the metaphysis although contour of the former is still clearly recognizable. The capping may still be detectable. Reported as MP3-H [32]	After the pubertal growth spurt [32] or mandibular growth peak [37]
MPS5: epiphysis is totally fused with the metaphysis. Reported as SMI10 [35] or as MP3-I [32]	At the end of the pubertal growth spurt [32]

Table 4: Main longitudinal studies on the third finger middle phalanx maturation (MPM) method and mandibular growth peak in untreated subjects without major malocclusion.

Study	Sample origin and other information	Sample size and sex distribution/age range	Middle phalanx maturation assessment	Main mandibular parameter	Statistical analysis	Main results	Clinical implications according to the authors
Perinetti et al. 2016 [37]	Burlington growth study	15 F, 20 M/9–16 yrs	Five-stage custom method (Figure 2)	Co-Gn	Diagnostic performance	Stage 2 had a satisfactory but variable accuracy in the identification of imminent mandibular growth peak	The MPM method may be useful in treatment timing

Co, Condylion; Gn, Gnathion.

the MPM method, current evidence is still little. The present investigations [36, 38, 78, 86–88] are limited by the cross-sectional designs in which the MPM method was analyzed in correlation [36, 38, 86–88] or in diagnostic agreement [78] with the CVM method. Indeed, such analyses do not prove the diagnostic reliability of the method in the identification of the pubertal/mandibular growth peak. The results for the recent longitudinal study [37] on diagnostic reliability (Table 4) showed that the MPM stage 2 (MPS2) precedes the mandibular growth spurt, which is generally concomitant of MPS3. However, even though the overall diagnostic accuracy of 0.91 was satisfactory, the overall positive predictive value was 0.73, thus meaning that false positives may be encountered. This evidence was mainly due to the duration of the MP2 that in some cases lasted for 2 years and it was more evident in the older age groups. Again, the following of the ossification events should be preferred instead of basing growth prediction on single stages [54].

4.2. Clinical Implications. Although further investigations are needed, the MPS2 and MPS3 may be considered to be associated with the onset and maximum mandibular growth peak, respectively, in most of the subjects, and may therefore be used for planning treatment timing for functional treatments especially for skeletal Class II malocclusion [4]. According to the minimal radiation exposure, longitudinal monitoring is recommended to follow closely the ossification events. Finally, a combinational use of the MPM method with a further noninvasive indicator of pubertal growth spurt, that is, standing height, especially in the older adolescents, might increase diagnostic reliability [37].

5. Cervical Vertebral Maturation Method

The CVM method was initially proposed by Lamparski [39] and then modified by others [20, 33, 46, 49]. In this procedure, the shape of the first cervical vertebrae is analyzed to carry out information on the different growth phase of the subject. In particular, the original method by Lamparski [39] uses vertebrae that can be obscured by the thyroid collar and relied on interstage comparisons, while the subsequent variants of the CVM method [20, 33, 46, 49] were less or

Table 5: Description of the stages of the most common cervical vertebral maturation (CVM) method according to Baccetti et al. [20] with corresponding codes.

Stage description	Attainment
CS1: lower borders of the second, third, and fourth vertebrae (C2, C3, and C4) flat and the bodies of C3 and C4 trapezoid in shape	At least 2 years before the pubertal growth spurt
CS2: only the lower border of C2 with concavity and the bodies of C3 and C4 trapezoid	About 1 year before the pubertal growth spurt
CS3: lower borders of C2 to C3 with concavities and the bodies of C3 and C4 either trapezoid or rectangular horizontal in shape	At coincidence of the ascending portion of the pubertal growth spurt
CS4: lower borders of C2 to C4 with concavities and the bodies of both C3 and C4 both (or at least one, [a]) rectangular horizontal	At coincidence of the descending portion of the pubertal growth spurt
CS5: lower borders of C2 to C4 with concavities and at least one or both of the bodies of C3 and C4 squared.	About 1 year after the pubertal growth spurt
CS6: lower borders of C2 to C4 with concavities and at least one or both of C3 and C4 rectangular vertical	At least 2 years after the pubertal growth spurt

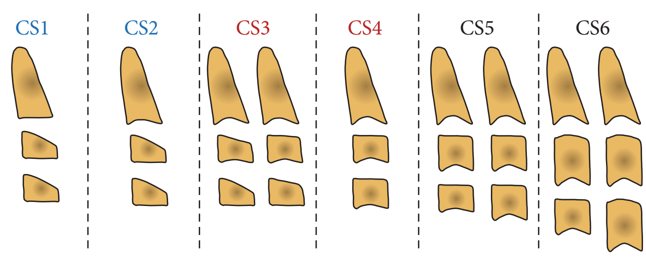

Figure 3: Diagram of the stages of the most common cervical vertebral maturation (CVM) method according to Baccetti et al. [20]. Blue, prepubertal stages; red, pubertal stages; black, postpubertal stages. See Table 5 for details.

not dependent on interstage comparisons. The most common CVM methods are the variants proposed by Hassel and Farman [33] and Baccetti et al. [20], where mandibular growth peak has been reported to occur between stages 3 and 4 [20, 21, 46, 49]. Among the main advantages of the CVM method is the fact that it does not require supplementary radiographic exposure, as for the HWM method, since lateral head film is usually available as a pretreatment record. Details of the 6-stage CVM method according to Baccetti et al. [20] are summarized in Table 5 and shown in Figure 3, while main studies in relation to mandibular growth in untreated subjects without major malocclusion are summarized in Table 6.

5.1. Current Evidence. According to previous evidence [20, 46, 49], maturation of the cervical vertebrae occurs in females earlier than in males. Ideally, CVM stages from 2 to 4 should have precise durations in a way that interventions may be easily planned on a basis of a single lateral head film. In this regard, the duration of each CVM stage from 2 to 5 has been reported to last 1 year according to Franchi et al. [49] (Table 6), while little data has been reported to date on the individual durations of the CVM stages [47, 53, 61]. This does not allow the easy planning of the timing of intervention based only on a single lateral head film. A further study by Ball et al. [47] (Table 6) reported very different results with the CVM stages 2, 3, 4, and 5 with longer durations of about 1.9, 1.8, 3.8, and 2.9 years, respectively. On the contrary, another longitudinal investigation [61] reported mean duration of about 1 year for the CVM stages from 2 to 4. Interestingly, longer and shorter CVM stages 3 to 4 intervals have been reported for Class III [89] and Class II subjects [90], respectively, as compared to that of Class I subjects. However, these studies [89, 90] were limited by their cross-sectional design not allowing the detection of any individual variation in the duration of single CVM stages. Longitudinal studies correlating facial growth patterns with duration of CVM stages are still missing.

Many previous studies were limited to the correlation analyses between the different CVM and HWM methods [33, 36, 48, 59, 86–88, 91, 92] with no information on the mandibular growth (or standing height) peak; other studies were limited to the longitudinal investigation of the cervical vertebral maturational changes [56] or investigated the potential of the CVM method to detect postpubertal mandibular growth [50]. A further investigation [62] was focused on the capability of the CVM method to predict the total amount of mandibular growth from prepubertal to postpubertal phases, irrespective of timing of pubertal growth peak [93], and it included exclusively Class II female subjects, where mandibular growth peak has been shown to be minimal or absent [23].

TABLE 6: Main longitudinal studies on the cervical vertebral maturation (CVM) method and mandibular growth peak in untreated subjects without major malocclusion.

Study	Sample origin and other information	Sample size and sex distribution/age range	Cervical vertebral maturation assessment	Main mandibular parameter(s)	Statistical analysis	Main results	Clinical implications according to the Authors
O'Relly and Yanniello 1988 [64]	Broadbent-Bolton growth study	13 F/9–15 yrs	Six-stage Lamparski's standards	Ar-Pog, Ar-Go, Go-Pog	Differences among stages	Stages 1–3 occurring the year preceding the peak in most cases	The CVM can be used to assess timing of mandibular growth
Franchi et al. 2000 [49]	Michigan growth study	15 F, 9 M/7–16 yrs	Six-stage modified Lamparski's standards	Co-Gn, Co-Goi, Goi-Gn	Differences among stages	Total mandibular length showed the greatest significant increment between stages 3 and 4	The CVM is a valid method for the evaluation of skeletal maturity and mandibular growth peak
Gu and McNamara 2006 [52]	Part of the Mathews and Ware implant sample [143]	13 F, 7 M/≈7–17 yrs	Six-stage method according to Baccetti et al. [20] (Figure 3)	Co-Gn, Co-Go, Go-Me	Differences among stages	Peak in mandibular length observed between stages 3 and 4	Not reported
Chen et al. 2010 [108]	Research Centre of Craniofacial Growth and Development at Beijing University.	55 F, 32 M/8–18 yrs	Four-stage quantitative method [94]	Ar-Gn, Ar-Go, Go-Gn	Differences among stages (as absolute and relative growth increment)	Maximum growth increments were seen during stage II (b) with relative increments more consistent than absolute ones	Use of the quantitative CVM method is recommended for treatment planning
Ball et al. 2011 [47]	Burlington growth study	90 M/9–18 yrs	Six-stage method according to Baccetti et al. [20] (Figure 3)	Ar-Gn	Differences among stages in groups of advanced, average, and delayed maturation	Mandibular growth peak occurred mainly during stage 4 (which lasted 3.8 yrs)	The CVM method cannot predict the onset of the mandibular growth peak
Mellion et al. 2013 [53]	Broadbent-Bolton growth study (a)	50 F, 50 M/8 and 10 yrs at least for females and males, respectively, with 6 to 11 annual recordings	Six-stage method according to Baccetti et al. [20] (Figure 3)	Co-Gn	Actual age at onset and peak in mandibular growth used as the gold standards against which key ages inferred from CVM method was compared	The CVM stages showed only a weak to moderate relationship to the timing for the onset and peak in mandibular growth	Use of the CVM method is not recommended for treatment planning
Gray et al. 2016 [61]	Burlington growth study	12 F, 13 M/10–16 yrs	Six stage method according to Baccetti et al. [20] (Figure 3)	Ar-Gn	Mixed linear regression	Mandibular length changes were not significantly associated with CVM stages	The CVM method does not accurately identify the mandibular growth peak
Perinetti et al. 2016 [21]	Same as Franchi et al. [49]	Same as Franchi et al. [49]	Same as Franchi et al. [49]	Co-Gn, Co-Goi, mMG	Diagnostic performance	Stages 3-4 have variable diagnostic accuracy in the identification of mandibular growth peak	The CVM can be used in clinical practice. Limitations due to the use of the same sample from which the method was derived

Studies using maturation method based on ossification events (stages) are represented. Ar, Articulare; Pog, Pogonion; Go, Gonion; Co, Condylion; Gn, Gnathion; Goi, Gonion intersection; mMG, mean mandibular growth ([Co-Gn + Goi-Gn]/2). *Note*. a: it may include some Class II subjects; b: stage II equivalent to stage 3 in the 6-stage CVM method.

However, as for the HWM method, the most relevant information may be derived from longitudinal studies investigating the capabilities of these methods in detecting the mandibular growth peak, possibly in individual subjects. Previous studies on the CVM method and mandibular growth peak have reported contrasting results of negligible [47, 48, 53, 61, 62] and noteworthy [49, 52, 64, 66] correlations. Interestingly, only few studies [21, 47, 49, 52, 53, 61, 64, 94] (Table 6) correlated the CVM method (as stage system) with mandibular growth under longitudinal monitoring. According to this evidence, a total of five studies [21, 49, 52, 64, 94] reported mandibular growth peak to occur during stages 3 and 4, and four [21, 49, 64, 94] of them recommended the use of the CVM method in treatment planning. One study [21], however, used the same sample of Franchi et al. [49] from which the CVM method was derived. The remaining three studies [47, 53, 61] failed to detect a significant correlation between the CVM and mandibular growth peak and did not recommend the method for treatment planning.

5.2. Current Controversies. When reporting on the CVM method, the different variants of the method [20, 33, 46, 48, 84] have to be taken into account and results should be limited to the investigated methods or parameters [95]. Significant differences in study designs, cephalometric recordings, and data analysis have to be taken into account when dealing with clinical usefulness of the CVM method. For instance, apart from the study [21] using the same sample reported by Franchi et al. [49] (Table 6), the only investigation [66] that has reported on the diagnostic capability of the CVM method in the identification of the mandibular growth peak used receiver operating characteristics curves. However, this study [66] was based on a cross-sectional sample and it was limited to the analysis of the area under the curve, which is not enough to describe in full the diagnostic reliability of the method. Therefore, conclusions on the diagnostic reliability of the CVM method in the identification of the mandibular growth peak have conjecturally been based on difference among groups/stages [47, 49, 52, 64, 94], regression analyses [61], or other analyses missing diagnostic capabilities [53].

Another relevant issue when dealing with the CVM method resides in its repeatability. The method has been reported to have poor repeatability [96, 97]. Although this limitation may be avoided by proper training [98], poor repeatability has been seen even in studies correlating the CVM method with mandibular growth [62], while longitudinal investigations herein considered (Table 6) reported no information [52, 53, 64, 94] or good to high repeatability [47, 49, 61] in the CVM stage assignment. Finally, when assigning the CVM stage, it has been suggested that exceptional cases, that is, cases outside the reported norms, may exist [98] and this may be responsible for doubtful interpretation and poor reproducibility.

5.3. Clinical Implications. As for the HWM method, the CVM methods require films that are usually available as a pretreatment record, while optimal treatment timing is to be delayed for an undermined term after the diagnosis. Therefore, further reevaluation of the growth phase needs a reexecution of a lateral head film, which would not be indicated. Moreover, the cervical vertebrae might be partially covered by the protection collar, which would be necessary to reduce radiation exposure [99]. Apart from this consideration, the use of the CVM method requires proper training in stage assignment and knowledge of exception cases [98]. Moreover, variability in duration of the CVM stages 2 to 4 [47, 56] has been taken into account and functional treatment requiring the inclusion of the mandibular growth spurt in the active treatment period should last until attainment of CS5 [21]. Future longitudinal studies on diagnostic reliability of the CVM method in the identification of the mandibular growth peak are still necessary to fully elucidate the clinical usefulness of the method.

6. Dental Maturation Method

Dental maturity can be assessed by the exfoliation of deciduous teeth, such as the second molars [100], phases of dentition [101], dental emergence [5, 32], or calcification stages through the evaluation of tooth formation [40]. Calcification stages of the teeth can be carried out on panoramic radiographs that are routinely used for different purposes, with mandibular teeth preferred over maxillary ones being less subjected to superimpositions from other skeletal structures. Even intraoral radiograph may be used with minimal irradiation to the patient. Therefore, dental maturation has been proposed as a further useful method for assessing the growth phase in individual subjects [31]. The most common method used for scoring dental maturation is the one described by Demirjian et al. [40]. This method has the advantage of using relative values of the root formation to the crown height, rather than absolute lengths. Foreshortened or elongated projections of developing teeth will not affect the reliability of this assessment [40]. Details of the dental maturation method according to Demirjian et al. [40] are summarized in Table 7 and shown in Figure 4, while main cross-sectional studies of diagnostic reliability using the HWM or CVM methods in untreated subjects without major malocclusion are summarized in Table 8.

6.1. Current Evidence. The period corresponding to the exfoliation of the deciduous second molars has been advocated as favorable for the beginning of a one-phase orthodontic treatment in growing subjects [102]. However, as previously reported [100], the exfoliation of the deciduous second molars has no significant relationship with the onset of the pubertal growth spurt (Table 8). Similarly, the assessment of the phase of dentition (as deciduous, early mixed, mixed, and permanent) is a simple procedure and has been used to assess the effects of different treatment timing in Class II patients [103]. However, the only study [101] on diagnostic reliability (Table 6) reported that neither the early mixed nor the mixed dentition phases are valid indicators of the pubertal growth spurt. Therefore, the use of the exfoliation of the deciduous second molar or phases of dentition is not recommended

Table 7: Description of the stages of the most common dental maturation method according to Demirjian et al. [40].

Stage description	Attainment
Stage D. When (1) the crown formation is complete down to the cementoenamel junction; (2) the superior border of the pulp chamber in the single-root teeth has a definite curved form, with it being concave towards the cervical region; the projection of the pulp horns, if present, gives an outline shaped like the top of an umbrella and (3) the beginning of root formation is seen in the form of a spicule	Canine, premolars, and second molar before the pubertal growth spurt [28, 57, 110, 112]
Stage E. When (1) the walls of the pulp chamber form straight lines, the continuity of which is broken by the presence of the pulp horn, which is larger than in the previous stage and (2) the root length is less than the crown height	Mostly, canine and first premolar before the pubertal growth spurt [28, 57, 110, 112]
Stage F. When (1) the walls of the pulp chamber form a more or less isosceles triangle, with the apex ending in a funnel shape and (2) the root length is equal to or greater than the crown height	Sometimes, canine before the pubertal growth spurt [28, 57, 112]
Stage G. When the walls of the root canal are parallel and its apical end is still partially open	Canine, premolars, and second molar before, during, and after the pubertal growth spurt [28, 57, 110, 112]
Stage H. When (1) the apical end of the root canal is completely closed and (2) the periodontal membrane has a uniform width around the root and the apex	Second molar after the pubertal growth spurt [28, 57, 112]

Only stages D to H are summarised due to their relevance with the circumpubertal growth phase. In molars, the distal root is considered in assessing the stage [40]. Only results from studies reporting diagnostic reliability analysis are shown regarding the moment of attainment of the different stages for mandibular teeth.

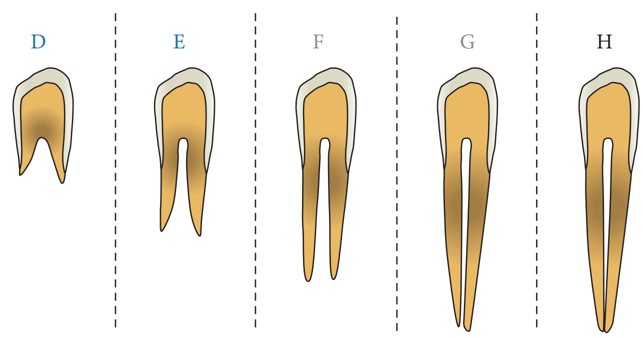

Figure 4: Diagram of the stages of the most common dental maturation method according to Demirjian et al. [40]. Only the stages D to H are represented due to their relevance with the circumpubertal growth phase. In molars, the distal root should be considered in assessing the G and H stages. Blue, prepubertal stages; grey, any stage; black, postpubertal stages. See Table 7 for details.

for treatment planning. Similarly, dental emergence has also been reported to be poorly correlated with pubertal growth spurt [5, 32]. Regarding dental calcification stages, high correlations with skeletal maturity have been reported by most of the investigations performed to date using the CVM [31, 60, 86, 104–109], HWM [106, 110, 111] or MPM [86, 112] methods. As a consequence, most of the studies have proposed the staging of dental maturation as a reliable indicator of the individual skeletal maturity, which has major diagnostic implications [31, 60, 106–109, 111, 113–117]. On the contrary, other studies [104, 105, 110, 112] (Table 8) including a meta-analysis [118] reported a very limited clinical usefulness of dental maturation in the identification of the pubertal growth spurt.

6.2. Current Controversies. The apparent inconsistency among all the current investigations on dental and skeletal maturation (all cross-sectional) resides in the use of proper diagnostic reliability analysis. The present evidence on diagnostic reliability [104, 105, 110, 112] has revealed that the conclusions reported in previous investigations based on correlational analyses [31, 60, 106–109, 111, 113–117] were not actually supported by the results obtained in those studies. The few exceptions seen for early dental developmental stages, which were reliable in the identification of the prepubertal growth phase [105, 110, 112, 118], would have poor clinical meaning since early mixed and intermediate mixed dentition may be used instead for the same purpose [5, 32, 101]. Longitudinal studies on the diagnostic reliability

Table 8: Main cross-sectional studies on the dental emergence and dental maturation method according to Demirjian et al. [40] and hand and wrist or cervical vertebral maturation in untreated subjects without major malocclusion.

Study	Sample size and sex distribution/age range	Dental maturation assessment	Skeletal maturation assessment	Statistical analysis	Main results	Clinical implications according to the authors
Tassi et al. 2007 [100]	428 (a)	Exfoliation of the deciduous second molars	CVM, 6-stage method according to Baccetti et al. [20]	Sensitivity, specificity, PPV, positive LHR	No significant relationship between the moment of exfoliation of deciduous second molars and the onset of the pubertal growth spurt	Not recommended for treatment planning
Franchi et al. 2008 [101]	500 F, 500 M/≈6–14 yrs	Early mixed, mixed, late mixed, and permanent	CVM, 6-stage method according to Baccetti et al. [20]	Sensitivity, specificity, PPV, positive LHR	Mixed dentition and early permanent dentition are not valid indicators for the onset of the pubertal growth spurt	Not recommended for treatment planning
Perinetti et al. 2012 [57]	208 F, 146 M/6.8–17.1 yrs	Mandibular teeth	CVM, 6-stage method according to Baccetti et al. [20]	Sensitivity, specificity, PPV, NPV, accuracy, positive LHR	Dental maturation assessment is reliable in the identification of prepubertal and postpubertal growth phases	Not recommended for treatment planning
Perillo et al. 2013 [28]	192 F, 108 M/6.8–17.1 yrs	Mandibular canine and second molar	CVM, 6-stage method according to Baccetti et al. [20]	Sensitivity, specificity, PPV, NPV, accuracy, positive LHR	Combined canine and second molar maturation has little role in the identification of the pubertal growth spurt	Not recommended for treatment planning
Surendran and Thomas 2014 [112]	71 F, 79 M/8–16 yrs	Mandibular teeth	MP3, 6-stage method according to Rajagopal and Kansal [36]	Positive LHR	Dental maturation assessment is reliable in the identification of prepubertal and postpubertal growth phases	Recommended only for planning treatments that need to be performed in prepubertal patients
Cericato et al. 2016 [110]	314 F, 262 M/7–18 yrs	Mandibular teeth	CVM, 6-stage method according to Hassel and Farman [33] and Baccetti et al. [20]	Positive LHR	Dental maturation assessment is reliable in the identification of prepubertal growth phases	Not reported

Only studies reporting diagnostic performance are represented. No longitudinal study has been reported to date. CVM, cervical vertebral maturation; PPV, positive predictive value; LHR, likelihood ratio; NPV, negative predictive value; a, other information not provided.

of dental maturation, mainly as calcification stages, in the identification of the mandibular growth peak are still missing.

6.3. Clinical Implications. Irrespective of the mandibular tooth, none of the dental maturation stages may be reliably used to identify in individual subjects the pubertal growth spurt (Table 8). Other indicators remain preferable for the determination of the growth phase in individual growing patients [118].

7. Other Indicators

7.1. Standing Height. Standing height has been used as an indicator of the pubertal growth spurt from several decades ago [3, 5, 119, 120]. This procedure requires several measurements of standing height repeated at regular intervals to construct an individual curve of growth velocity and has the advantage of being noninvasive. The peak in standing height has been reported to precede [3, 119] or to be in concurrence [120, 121] with the peaks in facial bones growth. Other evidence reported that standing height had little predictive value in determining the growth profile of any of the mandibular parameters except for Ar-Pog for females [63]. Mandibular growth peak has been seen to occur in concurrence with or slightly after the peak in standing height for males and females, respectively [35]. In a more recent investigation [53], the peak in stature had a shorter duration and tended to occur a few months before that of the face and mandible. Although all of these investigations [3, 5, 32, 34, 49, 53, 119–121] reported a satisfactory degree of correlation between the standing height and mandibular growth, data on diagnostic reliability of standing height peak in the identification of the mandibular growth peak has been reported only in one study [21]. In particular, a variable diagnostic accuracy (between 0.61 and 0.95) was seen for the standing height peak in the identification of the mandibular growth peak (as greatest annual increments in Co-Gn or in mean value between Co-Gn and Co-Go) [21]. From a clinical perspective, therefore, the recording of standing height may be useful, especially in conjunction with other radiographical indicators.

7.2. Chronological Age. Several investigations [32, 35, 53, 122, 123] reported that the average ages at the onset and peak of pubertal growth in stature are about 12 and 14 years in boys and 10 and 12 years in girls. However, a noteworthy variability was also seen when pubertal growth spurt was defined as standing height peak [21, 35, 54, 63, 65, 76, 84, 92] or mandibular growth peak [37, 49, 52, 64]. To date, only one cross-sectional study [124] reported on diagnostic performance of chronologic age in the identification of the pubertal growth phase (according to the CVM method [20]). In males, age up to 9 years can reliably identify a prepubertal stage of skeletal development, and in females an age of at least 14 years can reliably identify a postpubertal stage. In both males and females, chronologic age could not reliably identify the onset of the pubertal growth phase [20]. Therefore, in spite of the simplicity of the method, its clinical applicability as an indicator of the onset of the pubertal growth spurt in the individual patient is limited [20, 21, 32, 37]. On the contrary, the study by Mellion et al. [53] reported that chronological age would have only a slightly greater error, as compared to that of the HWM according to Fishman [35], in the identification of the mandibular growth peak and it is therefore recommended for the treatment planning. However, this only evidence [53] derived from an old sample (Tables 2 and 6) has to be confirmed by further investigation, especially considering that onset of puberty can be influenced by several factors including genetics, ethnicity, nutrition, and socioeconomic status [82] responsible for a secular trend [81].

7.3. Menarche and Voice Change. Menarche usually occurs immediately after [123, 125] or 1 year after the pubertal growth spurt [5, 126]. According to other evidence [65], menarche would occur after the mandibular growth peak in the early- and average-maturing girls, while in late-maturing girls it may generally occur before the mandibular growth peak. However, late-maturing girls would represent a minority of the population rendering this indicator useless [65]. Similarly, in boys, the voice change occurs during or after the pubertal growth spurt [54, 125]. Therefore, these two indicators are not usable in planning treatment timing in orthodontics.

7.4. Biomarkers. The use of biomarkers has been proposed very recently as a new aid in assessing individual skeletal maturity, with the advantage of being related to the physiology of the patient and of avoiding the use of radiations. The very scarce data reported to date include molecular constituents from the serum, such as insulin-like growth factor I (IGF-I) [42, 43, 127], or from the gingival crevicular fluid (GCF), such as alkaline phosphatase (ALP) [41, 44] or total protein content [45]. These studies reported increased levels of the investigated biomarkers during the pubertal growth spurt as compared to the prepubertal and postpubertal growth phases [41–44, 127] with the exception of the GCF total protein content [45]. However, these studies followed cross-sectional designs and used the CVM method to assess pubertal growth phase [41–45], with one exception where a sample of 25 subjects was followed longitudinally in their mandibular growth [127]. Of particular interest are the biomarkers from the GCF, since its sampling involves a very simple, rapid, and noninvasive procedure that can be performed in a clinical setting. However, even though dental permutation has been reported not to influence significantly the GCF ALP activity [128], variability among the subjects and method errors [129] have to be taken into account. Moreover, optimal gingival conditions without plaque accumulation or clinically evident inflammation is necessary as the GCF ALP activity reflects local tissue inflammation [130]. Future studies on the diagnostic reliability of these biomarkers in the identification of the pubertal growth spurt or mandibular growth peak are warranted.

8. Efficiency of Functional Treatment for Skeletal Class II Malocclusion

8.1. Current Evidence. Herein, to report and evaluate critically current evidence on functional treatment for skeletal Class II malocclusion, data from most recent meta-analyses has been reviewed. Several meta-analyses on the efficiency of functional treatment for Class II malocclusion (skeletal or not) [11–19, 131–133] have been published reporting contrasting results. Some evidence has shown how functional treatment for skeletal Class II malocclusion may be effective in terms of mandibular elongation [17, 18, 132, 133] or dentoalveolar compensation [15, 16]. On the contrary, other evidence reported minimal effects for such treatment [11, 13, 131]. The reason for this apparent inconsistency might reside in the different interventions performed [19, 134], in the large variation in individual responsiveness to functional treatment [17, 18] in conjunction with the absence of an analysis of potential prognostic factors [135], type of appliance [14, 17, 18, 131, 132], and patient's compliance for the removable appliances. Most recent meta-analyses [14–18, 131, 133] including untreated matched Class II control subjects with contrasting outcomes have been herein summarized (Table 9). In particular, these meta-analyses have been analysed according to the main sources of controversies such as design of clinical trials, definition of Class II malocclusion, and skeletal maturity.

8.2. Design of Clinical Trials. When performing clinical trials on the efficiency of functional treatment for Class II malocclusion, a relevant ethical issue relates to the leaving of subjects with relevant malocclusions without orthodontic treatment during the pubertal growth spurt. This issue has limited the execution of randomized clinical trials (RCTs) at this stage of development. Therefore, reviews including exclusively RCTs [11–13] might have been focused mostly on prepubertal subjects, leaving the potential effects of treatment on pubertal patients excluded from the analysis. To date the only exception is for an RCT [24] executed on a group of pubertal patients reporting clinically relevant effects for functional treatment in reducing the entity of the skeletal Class II malocclusion. On the contrary, other most relevant RCTs performed to date included exclusively [27, 29] or mostly [136] prepubertal patients. For this reason, the consideration of controlled clinical trials (CCTs) with reasonable methodological quality has been advocated [137], especially considering that whenever RCTs are not available for meta-analysis, CCTs or observational studies may be used with essentially similar outcomes [138]. In spite of a previous meta-analysis including exclusively RCTs [13], the most recent ones herein summarized included both RCTs and CCTs, although an attempt has been made in several cases to the inclusion of prospective trials over retrospective investigations (Table 9).

8.3. Definition of Class II Malocclusion. A clear distinction should be made between skeletal and dentoalveolar Class II malocclusion. Interestingly, clinical trials [27, 29] on the efficiency of functional treatment for Class II malocclusion used overjet (equal or above 7 mm) as the only diagnostic criterion for Class II malocclusion. However, such an overjet as a sole diagnostic parameter has been shown to be not fully reliable in the identification of a skeletal Class II malocclusion [139]. On the contrary, other trials [140, 141] used specific cephalometric parameters to assure the inclusion of skeletal Class II patients. In the meta-analyses herein reported, trials were included according to dental parameters alone [15, 16, 131], to a combination of ANB angle equal to or above 4° in combination with at least half-cusp Class II molar relationship [17, 18], or to nonspecified criteria [14, 133]. Therefore, conclusions on the supplementary mandibular elongation consequent to functional treatment should be limited to those trials including true skeletal Class II patients due to retrognathic mandible [17, 18].

8.4. Skeletal Maturity. In spite of the previous evidence suggesting skeletal maturity as a potential prognostic factor in terms of skeletal effects produced by functional treatment in skeletal Class II patients [4, 25, 134, 142], to date few clinical trials have focused on the timing of intervention. The assessment of skeletal maturity, with clear distinction among prepubertal, pubertal, and postpubertal groups, was an inclusion criterion only for 2 meta-analyses [17, 18], while it was not considered for all the others [14–16, 131, 133]. However, information on skeletal maturity, when available, was extracted in most of the meta-analyses (Table 9). Subgroup analysis for the different growth phases (mainly prepubertal versus pubertal patients) was performed in 4 meta-analyses [15–18], even though it was inconclusive in 1 case [15] because of limited data available, while, in another case, prepubertal and pubertal patients were pooled [16]. Of note, meta-analyses in which skeletal maturation was not considered or not analyzable [14, 15, 131] reported minimal effects of dentoalveolar nature, while meta-analyses evaluating specifically [17, 18] or mostly [133] pubertal patients reported clinically relevant effects in terms of mandibular elongation and reduction of the skeletal Class II malocclusion (Table 9).

8.5. Other Limitations of the Current Studies. The current investigation on the effects of functional treatment of Class II malocclusion is inherently hampered by other factors [14–18, 131, 133]. For instance, in spite of the use of annualized changes, observational terms may include not only the effective functional treatment, but also variable periods of time of retention or of further management of the dentition. Therefore, skeletal changes might occur not uniformly during the entire observational term skewing the analysis of treatment outcomes [12]. It is hard to avoid heterogeneity of the selected studies because of small sample sizes, inclusion of retrospective trials with historical control groups, and similar skeletal outcomes defined by different cephalometric parameters. Finally, an analysis of the potential responsiveness to treatment according to specific prognostic factors is still not feasible, and current evidence is mostly focused on the short-term effects.

Table 9: Most recent meta-analyses including controlled trials on mandibular effects produced by functional treatment in Class II patients.

Study	Included trials: Design	Included trials: Definition of Class II malocclusion	Included trials: Appliance	Skeletal maturity: Inclusion criterion	Skeletal maturity: Data extraction	Skeletal maturity: Subgroup analysis	Further notes or results on skeletal maturity	Clinical Implications on functional treatment for Class II malocclusion according to the authors
Removable appliances								
Ehsani et al. 2015 [14]	RCTs, CCTs (prospective or retrospective)	Not specified	Twin-block	No	No	No	Not reported	Individual changes were of limited clinical significance, but when combined reached clinical relevance
Koretsi et al. 2015 [15]	RCTs, CCTs (prospective)	A combination of dental and skeletal parameters or only dental parameters	Various	No	Yes	Prepubertal versus pubertal	Comparisons between pubertal and prepubertal inconclusive because of limited data available	Effective, although main effects seem to be mainly dentoalveolar rather than skeletal
Perinetti et al. 2015 [18]	RCTs, CCTs (prospective or retrospective)	ANB > 4° and Class II molar relationship, at least	Various	Yes	Yes	Prepubertal versus pubertal	Annualized supplementary total mandibular elongation was 0.9 mm and 2.9 mm in prepubertal and pubertal patients, respectively.	Effective, with clinically relevant skeletal effects only if performed during the pubertal growth phase
Fixed appliances								
Al-Jewair 2015 [131]	RCTs, CCTs (prospective or retrospective)	Molars in at least an end-to-end relationship	MARA	No	Yes	No	Five out of 7 studies included subjects at onset or pubertal growth phase	Effects may be not clinically relevant (although statistically significant)
Perinetti et al. 2015 [17]	RCTs, CCTs (prospective or retrospective)	ANB > 4° and Class II molar relationship, at least	Various, with or without FFAs	Yes	Yes	Pubertal versus postpubertal	Supplementary total mandibular elongation was 2.2 mm and 0.4 mm in pubertal and postpubertal patients, respectively. Little data available on the postpubertal subjects	Effective, with clinically relevant skeletal effects only if performed during the pubertal growth phase
Yang et al. 2016 [133]	CCTs (prospective)	Skeletal Class II	Herbst	No	Yes	No	Most of the subjects were treated during the pubertal growth spurt	Effective, with relevant changes on dental discrepancy and skeletal changes
Zymperdikas et al. 2016 [16]	RCTs, CCTs (prospective)	A combination of dental and skeletal parameters, or only dental parameters	Various	No	Yes	Prepubertal and pubertal (merged) versus postpubertal	Trend towards more favourable changes in the prepubertal and pubertal than in the postpubertal patients although not statistically significant	Effective, although main effects seem to be mainly dentoalveolar rather than skeletal

Meta-analyses published over the last 2 years are reported. Notes: RCTs, randomized clinical trials; CCTs, controlled clinical trials; MARA, mandibular anterior repositioning appliance; FFAs, full fixed appliances. Results are limited to the short-term effects.

9. Concluding Remarks

Current evidence on both the reliability of growth indicators and efficiency of functional treatment for skeletal Class II malocclusion is still controversial and highly heterogeneous. Although no skeletal maturity indicator may be considered to have a full diagnostic reliability in the identification of the pubertal growth spurt or mandibular growth peak, treatment timing according to available indicators (mainly HWM and CVM methods) has yielded more favorable outcomes in terms of mandibular elongation and reduction of the Class II malocclusion. The use of the HWM or CVM methods (or others) may still be recommended for treatment planning, even though large individual responsiveness and dentoalveolar compensations have been reported even in pubertal patients. Future investigation will have to further elucidate the controversies reported herein and follow more robust designs.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

The 3D Tele Motion Tracking for the Orthodontic Facial Analysis

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Aim. This study aimed to evaluate the reliability of 3D-TMT, previously used only for dynamic testing, in a static cephalometric evaluation. *Material and Method.* A group of 40 patients (20 males and 20 females; mean age 14.2 ± 1.2 years; 12–18 years old) was included in the study. The measurements obtained by the 3D-TMT cephalometric analysis with a conventional frontal cephalometric analysis were compared for each subject. Nine passive markers reflectors were positioned on the face skin for the detection of the profile of the patient. Through the acquisition of these points, corresponding plans for three-dimensional posterior-anterior cephalometric analysis were found. *Results.* The cephalometric results carried out with 3D-TMT and with traditional posterior-anterior cephalometric analysis showed the 3D-TMT system values are slightly higher than the values measured on radiographs but statistically significant; nevertheless their correlation is very high. *Conclusion.* The recorded values obtained using the 3D-TMT analysis were correlated to cephalometric analysis, with small but statistically significant differences. The Dahlberg errors resulted to be always lower than the mean difference between the 2D and 3D measurements. A clinician should use, during the clinical monitoring of a patient, always the same method, to avoid comparing different millimeter magnitudes.

1. Introduction

During the last years, three-dimensional (3D) imaging techniques have been developed, gaining a precious place in any field of dentistry [1, 2] and especially in orthodontics [3].

Over the years, orthodontic diagnosis and treatment planning were based essentially on 2-dimensional (2D) static imaging techniques that cannot give information about deepness of craniofacial structures [4, 5].

Inappropriate orthodontic treatment can produce adverse results and it is essential that full examination of skeletal form, soft tissue relationships, and occlusal features are performed prior to undertaking treatment. Lateral cephalograms are above all the predominantly used radiographic tool in orthodontics. They are the standard diagnostic tools in orthodontic diagnosis, the study of growing process, and control of treatment outcome. But posteroanterior X-rays are a more valid diagnostic tool for craniofacial asymmetries and transverse deficiencies. Trauma, cleft lip and palate, and unilateral condylar or mandibular hypertrophy are additional indications for posteroanterior view. The benefits gained from studying these radiographs range from assisting the orthodontist during diagnosis, as a tool to study growth in an individual through superimposition of structures on a longitudinal basis, and during evaluation of orthodontic treatment results.

In order to precisely replicate and describe the anatomy of the interested structures, 3D imaging has been applied in orthodontics to evaluate and record size and form of facial soft and hard tissues and dentition [6].

In 3D imaging evaluations stereophotogrammetry could be applied. Stereophotogrammetry consists in photographing a 3D object from 2 different coplanar planes in order to acquire a 3D reconstruction of the images. This technique has proven to be effective in the face display. Two cameras are configured as a stereo pair and are used to recover the

Figure 1: Reconstruction cephalometric digital with 3D-TMT and anatomical landmarks for placement of the markers: (1) Trichion; (2) glabella; (3) left and right frontozygomatic suture; (4) the most concave point of the left and right maxillary tuberosity (JL/JR); (5) left and right gonion; (6) menton.

3D distance to features of the surface of the face [7]. Its software is therefore able to dynamically calculate geometric relationships between different facial points producing a 3D image and graphically represent their movements. [8]. The equipment is also able to calculate angles, distances, and associated kinetic variables [9].

Placing markers by using double-sided adhesive film, gel, or other ways in predetermined anatomical landmarks, it is possible to follow their movement in real time. The markers must be covered with reflective material. This instrument is now one of optoelectronic systems for medical use more technologically advanced and meets all the necessary requirements for cephalometric analysis: it is presented as noninvasive, does not create space because it uses passive markers, and does not interfere with the natural movement of the head of the subject or with the functionality of the soft tissues.

The vision system is composed of (i) two photoreceivers placed at the ends of the device, necessary for the three-dimensional reconstruction using stereophotogrammetric procedures; (ii) photoemitters that generate intermittently infrared light for the detection of the markers, and (iii) yellow LEDs that light up at the same time of photoemitters and allow seeing when the unit is in operation (Biomedical Sciences Research Institute 2008).

Aim of the Study. This pilot study aims to evaluate the applicability of 3D-TMT in a cephalometric evaluation of an orthodontic patient, comparing the data obtained with 3D-TMT with those obtained through a traditional cephalometric evaluation in frontal view.

2. Material and Methods

A group of 40 patients (20 males and 20 females; mean age 14.2 ± 1.2 years, range 12 to 18 years) in permanent dentition was included in the study. For each subject the measurements obtained by the 3D-TMT cephalometric analysis were compared with a cephalometric analysis carried out on radiographs in the frontal view.

2.1. Description of the Device. The 3D Tele Motion Tracking (3D-TMT, MS Webcare, Division of Microsystems Srl, Milan, Italy) (Figure 1) is composed by a unit of vision, a telescopic support, and a tripod. The vision area can be chosen by varying the resolution used by the cameras: the sensors of the cameras can operate at different resolutions, that is, using various numbers of pixels. Higher resolutions allow fields of vision larger but, at the same time, lower frequencies of acquisition (fps); fps represents the maximum number of frames that the camera is able to capture every second. The typical frequency of acquisition (fps) of the images by the photoreceivers is 30 hz. The equipment is able to calculate angles, distances, and associated kinetic variables placing reflective markers by using double-sided adhesive film, gel, or other ways in predetermined anatomical landmarks; it is also possible to follow their movement in real time.

2.2. Preliminary Study on the Accuracy of the Instrument. For the assessment of the accuracy of the instrument, static tests were carried out preliminarily measuring known distances (15 cm) between markers placed on a rigid and static bar. The average values measured during the static tests and the related standard deviations were compared. The accuracy of the instrument denotes the closeness of computations or estimates to the exact or true values. A measurement is said to be more accurate when it offers a smaller measurement error. The accuracy was measured quantitatively by using relative error:

$$\text{relative error} = \frac{\text{measured value} - \text{expected value}}{\text{expected value}}. \quad (1)$$

The accuracy has been established because the relative errors were lower than 1/100 of the expected values.

2.3. Outcomes. A 3D-TMT static evaluation was performed. Passive reflective markers with a diameter of 6 mm were used and the subject was placed at a distance of 2 meters from the photoreceiver for proper detection. The position of the markers was registered by the optoelectronic system.

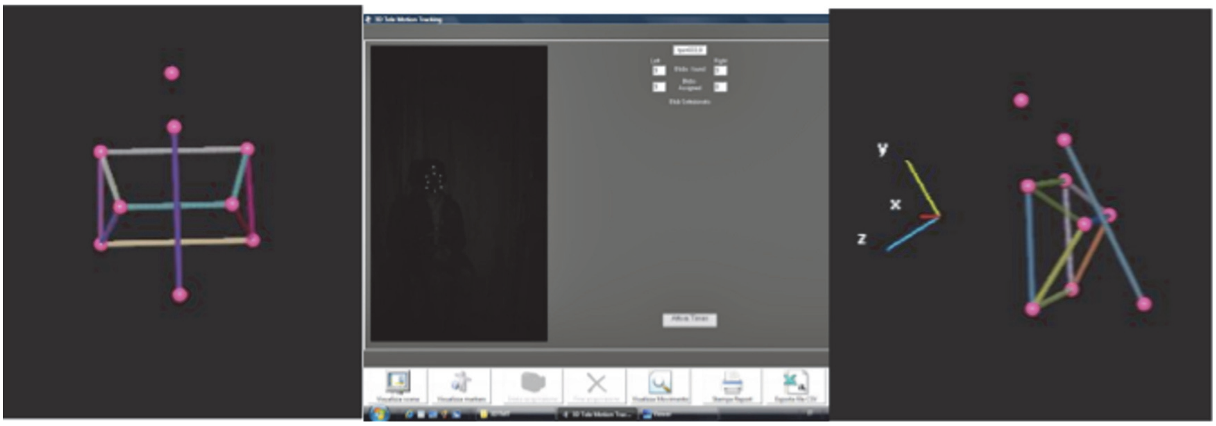

Figure 2: The three-dimensional reconstruction with 3D-TMT and scanned image in the 3D-TMT.

Eight markers were positioned on the skin of the face for the detection of the face (Figure 2). These were chosen as the most common points used for the frontal cephalometric analyses [10–12]:

The anatomical landmarks chosen for the detection were

trichion: point where the hairline meets the midpoint of the forehead,

glabella: point of smooth elevation of the frontal bone just above the bridge of the nose,

left and right frontozygomatic suture (ZL/ZR),

most concave point of the left and right maxillary tuberosity (JL/JR),

left and right gonion and menton.

The following planes were analyzed [10–12]:

(i) Median sagittal plane: derived from the intersection between glabella point and menton point; when there is facial symmetry, this plan allows to define the problems of midline deviation and lateral deviations

(ii) Dentomaxillary frontal plan or zygomatic plane JL-AG or JR-GA: it is the reference plane of the molars in relation to their maxillary and mandibular bases

(iii) Frontofacial plan ZL-AG or ZR-GA: it is the reference plane of the maxillary base that allows the differential diagnosis between dental or skeletal cross-bites

(iv) Orbitofrontal horizontal plane ZL - ZR: plane between the right and left frontozygomatic sutures

(v) Horizontal plane JL - JR: plane passing between the concave points of the maxillary tuberosities

(vi) Horizontal mandibular AG - GA or antegonial plan: passing between the right and left gonion.

The examination was performed with the patient sitting in front of the 3D-TMT.

2.4. Analysis of Data. Data are described as mean and SD.

Student's t-test for independent sample was performed to compare mean and SD of the variables measured with the traditional and the 3D-TMT methods, because the preliminary Kolmogorov-Smirnov Z attested a normal distribution of data (Z varied from 1.03 to 1.08; p varied from 0.15 to 0.19). For each test, p was set at 0.05 level.

A Pearson's correlation coefficient was also calculated between traditional and 3D-TMT measurements.

To detect any random error which may be of relevance, a proper analysis of the method error between the two recording methods was performed to quantify any random error (Dahlberg formula), in which the Dahlberg error, D, is defined as

$$D = \sqrt{\sum_{i=1}^{N} \frac{d_i^2}{2N}}, \quad (2)$$

where d_i is the difference between the first and second measure and N is the sample size which was remeasured.

3. Results

The cephalometric results, carried out with 3D-TMT and with traditional posterior-anterior cephalometric analysis, are shown in Table 1. Mean values recorded using the 3D-TMT system are slightly higher than the values measured on radiographs. After application of Student's t-test. significant differences were observed between the measurements obtained with traditional methods and the 3D-TMT method.

Correlation analysis conducted using Pearson's correlation coefficients showed high correlations between traditional and 3D-TMT variables.

The Dahlberg formula gave results that are reported in Table 2.

For each variable, the relative form of Dahlberg error (RDE) was also reported in Table 2 as the proportion of Dahlberg error on the average difference between two comparative measures: RDE = Dahlberg error/mean of difference between two corresponding measurements.

For each variable, the Dahlberg errors resulted to be always lower than the mean difference between the 2D and 3D measurements, but in proportion, they resulted to be about 67.8%–71% of the average difference.

Table 1: Difference between the values of the frontal cephalometric traditional analysis and 3D-TMT.

	2D		3D		Difference		p value	Pearson's correlation coefficient
	Mean	SD	Mean	SD	Mean	SD		
AG-PSM	53.68	9.63	54.44	9.76	−0.76	0.82	0.0000	0.997
GA-PSM	53.59	9.42	54.26	9.76	−0.68	0.91	0.0001	0.996
JL-AG	50.50	8.69	51.09	8.75	−0.59	0.96	0.0011	0.994
JL-PSM	36.09	3.32	36.71	3.45	−0.62	0.89	0.0003	0.966
JLZL	59.56	5.24	60.15	5.26	−0.59	0.78	0.0001	0.989
JR-GA	50.82	9.13	51.47	9.22	−0.65	1.01	0.0007	0.994
JR-PSM	35.74	3.70	36.35	3.69	−0.62	0.89	0.0003	0.971
JR-ZR	59.71	5.32	60.56	5.28	−0.79	0.55	0.0000	0.994
PSM	131.29	7.68	131.71	7.58	−0.41	0.99	0.0207	0.992
ZL-AG	91.59	14.08	92.21	14.15	−0.62	0.82	0.0001	0.998
ZL-PSM	49.50	4.24	50.26	4.40	−0.76	0.92	0.0000	0.978
ZR-GA	96.18	14.65	96.71	14.69	−0.53	0.79	0.0251	0.999
ZR-PSM	47.26	5.24	47.85	5.34	−0.59	0.89	0.0005	0.986

PSM = Sagittal median plane.
JL-AG = Distance between JL and AG points.
JR-GA = Distance between JR and GA points.
ZL-AG = Distance between ZL and AG points.
ZR-GA = Distance between ZR and GA points.
ZL-PSM = Distance between ZL point and PSM.
ZR-PSM = Distance between ZR point and PSM.
JL-PSM = Distance between JL point and PSM.
JR-PSM = Distance between JR point and PSM.
GA-PSM = Distance between GA point and PSM.
AG-PSM = Distance between AG point and PSM.
JL-ZL = Distance between JL and ZL points.
JR-ZR = Distance between JR and ZR points.

Table 2: Method error analysis.

	2D		3D		Difference		$\sum d^2$ ($n = 40$)	$D = \sqrt{\sum_{i=1}^{N} \frac{d_i^2}{2N}}$	RDE (relative form of Dahlberg error)
	Mean	SD	Mean	SD	Mean	SD			
AG-PSM	53.68	9.63	54.44	9.76	−0.76	0.82	22.63	0.53	70%
GA-PSM	53.59	9.42	54.26	9.76	−0.68	0.91	18.94	0.48	70.6%
JL-AG	50.50	8.69	51.09	8.75	−0.59	0.96	13.26	0.4	67.8%
JL-PSM	36.09	3.32	36.71	3.45	−0.62	0.89	15.65	0.44	70.9%
JLZL	59.56	5.24	60.15	5.26	−0.59	0.78	13.21	0.4	67.8%
JR-GA	50.82	9.13	51.47	9.22	−0.65	1.01	16.2	0.45	69.2%
JR-PSM	35.74	3.70	36.35	3.69	−0.62	0.89	15.24	0.43	69.3%
JR-ZR	59.71	5.32	60.56	5.28	−0.79	0.55	24.26	0.55	69.6%
PSM	131.29	7.68	131.71	7.58	−0.41	0.99	6.83	0.29	70.7%
ZL-AG	91.59	14.08	92.21	14.15	−0.62	0.82	15.23	0.43	69.3%
ZL-PSM	49.50	4.24	50.26	4.40	−0.76	0.92	23.52	0.54	71%
ZR-GA	96.18	14.65	96.71	14.69	−0.53	0.79	11.21	0.37	69.8%
ZR-PSM	47.26	5.24	47.85	5.34	−0.59	0.89	13.78	0.41	70%

4. Discussion

The 3D-TMT can be used to conduct, through reflective markers placed at specific anatomical points, a cephalometric analysis on 3D plans for the study of an orthodontic patient, with the assessment of facial symmetry even at different depths within the craniofacial complex. The analysis with 3D-TMT also allows a dynamic and prognostic evaluation of the growth process of the patient. The evaluation with 3D-TMT is based on the localization of anatomical points on the skin surface of the face, analyzing the subject "aesthetics" and giving an important role to the soft tissues [13, 14].

During the last years many clinicians and authors underlined the underestimated importance of the soft tissues in the orthodontic treatment and a main aspect to be taken into consideration for judging the success of the treatment itself [15]. The analysis with 3D-TMT seems to allow a dynamic and prognostic evaluation of the facial structure growth process of the patient without exposure to ionizing radiation (X-rays) and thus absolutely being noninvasive and not harmful to biological level with no risk for the health of the patient [16].

In full accordance with the as Low as Reasonably Achievable (ALARA) principle this feature could bring this system to a wider diffusion replacing the traditional radiographic analysis [16, 17].

An advantage is represented by a survey carried out without exposure of the patient to ionizing radiation (X-rays), since the device acquires the images of the markers illuminated intermittently with infrared light, through two vision systems. It is therefore a noninvasive analysis and not harmful to biological level; it poses no risk to the health of the patient and can be repeated several times without risks. For this reason the test can be repeated several times on the same patient without damage, allowing a longitudinal evaluation during growth and during orthodontic treatment. The device captures three-dimensional images with a great accuracy in the localization of anatomical landmarks used for cephalometric analysis. A limitation of the instrument is that objects able to reflect the infrared beam could interfere with the actual uptake of the markers; thus, before starting the analysis, all objects in the visual field of reflectors which can be obstacles and generate artifacts should be removed.

From the results obtained, both precision and accuracy of the 3D-TMT are satisfactory and highly correlated with those obtained with cephalometric analysis in frontal view; thus the 3D-TMT seems a reliable instrument to easily analyze the facial pattern with cephalometry.

As expected, there was a statistically significant difference between measures obtained with 3D-TMT and cephalometric measures on frontal radiographs; in fact, 3D-TMT calculates the distances between cutaneous landmarks, while cephalometry indicates distances between skeletal points, not considering the thickness of soft tissues [18, 19].

Nevertheless, these mean differences are ever smaller than 1 mm and the comparison between 3D-TMT and frontal cephalometric measures showed a high correlation, thus suggesting they can guide the clinician toward the same diagnosis about facial morphology. The method error analysis, performed with the Dahlberg formula, revealed that a random method error could be about 67.8–71% of the mean difference between 3D and 2D values.

Our data are in accordance with the hypothesis that although we are examining the soft tissue outline, this also gives an indication of the underlying skeletal pattern. Obviously the soft tissue thickness may vary and mask the A-P skeletal pattern to some degree but the underlying skeletal pattern is therefore often reflected in the soft tissue pattern.

3D-TMT could be used in conjunction with other diagnostic tests performed routinely in orthodontic check-up, providing a complete picture of the situation of facial components in their entirety, even during motion. In addition. by examining them at the various stages of therapy, this instrument could allow checking in real time the physiological response to any phase of treatment, allowing assessing its suitability, and can be used effectively for cephalometric analyses and “aesthetics” analysis of the soft tissues. The 3D-TMT could also be useful for the research protocols on the study of the growing development of adolescents, to avoid X-rays exposure.

The disadvantage of using a 3D capture system is that the positioning of some cutaneous landmarks such as gonion and frontozygomatic suture is difficult and usually defined by the bone shape and found by touching the subject’s body [20]. Because we were concerned about this problem empirically in the early stage of this study, we paid special attention to the positioning of these landmarks. The clinician must always keep in mind this disadvantage of 3D capture system, in each actual clinical case. In recent years. X-rays computed tomography technologies have been used in skeletal morphology research [19] as this technology provides positional data of the face surface and skeleton of a living person. We expect to obtain more accurate data of measurements related to bony landmarks in the near future also with this 3D capture system.

This study aims to introduce the Tele 3D Motion Tracking, stereophotogrammetric equipment, capable of replacing the traditional two-dimensional cephalometric analysis performed on cephalometric skull in posterior-anterior projection. An advantage is represented by a survey carried out without exposure of the patient to ionizing radiation (X-rays), since the 3D system-TMT acquires through two vision systems the images of the markers passive reflectors illuminated intermittently with infrared light. It is therefore an analysis that is completely noninvasive and not harmful to biological level that poses no risk to the health of the patient, unlike what occurs in normal cephalometric radiography that is required. For this reason the test can be repeated several times on the same patient without damage, also allowing a longitudinal evaluation during growth and during orthodontic treatment, as, for example, after the palatal expansion, or during an orthopedic-functional treatment. Moreover, the 3D-TMT allows you to make the cephalometric analysis extremely quickly.

5. Conclusions

This study aims to introduce the Tele 3D Motion Tracking, a stereophotogrammetric equipment able to do a cephalometric study of the soft tissues. The recorded values obtained using the 3D-TMT analysis were correlated to cephalometric analysis, although the millimetric values have small but statistically significant differences, and the method error analysis revealed the possibility of high error values.

A clinician should use, during the clinical monitoring of a patient, always the same method (traditional cephalometric analysis or 3D-TMT analysis), to avoid comparing different millimeter magnitudes. With this recommendation, the 3D-TMT analysis seems a viable method for the study of facial morphology and its monitoring during the growth of a patient, or during a therapy.

Further studies should be carried out to evaluate results during motion and other orthodontic applications of the 3D-TMT in diagnosis and follow-up of an orthodontic treatment.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

S. Mummolo conceived the study, recorded the data, drafted the manuscript, directed the research, and reviewed the final manuscript. A. Nota reviewed literature, made statistical tests, and made discussion. E. Marchetti drafted the manuscript. G. Padricelli recorded the data. G. Marzo directed the entire process and reviewed the final manuscript.

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Research Article

Sagittal and Vertical Craniofacial Growth Pattern and Timing of Circumpubertal Skeletal Maturation: A Multiple Regression Study

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The knowledge of the associations between the timing of skeletal maturation and craniofacial growth is of primary importance when planning a functional treatment for most of the skeletal malocclusions. This cross-sectional study was thus aimed at evaluating whether sagittal and vertical craniofacial growth has an association with the timing of circumpubertal skeletal maturation. A total of 320 subjects (160 females and 160 males) were included in the study (mean age, 12.3 ± 1.7 years; range, 7.6–16.7 years). These subjects were equally distributed in the circumpubertal cervical vertebral maturation (CVM) stages 2 to 5. Each CVM stage group also had equal number of females and males. Multiple regression models were run for each CVM stage group to assess the significance of the association of cephalometric parameters (ANB, SN/MP, and NSBa angles) with age of attainment of the corresponding CVM stage (in months). Significant associations were seen only for stage 3, where the SN/MP angle was negatively associated with age (β coefficient, −0.7). These results show that hyperdivergent and hypodivergent subjects may have an anticipated and delayed attainment of the pubertal CVM stage 3, respectively. However, such association remains of little entity and it would become clinically relevant only in extreme cases.

1. Introduction

The knowledge of the associations between the timing of skeletal maturation and craniofacial growth is of primary importance when planning a functional treatment for most of the skeletal malocclusions, including those on the sagittal [1] and vertical dimensions [2, 3]. Although being a controversial issue [4–6], functional treatment for Class II malocclusion would induce clinically relevant mandibular elongation when performed during the pubertal growth phase [7, 8], while, Class III malocclusion requires early treatment [1]. Finally, both excessive vertical facial growth [2] and deepbite [3] have also been reported to be best treated during the pubertal growth phase. These aspects are of particular importance also in consideration that skeletal Class III malocclusion [9] and vertical facial growth pattern [10] tend to aggravate when not treated. Therefore, the knowledge of whether attainment of a specific growth phase is also dependent on the different sagittal and vertical craniofacial growth pattern has a clinical relevance in terms of timing of intervention. In this regard, the most common procedures to monitor the different growth phases are the radiographic methods of maturational stages of the cervical vertebral maturation (CVM) [1, 11] and hand-and-wrist maturation (HWM) (for review, see [12]).

To date very little research has focused on the possible association between the timing of the circumpubertal skeletal maturation phases and sagittal craniofacial growth, that is, skeletal class [13–15]. Moreover, none of these previous studies investigated possible associations of vertical craniofacial facial growth and timing of attainment of skeletal maturation phases. These studies were further limited by the use of univariate analyses [14, 15] with only one exception, where a multivariate model was used [13]. Finally, a further study [16] used an overall craniofacial composite measured, derived from multiple measurements; thus, it was not able to discriminate between sagittal and vertical growth patterns.

Investigation on the craniofacial vertical growth pattern and timing of skeletal maturation becomes of interest also in consideration of the previous evidence reporting an earlier dental maturation in hyperdivergent subjects [17].

Therefore, through multivariate models, this cross-sectional study was aimed at evaluating whether sagittal and vertical craniofacial growth pattern, as described by common cephalometric parameters, has an association with the timing of circumpubertal skeletal maturation, that is, age of attainment of the maturation phases as defined by the CVM method.

2. Materials and Methods

2.1. Study Population and Design. The database between January 2009 and December 2015 of the Sections of Stomatology of the Department of Medical, Surgical and Health Sciences, University of Trieste, was screened. This study included subjects who were seeking orthodontic treatment and who had never been treated before. As a routine procedure, a signed informed consent for releasing diagnostic material for scientific purposes was obtained from the patients' parents prior to entry into treatment, procedures followed adhered to the World Medical Organization Declaration of Helsinki [18], and the protocol was reviewed and approved by the local Ethical Committee. In particular, in the first clinical session a lateral cephalograms was taken as a part of the pretreatment clinical recording. The following inclusion criteria were applied: (i) age between 7 and 17 years; (ii) circumpubertal skeletal maturation between CVM stages 2 and 5; (iii) absence of any craniofacial anomaly or extensive dental caries or restorations; (iv) good general health with no signs of symptoms of temporomandibular disorders; (v) no history of trauma at the craniofacial region; and (vi) Caucasian ethnicity. A dedicated X-ray machine (KODAK 8000C; Eastman Kodak Company) was employed for the recording of lateral head cephalograms. Settings were of 73–77 kV, 12 mA with an exposure time of 0.80 seconds. Images were saved at 300 dpi resolution and radiographs of low quality were excluded. An experienced orthodontist (LC) assisted by a second operator (LR) screened the cases for inclusion. A further experienced orthodontist (GP) was involved to ensure correct enrollment and, in case of disagreement, discussion was made until satisfaction of both operators. From an initial sample of over 450 subjects, total of 320 subjects (160 females and 160 males) were included in the study (mean age, 12.3 ± 1.7 years; range, 7.6–16.7 years).

2.2. Cephalometric Analysis for the Face and Cervical Vertebrae. A customized digitization regimen and analysis with cephalometric software (Viewbox, version 3.0, dHAL Software, Kifissia, Greece) were used for all cephalograms examined in this study. The cephalometric analysis of the face required the digitization of 9 landmarks (Figure 1) [19]. The customized cephalometric analysis included 4 angular measurements as follows (Figure 1): maxillary prognathism (SNA angle), mandibular prognathism (SNB angle), maxillo-mandibular relationship (ANB angle), maxillary inclination

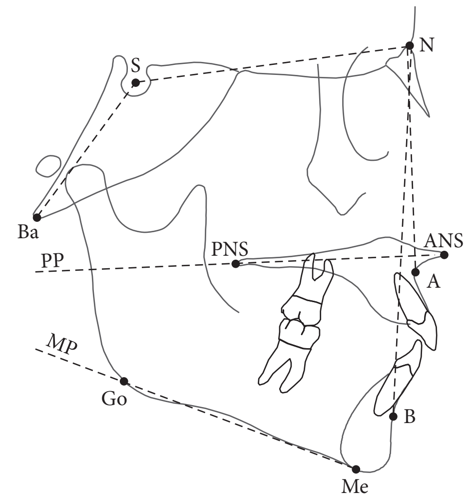

Figure 1: Diagram of the cephalometric measurements of the craniofacial complex. Landmarks: A, subspinale; B, supramentale; N, nasion; S, centre of the sella turcica; Ba, Basion; ANS, anterior nasal spine; PNS, posterior nasal spine; Me, menton; Go, Gonion; Planes: PP, palatal plane; MP, mandibular plane. See text for details.

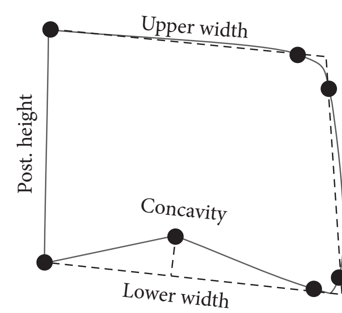

Figure 2: Diagram of the cephalometric measurements of the cervical vertebrae. Only a vertebral body is shown for clarity. In cervical vertebra 2, only concavity was measured. See text for details.

relative to the cranial base (SN/PP angle), mandibular inclination relative to the cranial base (SN/MP angle), and cranial base angle (NSBa angle).

Regarding the body of the cervical vertebrae, a quantitative assessment of the shape (maturation) was also performed. The customized cephalometric analysis included measurements generated from 17 landmarks from which 11 linear and 8 angular variables were derived. Among the linear variables, 3 were for concavities of lower borders of C2–C4 and 8 related to the anterior and posterior heights and upper and lower widths for the C3 and C4 (Figure 2) [20]. Among angular variables, 4 were for the inner angles of the C3 and other 4 were for the inner angles of the C4. The data were used to calculate presence/absence of concavity and shape of the vertebral body through a dedicated Excel data sheet where linear and angular measurements were used in combination. The used method was independent of absolute recordings; instead we used relative dimensions to assess the shapes of the C3 and C4, while the concavity was assessed when it was at least 10% of the corresponding posterior height of the cervical body. The posterior height of the C3 was considered when assessing the concavity in the C2. Each CVM stage was retrieved according to the concavities of the C2–C4 and shapes of the C3 and C4 as reported below.

Lateral cephalograms were standardized as to real dimensions, that is, magnification factor of 0%. All of cephalograms were traced by a last year resident (LR), and a second investigator (GP) checked each tracing for accuracy. Both the Viewbox.vbr and Excel worksheet.xlsx files are available upon request to the corresponding author.

2.3. Cervical Vertebral Maturation Assessment. The CVM method according to Baccetti et al. [1] with minor modifications has been applied herein. The method has 6 stages: 2 prepubertal (1 and 2), 2 pubertal (3 and 4), and 2 postpubertal (5 and 6). These stages were briefly defined as follows: *stage 1*, when the lower borders of the second, third, and fourth vertebrae (C2, C3, and C4) are flat and the bodies of C3 and C4 are trapezoid in shape; *stage 2*, when only the lower border of C2 is concave and the bodies of C3 and C4 are trapezoid; *stage 3*, when the lower borders of C2 to C3 have concavities and the bodies of C3 and C4 are either trapezoid or rectangular horizontal in shape. Alternatively, when the concavity is present only at the lower border of the C3 with the bodies of C3 and C4 either trapezoid or rectangular horizontal in shape; *stage 4*, when the lower borders of C2 to C4 have concavities and the bodies of both C3 and C4 are both rectangular horizontal or at least one rectangular horizontal and the other trapezoidal; *stage 5*, when the lower borders of C2 to C4 have concavities, and at least one or both of the bodies of C3 and C4 are squared. Alternatively, when at least the body of either C3 or C4 is squared with a lack of concavity at the lower border in either C3 or C4; *stage 6*, when the lower borders of C2 to C4 have concavities, and at least one or both of C3 and C4 are rectangular vertical. Exceptional cases, that is, outside the reported norms, were managed as previously reported [20].

2.4. Method Error. With the aim of quantifying the full method error of the recordings for each recorded parameter, the method of moments variance estimator [21] was used on a random sample of 20 replicate measurements. Therefore, the mean error and 95% confidence intervals (CIs) between the repeated recordings were calculated using the MME variance estimator. Moreover, the repeatability in the CVM stage assignment in the same pairs of measurements was evaluated using the percentage of agreement and by both unweighted and linear weighted kappa coefficients presented as mean and 95% CI. The kappa coefficient ranges from zero for no agreement to 1 for perfect agreement [22].

2.5. Statistical Analysis. The SPSS software version 20 (SPSS® Inc., Chicago, IL, USA) and the G*Power software version 3.1.9.2 (http://www.gpower.hhu.de/en.html) were used to perform the subsequent data analysis. After testing the normality of the data with the Shapiro-Wilk test and Q-Q normality plots of the residuals and the equality of variance among the datasets using a Levene test, parametric methods were used for data analysis [23]. The significance of the difference in each craniofacial and cervical vertebral cephalometric parameter among the CVM stage groups was evaluated through a one-way analysis of variance [23].

Table 1: Chronological age for each CVM stage according to the sexes.

Sex	Cervical vertebral maturation stage group			
	CVM stage 2 ($N = 80$)	CVM stage 3 ($N = 80$)	CVM stage 4 ($N = 80$)	CVM stage 5 ($N = 80$)
Females	10.1 ± 1.2	11.5 ± 0.8	12.0 ± 1.2	12.7 ± 1.6
Males	11.4 ± 1.4	12.8 ± 1.5	13.3 ± 1.4	14.1 ± 1.2
Diff.	*0.000; S*	*0.000; S*	*0.000; S*	*0.000; S*

Each CVM stage group includes equal number of females and males. Data on age are presented as mean ± SD. Diff., significance of the difference between the sexes within each CVM stage group. S, statistically significant.

Moreover, within each CVM stage group, the association of each of the craniofacial parameters (explanatory variables) with the chronological age in months (dependent variable) was investigated by means of backward multiple linear regressions. In particular, a bivariate correlation matrix with Pearson coefficient was executed for each CVM stage group including all the craniofacial cephalometric parameters, according to which the SNB and SN/PP angles were excluded from the multivariate models. Thus, explanatory variables were sex (male), SNA angle, ANB angle, SN/MP angle, and NSBa angle. The cut-off levels of significance used were 0.01 and 0.05 for entry and removal, respectively. For each multiple regression model, multicolinearity among the remaining explanatory variables was also again checked for through the tolerance and variance inflation factor parameters. Finally, in *a posteriori* power analysis with 80 cases *per* model, considering an F^2 equal to 0.15, an alpha level of 0.05 and with 5 explanatory variables, the resulting power was 92.8%.

A $p < 0.05$ was used for rejection of the null hypothesis.

3. Results

For the face measurements, greatest method error of 1.06° (0.81–1.55) was for the SN/MP angle. For the cervical vertebrae measurements, greatest method errors were 0.18 mm (0.14–0.27), 0.24 mm (0.18–0.36), and 1.94° (1.48–2.84), for the concavities, linear, and angular measurements, respectively. The overall percentage of agreement for the CVM stages was 90% (18 cases out of 20). The unweighted kappa coefficient was 0.82 (0.71–1), and the weighted kappa coefficient was 0.93 (0.84–1).

Chronological ages for each group according to the sexes are reported in Table 1. For females, mean ages ranged from 10.1 to 12.7 years in CVM stage 2 and CVM stage 5 groups, respectively. For males, mean ages ranged from 11.4 to 14.1 years in CVM stage 2 and CVM stage 5 groups, respectively. The difference between the sexes within each group was significant ($p = 0.000$, each).

Table 2: Descriptive statistics for the craniofacial parameters (in degrees) for each group.

Parameter (degree)	Cervical vertebral maturation stage group				Diff.
	CVM stage 2 ($N = 80$)	CVM stage 3 ($N = 80$)	CVM stage 4 ($N = 80$)	CVM stage 5 ($N = 80$)	
SNA angle	80.7 ± 3.6	81.2 ± 3.5	80.3 ± 3.2	81.2 ± 3.4	0.301; NS
SNB angle	77.0 ± 3.9	77.2 ± 3.6	76.7 ± 3.7	77.7 ± 3.7	0.365; NS
ANB angle	3.7 ± 2.0	3.9 ± 2.1	3.6 ± 2.2	3.5 ± 2.3	0.558; NS
SN/PP angle	7.0 ± 3.4	7.1 ± 3.9	7.9 ± 3.3	8.1 ± 2.8	0.200; NS
SN/MP angle	31.2 ± 5.6	30.4 ± 5.9	30.8 ± 5.9	30.6 ± 5.3	0.848; NS
NSBa angle	129.6 ± 5.2	129.4 ± 4.6	130.0 ± 4.9	130.7 ± 4.7	0.375; NS

Each CVM stage group includes equal number of females and males. Data on age are presented as mean ± SD. Diff., significance of the levels of differences among the CVM stage groups for each cephalometric parameter. NS, not statistically significant.

Table 3: Results of the backward multiple linear regressions for the association of craniofacial cephalometric parameters with the chronological age (in months) for each CVM stage.

Explanatory variable	β (SE)	t	Sig.
Model 1: age of attainment of CVM stage 2 (N = 80), R^2 = 0.213			
Sex (male)	17.0 (3.6)	4.754	0.000; S
ANB angle	1.6 (0.9)	1.793	0.077; NS
Model 2: age of attainment of CVM stage 3 (N = 80), R^2 = 0.269			
Sex (male)	13.6 (3.2)	4.311	0.000; S
MP/SN angle	−0.7 (0.3)	2.477	0.015; S
Model 3: age of attainment of CVM stage 4 (N = 80), R^2 = 0.194			
Sex (male)	15.4 (3.6)	4.339	0.000; S
NSBa angle	0.6 (0.4)	1.700	0.093; NS
Model 4: age of attainment of CVM stage 5 (N = 80), R^2 = 0.165			
Sex (male)	16.3 (4.0)	4.080	0.000; S

Independent variables entered in each model: sex, SNA angle, ANB angle, SN/MP angle, and NSBa angle, with variables having a p value above 0.1 removed from the model. Results of the multiple linear regressions are presented as β (SE); R^2, coefficient of determination. Sig., level of significance; S, statistically significant; NS, not statistically significant.

Descriptive statistics for each analysed parameter is reported in Table 2. The SNA angle ranged from 80.3° ± 3.2 (CVM stage 4) to 81.2° ± 3.4 (CVM stage 5); the SNB angle ranged from 76.7° ± 3.7 (CVM stage 4) to 77.7° ± 3.7 (CVM stage 5); the ANB angle ranged from 3.5° ± 2.3 (CVM stage 5) to 3.9° ± 2.1° (CVM stage 3); the SN/PP angle ranged from 7.1° ± 3.9 (CVM stage 3) to 8.1° ± 2.8 (CVM stage 5); the SN/MP angle ranged from 30.4° ± 5.9 (CVM stage 3) to 31.2° ± 5.6 (CVM stage 2); the NSBa angle ranged from 129.4° ± 4.6 (CVM stage 3) to 130.7° ± 4.7 (CVM stage 5). For all of these craniofacial cephalometric parameters the differences among the groups were not statistically significant.

Results of the backward multiple linear regression models according to each CVM stage group are reported in Table 3. In the CVM stage 2 group (Model 1) R^2 was of 0.213 with the sex (male) and ANB angle positively associated with the age of attainment of the CVM stage 2 with β coefficients of 17.0 and 1.3, respectively. However, only the sex reached the statistical significance ($p = 0.000$), while the ANB angle did not ($p = 0.077$). In the CVM stage 3 group (Model 2) R^2 was of 0.269 with the sex (male) and SN/MP angle positively and negatively associated with β coefficients of 13.6 and −0.7, respectively ($p = 0.015$, at least). In the CVM stage 4 group (Model 3) R^2 was of 0.194 with the sex (male) and NSBa angle positively associated with the age of attainment of the CVM stage 4 with β coefficients of 15.4 and 0.6, respectively. However, only the sex reached the statistical significance ($p = 0.000$), while the NSBa angle did not ($p = 0.093$). Finally, In the CVM stage 5 group (Model 4) R^2 was of 0.165 with only the sex (male) positively associated with the age of attainment of the CVM stage 5 with a β coefficient of 16.3 ($p = 0.000$).

4. Discussion

Through multivariate models, the present study demonstrates a little association of the sagittal and vertical craniofacial growth pattern with the timing of skeletal maturation. While females had anticipated attainment of each CVM stage as compared to males (Table 1), the different cephalometric parameters showed no significant differences among the CVM stage groups (Table 2), allowing a more reliable comparison of the regression models.

The previous investigations [13–15] on sagittal craniofacial growth pattern and timing of skeletal maturation were focused on the CVM stages 3 and 4. Therefore, present data on the timing of the CVM stages 2 and 5 are not comparable with previous evidence. Of interest, R^2 retrieved for the models ranged from 0.165 to 0.269 (Table 3). Although such values were not particularly high, the greatest value was seen for the pubertal CVM stage 3 while, generally, the values decreased as maturation progresses into the postpubertal phases. Thus, in spite of the significant associations, the different CVM stages, sex, and craniofacial parameters all together accounted for no more than ≈27% of the total variability of corresponding ages. This evidence demonstrates how other relevant factors are responsible for the timing of skeletal maturation such as genetics, ethnicity, nutrition, and socioeconomic status [24].

As expected, sex was the most significant factor associated with the age of attainment of each CVM stage from 2 to 5 (Tables 1 and 3). According to the β coefficients, the male subjects had on average a delayed attainment of the different stages about 15 months later as compared to females. This evidence is in line with previous studies using the CVM [1] or other radiographic maturational methods [25, 26].

Herein, the ANB, SN/MP, and NSBa angles yielded the most relevant associations with the mean age for the attainment of the CVM stages 2, 3, and 4, respectively (Table 3). In particular, the greater the ANB angle, the greater the mean age for the attainment of the CVM stage 2, while, the greater the MP/SN angle, the lower the age for the attainment of the CVM stage 3; finally, the greater the NSBa angle, the greater the age for the attainment of the CVM stage 4. However, only the SN/MP angle yields an association that reached a statistically significant level ($p = 0.015$), while the ANB and NSBa angles yielded association very close to the significance level ($p < 0.1$), according to which they were kept in the final regression models. According to the β coefficients, unitary increments in ANB angle would account for about 1.6 months' retardation in the attainment of the CVM stage 2; unitary increments in SN/MP would account for about 0.7 months' anticipation of the attainment of the CVM stage 3, and unitary increments of the NSBa angle would account for about 0.6 months' anticipation of the attainment of the CVM stage 4. However, the relevance on the ANB angle in the age of attainment of the CVM stage 2 would also be limited by the concept that, from a clinical standpoint, the attainment of the pubertal CVM stages 3 and 4 is of primary importance in most of the functional treatments [1].

It has been suggested that the deficiency [27] and increased [9] mandibular length in Class II and Class III subjects at the pubertal growth spurt could be linked to the different duration of the pubertal peak in these subjects, as compared to those of Class I subjects [13–15]. Indeed, shorter and longer pubertal growth spurt, as recorded through the ages of attainment of CVM stages 3 and 4, have been reported for untreated Class II [15] and Class III [14] subjects, respectively.

The present results on the ANB angle and age of attainment of the CVM stage 2 group, although not statistically significant, are consistent with previous evidence showing that 8- to 14-year-old subjects with Class II malocclusion exhibited twice as much chance of being in CVM stage 1 or 2 than individuals with Class I malocclusion with similar age [13]. Regarding the pubertal stages, the duration of the maturation from CVM stage 3 to stage 4 has been reported for Class II subjects to be about 4 months shorter as compared to that of Class I subjects [15]. The present results do not support such evidence, with the CVM stages 3 and 4 not showing association with the craniofacial sagittal growth pattern. Differences in the study designs may explain such inconsistency (see also below).

In a previous investigation [14], the average age at onset of the pubertal peak was very similar for both skeletal Class I and Class III subjects. Therefore, the present data on the CVM stage 3 would be consistent with the concept that the sagittal growth has no influence on the age of attainment of the CVM stage 3 [14]. On the contrary, herein the sagittal growth had also no influence on the age of attainment of the CVM stage 4, while it has been reported that this stage is reached by Class III subjects about 5 months later compared to Class I subjects [14]. Possible explanations for such contrasting evidence would reside in the multivariate analysis used herein or in the concept that in the present study only 23 subjects showed an ANB angle ≤0°; thus, a full comparison for Class III subjects has to be done with caution. Moreover, the entity of Class III malocclusion also has to be taken into account along the concept that previous investigations were limited to subjects with normal vertical growth, that is, normodivergent [14].

Interestingly, the only previous investigation [13] using multiple regression models on the age of attainment of different CVM stages and sagittal growth of the face reported no significant difference between the Class I and Class III subjects. However, this study [13] missed the reporting of data regarding vertical growth, and this parameter was used for adjustments in the multiple regression model. Therefore, the question whether in Class III malocclusion subjects the interval between the ages of attainment of the CVM stages 3 and 4 is longer than that in Class I subjects is still an open issue.

Even considering the duration of each CVM stage from 2 to 4 lasting 1 year, as initially proposed [1], inherent error in the use of such discrete staging systems would make reliable and clinically relevant a variation in age of the attainment of each circumpubertal CVM stage when of at least 4–6 months [16]. Considering the mean values of ANB, SN/MP, and NSBa angles seen herein and the corresponding β coefficients (even those close to the statistical significance), estimations of ranges for these craniofacial parameters, from which relevant age variation in the attainment of the CVM stages is expected, may be carried out. In particular, subjects with expected age variation of at least 6 months in the attainment of the different stages would be as follows: (i) for the CVM stage

2, those with an ANB angle at least ±3.8° of the sample mean of 3.7° (10.0% of the whole group); (ii) for the CVM stage 3, those with an SN/MP angle at least ±8.6° of the sample mean of 30.4° (11.3% of the whole group); and (iii) for the CVM stage 3, those with an NSBa angle at least ±10.0° of the sample mean of 130.0° (3.8% of the whole group). However, the actual duration of each CVM stage is subjected to variability in individual subjects [28] that may not be uncovered in cross-sectional investigations. While this variability would not compromise the results obtained by correlation analyses in a group of subjects, it has to be taken into account when dealing with individual patients, especially when little associations are seen. Moreover, unless raters undergo dedicated training [20], the repeatability of the CVM stage assignment may be not satisfactory [29]. A further limitation of the present study is related to the contrasting evidence regarding the reliability of the CVM method in detecting the mandibular growth peak [16, 28, 30–33]. However, most of the current studies used different variants of the CVM method [16, 33, 34], making results poorly comparable, or were focused on Class II malocclusion subjects [35], limiting the external validity. However, such conclusions may only be applied to the mandibular sagittal growth, with correlations of the CVM stage with vertical growth still poorly investigated. The present study warrants further investigations using different growth indicators, such as hand-and-wrist maturation [36] or third finger middle phalanx maturation [37] methods or longitudinal designs. Of note, while potential biases due to temporomandibular disorders were excluded herein, the present study was based on a population of subjects seeking orthodontic treatment; thus, the present results have to be extended with caution to general population without evident malocclusion.

5. Conclusions

Age variations in the attainment of the different circumpubertal CVM stages 2 to 5 have been seen mainly for vertical craniofacial growth pattern, as recorded through the SN/MP angle, with hyperdivergent and hypodivergent subjects, having an anticipated and delayed attainment of the pubertal CVM stage 3. However, such association would become clinically relevant only in extreme cases that would have a low prevalence in a population of subjects seeking orthodontic treatment of about 1 case out of 10. Timing for functional treatment of vertical discrepancy that requires to be performed during the pubertal growth spurt may take advantage of this evidence.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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