Spheno-Occipital Synchondrosis Maturation As Related To The Development Of Cervical Vertebrae, Mandibular Canine And Chronologic Age: A Cone-Beam Computed Tomography Analysis

by

Richard Michael Halpern

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Department of Preventive Dental Sciences
University of Manitoba
Winnipeg

ABSTRACT

Objective: To investigate the relationship between maturation of spheno-occipital synchondrosis (SOS) with cervical vertebrae maturation (CVM), dental development of the mandibular canine (DI) and chronologic age.

Materials and Methods: Seventy-seven subjects (42 females and 35 males) were randomly selected for each of six age groups from retrospective cone-beam computed tomograms: (1) 9 year old females, (2) 11-12 year old females, (3) 16-17 year old females, (4) 10-11 year old males, (5) 13-14 year old males and (6) 18-21 year old males. Spearman correlation coefficients between SOS, CVM, DI, and age group, along with tabulations of stages of SOS, CVM and age were evaluated separately for gender.

Results: SOS maturation was significantly correlated with CVM (0.831 [females] and 0.870 [males]) ($p \leq .001$); and with chronologic age (0.830 [females] and 0.849 [males]) ($p \leq .001$). A weaker correlation coefficient was found between SOS maturation and DI (0.734 [females] and 0.638 [males]) ($p \leq .001$). All males with fused SOS were in CVM stage 4 or later, while all females were in at least CVM stage 3. No subjects with open SOS were in the oldest age group and no subjects with closed SOS were in the youngest age group. If the DI of a female or male were in stage E or F, the SOS would not have reached the complete union stage. Subjects with a DI in stage G were found in both sexes to be in all three stages of SOS maturation. SOS maturation showed substantial Inter-rater reliability ($p \leq 0.001$) of

0.757 (Cohen's Kappa) and intra-rater reliability ($p \leq 0.001$) of 0.750 (Cohen's Kappa).

Conclusion: SOS stages are valid indicators of potential craniofacial growth and development and correlate with measures such as CVM.

Key Words: Skeletal maturation; Spheno-occipital synchondrosis; Maturation indicators; Age determination; Growth prediction; Computed tomography, cone-beam, x-ray

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CHAPTER I

INTRODUCTION AND REVIEW OF THE LITERATURE

Introduction

The timing and decisions about treatment modalities are critically dependent upon the accurate assessment of individual growth and development. Predicting the optimal time to begin orthopaedic treatment may be discerned by several methods. The accuracy of maturational indices is limited and has a large error of measurement. For example, a female patient of 12 years old requiring headgear treatment may be delayed, or be ahead two years of the expected norm for her age and not yield expected outcomes (Fishman, 1979). Knowing the age of fusion of the spheno-occipital synchondrosis (SOS), the last synchondrosis in the cranial base to fuse, may alter when the timing of an orthopaedic treatment may be initiated.

While not necessarily the standard of care at present, the advances in radiology have helped render cone beam computed tomography (CBCT) commonplace in orthodontics in certain regions of North America (Scarfe, Farman & Sukovic, 2006). It has now become possible to discern anatomical structures, such as the SOS, and their development with increased clarity through images obtained using this technology.

The SOS has been investigated for its use as a maturation indicator (Bassed, Briggs & Drummer, 2010; Bassed, Briggs & Drummer 2011; Can, Ekizoglu, Hocaoglu, Inci, Sayin & Kaya, 2014; Franklin and Flavel, 2014). However, a comprehensive review of the literature has revealed a void in the English literature relating the SOS, viewed with CBCT images, in concert with other common maturational indices. Further, the reproducibility and reliability, using images obtained with decreased radiation, increased spatial and decreased contrast resolution with this technology, has not yet been reported (Angelopoulos, Scarfe & Farman, 2012).

Review of the Literature

Orthopaedic Treatment

The term orthopaedics originates from the Greek words "*orthos*" (to straighten) and "*paidion*" (child) (British Columbia Orthopaedic Association, http://www.bcoa.ca/join-bcoa/history-of-the-coa-and-orthopaedics-in-canada/, 2014), and refers to the practice of manipulating growth to a desired outcome different than the one genetically programmed. Human societies have been using orthopaedic techniques to modify their bone formation for thousands of years. For example, female ethnic minorities in Burma and South Africa wear neck rings that deform their clavicles and ribs to give an illusion of an esthetically appealing elongated neck (Walker, http://asiapacific.anu.edu.au/newmandala/2007/05/16/bound-by-tradition/, 2007; Vukuzenzele, http://www.vukuzenzele.gov.za/2007/number14/art_12.htm, 2007) and in China, foot binding is a technique girls use to prevent their feet from further growth potentially originating as a sign of elegance and beauty (Vento, http://www.fordham.edu/halsall/women/vento.asp, 1998).

In the specialty of orthodontics, orthopaedic treatment involves delivering distraction (applying tension across sutures/synchondroses to separate bony segments) and/or compressive forces changing natural growth of the facial complex. In 1902, Pierre Robin introduced functional jaw orthopaedics by creating a monobloc appliance to treat patients with retrognathic mandibles (Wahl, 2006c). The monobloc appliance positions the mandible forward creating a distraction of the condyle of the mandible from the glenoid fossa of the temporomandibular joint.

The other form of orthopaedic treatment involves compression. Gunnell, in 1822, is credited with having invented the first headgear (Wahl, 2005). This modality is used to restrain anterior and/or inferior growth of the nasomaxillary complex. A headgear is an extra-oral appliance that applies compressive force through an extra-oral spring-loaded strap around the back of the neck and/or occiput to a metallic facebow. Contemporarily, the facebow is most commonly connected to slots in metal bands that are affixed to the maxillary molars. The forces transmitted from the extra-oral spring-loaded straps are transmitted to the maxillary molars. The molars transmit this force across the area surrounding the tooth (the periodontal ligament) to the alveolar bone that supports the teeth within the bone. The force is transmitted from the alveolar bone to the nasomaxillary complex and through to the nasomaxillary complex is distributed across the sutures connecting the maxilla to the base of the skull restricting the innate direction of growth within the sutures. These sutures include: zygomaticomaxillary, zygomaticotemporal, zygomaticofrontal, nasomaxillary, nasofrontal, lacrimomaxillary, lacrimofrontal, sphenotemporal, sphenofrontal , occipitotemporal, the SOS and the pterygomaxillary junction (Henry, 1973; Holberg, Holberg, Rudzki-Janson, 2008).

Of those sites, there is particular interest in the SOS as, while it may not be the major such structure effected by orthopaedic treatment, it is the last to fuse and may provide valuable insight on treatment timing. Contrastingly, Fudalej, Kokich and Leroux (2007) showed that there is continued growth of the nasomaxillary complex far beyond the accepted age of fusion of the SOS. After the SOS has fused, any orthopaedic changes would be attributed to the numerous other sutures affected by the application of a headgear appliance or orthopaedic appliances that include a headgear, for example a Headgear Activator.

Another orthopaedic technique that applies distraction forces to the SOS is rapid maxillary expansion (RME). RME is used in patients whose maxilla is deficient in transverse width. RME delivers a separating force to orthodontic bands on the maxillary dentition. This force is delivered perpendicular to the midpalatal suture thereby separating nasomaxillary sutures from one another. Responsively, bone is deposited between the separated bones and a widened maxilla results. Rhesus monkeys were shown by Gardner and Kronman (1971) to have 0.5-1.0 mm opening of the SOS when RME was used. This amount of opening is pertinent only in showing that an opening of the SOS is required with this orthopaedic technique to be successful in achieving its goal of separating the maxillary bones. This finding was corroborated by similar significant findings of the SOS opening with RME in young human subjects using computed tomography (CT) and cephalometrics respectively (Leonardi, Cutrera & Barbato, 2010; Silvestrini-Biavati, Angiero, Gambino & Ugolini, 2013). Headgear treatment alone, or in combination with functional appliance treatment via headgear activators, and rapid maxillary expansion, continue to be orthopaedic treatments used today that require partially or completely open spheno-occipital synchondroses.

Timing is of the essence

Unlike orthopaedic treatment, orthognathic surgery is a technique requiring surgical osteotomies (intentional directional fractures and movements of bones) used to achieve desired repositioning of facial bones when the magnitude of the movement and/or amount of growth remaining is insufficient to achieve an ideal result otherwise. One of the most significant ways it differs from orthopaedic treatment is that it requires that a patient receive a surgical procedure in the operating room.

Proffit and White (1990) analyzed data collected from the National Centre for Health in the United States of America, published in the 1970s, to determine what percentage of patients were potential candidates for orthognathic surgery based on the severity of their malocclusion. Patients with Class I skeletal relationships are those with a normal antero-posterior relationship of their maxilla and mandible. A Class II skeletal relationship is the diagnosis of a retruded mandible compared to the maxilla and a Class III malocclusion is found when the mandible is protruded relative to the maxilla. While various norms exist, in America, 30% of the population has normal Class I occlusion, 50-55% have a Class I malocclusion, 15% have a Class II malocclusion and less than 1% have a Class III malocclusion (Proffit, 2007). Proffit and White (1990), found that 5% of Class II, and 33% of Class III patients, were potential candidates for orthognathic surgery.

In growing patients who present borderline orthopaedic treatment / orthognathic surgery cases, knowing a patient's maturation level can make the difference between planning extraction and/or orthognathic surgery versus an orthopaedic treatment (Smith, 1980). In those patients without early orthopaedic intervention, orthognathic surgery options are presented more frequently (Proffit, Phillips & Medland, 1992; Tulloch, Phillips, Proffit, 1998).

For example, Faltin, Faltin, Baccetti, Franchi, Ghiozzi and McNamara (2003) performed a controlled long-term study of Class II patients treated with the Bionator functional appliance (orthopedic treatment) followed by fixed orthodontics (orthodontic treatment). They followed an early treatment group, who completed their Bionator treatment prior to their peak in mandibular growth and a late treatment group, who began Bionator treatment before, and completed orthopaedic treatment after their peak. They compared these groups with respective untreated Class II controls from the University of Michigan Elementary and Secondary School Growth Study who were matched for cervical vertebral maturation (CVM) at each stage of treatment and gender. They found that when comparing the mandibular dimension on a cephalogram from condylion to pogonion, relative to their respective controls, from before Bionator treatment to a long-term observation time after completion of growth (unspecified), the early treatment group had increased that dimension 1.9 mm (not statistically significant) and 5.1 mm (statistically significant) in the late treatment group. These findings support that a larger magnitude or orthopaedic treatment can be achieved if the therapeutic intervention is begun before, and completed after the patient's peak in growth.

Depending on the particular circumstance, orthodontic treatment is proceeded by, or delivered concurrently with orthopaedic treatment as one or two phases of treatment. If orthopaedic treatment is delivered immediately preceding, or concurrently with, orthodontic treatment, it is considered one continuous phase of treatment. Alternatively, if orthopaedic treatment is delivered and then followed by a substantial amount of time after its completion prior to orthodontic treatment commencing, it is considered two separate phases of treatment. Tulloch Proffit and Phillips (2004) corroborated the results of Faltin, Faltin, Baccetti, Franchi, Ghiozzi and McNamara (2003), finding that initiating Class II orthopaedic treatment too early, followed by a second phase of orthodontic treatment is not as efficient as providing both treatments in a single phase during adolescence. Specifically, they found no reduction in the need for extraction and/or orthognathic surgery if orthopaedic treatment was initiated early. While early treatment does have advantages with respect to efficacy of treatment, disadvantages to beginning treatment too early include: requiring longer periods of patients compliance with retention (i.e. wearing their retainers), increasing total treatment time and decreased compliance in the orthodontic second phase of treatment, as well as the respective accompanying challenges (i.e. caries). Therefore it is of the utmost importance that the orthodontist knows the skeletal maturation of their patients in order to maximize treatment effectiveness.

The development of radiographs

In 1895, Wilhelm Conrad Röntgen discovered x-radiation (Farman, 1995). In 1931, the cephalometer was developed by Broadbent and Bolton to assess growth and developmental patterns in the craniofacial complex. From then on, orthodontic diagnoses, without the new information a cephalogram provided, were considered incomplete (Wahl, 2006a). This led to the development of the cephalometric analysis by Downs in 1970 (Wahl, 2006b).

The field of head and neck radiography progressed substantially when Cormack and Hounsfield, in 1972 and, independently of one another, developed the computed tomography (CT) scanner (Cormack, 1980; Hounsfield, 1980). This technology emits radiation levels higher than can be justified for routine orthodontic examination. A lower radiation emitting technology was developed not long after in the early 1970's when a precursor of the current cone beam computed tomography (CBCT) scanner was developed (Angelopoulos, Scarfe & Farman, 2012).

Following the historical progression of radiographic development in orthodontics, in 1995 the first CBCT scanner was used in Dentistry. Within a few years, in 1999 in Europe, the first scanner became commercially available (Angelopoulos, Scarfe & Farman, 2012). Currently, CBCT imagining, while not necessarily the standard of care at present, has become routine in certain regions particularly on the west coast of the United Sates of America (Scarfe, Farman & Sukovic, 2006). The prevalence of usage in Canada is unknown though the Canadian trend in this field is expected to be similar to that of the United States of America. The research presented here does not advocate obtaining a CBCT image for the purpose of assessing the maturation of the SOS. However, if the image had already been obtained, one should not overlook observing the maturation of the SOS as it could provide valuable information about treatment options.

Types of Biologic indicators

The chronologic age at which sexual maturity is reached varies for females and males due to the different age of onset of puberty (Proffit, 2007). The skeletal maturity of an individual can be assessed via several biological maturation indicators. These include changes in body height, weight and body mass index (Hunter, 1966; Proffit, 2007; Centers for Disease Control and Prevention, http://www.cdc.gov/growthcharts/clinical_charts.htm; 2009), and pubertal indicators such as voice changes and menarche (Tanner, Whitehouse and Takaishi, 1966a; Tofani, 1972; Hägg and Taranger, 1980). Radiographic indices are also used such as the development, emergence and eruption of the dentition (Nolla, 1960; Demirjian, Goldstein & Tanner, 1973; Coutinho, Buschang & Miranda, 1993), skeletal maturation of the hand and wrist (Greulich and Pyle 1950; Björk and Helm, 1967; Fishman, 1982); cervical vertebral maturation (Lamparski, 1972; Hassel and Farman, 1995; Franchi, Baccetti & McNamara, 2000; Baccetti, Franchi & McNamara, 2005) and SOS maturation (Irwin, 1960; Powell and Brodie, 1963; Melsen, 1972).

Plotting height changes on a stature-for-age chart

Increase in a patient's stature can be assessed to indicate mandibular skeletal maturity (Björk, 1963). In order to do so, at least three consecutive measurements on 3- to 6-month intervals must be made to compare with a stature-for-age chart (Tanner, Whitehouse, Takaishi, 1966b; Lewis, Roche & Wagner, 1985; Franchi and Baccetti, 2002). Similarly, for patients nearing their Peak Height Velocity (PHV), growth charts using weight-for age and BMI-for-age can be used as well (Centers for Disease Control and Prevention, http://www.cdc.gov/growthcharts/clinical_charts.htm; 2009). Growth rate can also be assessed with Wetzel grids that rely on consecutive measures of body size, body volume and physical energy expended (Wetzel, 1946).

The correlation between stature changes at puberty and that of the jaws has been established previously. Cephalometric studies have shown a peak at puberty in mandibular growth (Björk, 1963; Hunter, 1966; Lewis, Roche & Wagner, 1985).

Statistically significant correlations have been established between statural peak growth velocity and the mandibular growth rate with "substantial" coefficients ranging between r=0.76 to r=0.79 (Hunter, 1966; Grave, 1973; Landis and Koch, 1977). The increase in mandibular dimensions and increase in stature (PHV) occur at the same time or slightly after one another, with mandibular dimensional increase generally preceding PHV (Hunter 1966; Tofani 1972; Lewis; Roche & Wagner, 1985). Following PHV, there is a higher percentage of mandibular growth remaining than growth of the maxilla or anterior cranial base. Vertically at that time, there is more growth to occur in the posterior facial height than the anterior facial height (Hunter, 1966)

An advantage of this indicator is that the method does not expose the patient to potential harmful X-radiation (Franchi and Baccetti, 2002). A disadvantage is that there may be a loss of valuable treatment time while waiting to obtain serial measures. A second disadvantage is that sequential generations of humans are getting taller and reaching puberty sooner and the stature-for-age charts require updating every 10-15 years (Lavelle, 1972; Okasha, McCarron, McEwen & Smith, 2001).

<u>Pubertal Development</u>

Signs of sexual maturation provide insight on a patient's biologic development. Tofani (1972) found a significant positive relationship between menarche and the maximum growth increment in both corpus length and bigonial width. Hägg and Taranger (1980) found menarche and the PHV to have a moderate correlation (ρ

=0.77) and also found that changes in male voice and PHV have a moderate positive correlation (ρ=0.73).

An advantage of these indicators is that they also do not require exposure to x-radiation. Unfortunately, these pubertal development indicators have been regarded by some authors as useless in orthopaedics as females always achieve menarche, and men 98% of the time achieve their adult voice, after PHV (Hägg and Taranger, 1980; Franchi and Baccetti, 2002).

Dental Development Index

Dental development can be used to assess mandibular skeletal maturity (Lewis and Garn, 1960; Björk and Helm, 1967; Hellman, 1923). Studies have done this with different approaches quantifying emergence, eruption, crown and root development or using any combination of these methods (Nolla, 1960; Björk and Helm, 1967; Demirjian, Goldstein & Tanner, 1973; Hägg and Taranger, 1982; Coutinho, Buschang & Miranda, 1993; Proffit, 2007).

Relationships between dental emergence and PHV have been reported to range from no correlation to a poor or weak correlation (ρ=0.01; to ρ =0.42) between dental emergence and PHV (Björk and Helm, 1967; Hägg and Taranger, 1982). Björk and Helm, (1967) found that in boys, eruption to the occlusal plane of second molars, and in girls of canines and premolars, may occur several years before or after the PHV.

Nolla (1960) described 10 stages of tooth development; Demirjian, Goldstein and Tanner (1973) built on that work describing the Demirjian Index (DI) of stage A (initial cusp tip appearance of premolars and molars without fusion between cusps) through stage H (apical end of the root canal is completely closed) of dental development. Coutinho, Buschang and Miranda, (1993), recognizing the imperfection of this technique described that the dental calcification stages of the DI are easily recognized and readily available and are a good primary indicator of when further maturity indicators are merited.

Initiation of the pubertal growth spurt has been correlated with canine development stage F (Demirjian, Goldstein & Tanner, 1973), and Coutinho, Buschang and Miranda, (1993) found dental development stage G of the canine to be 0.4 years after PHV for girls, and 1.3 years for boys. No study could to be identified in the English literature that assessed the relationship of dental development with mandibular growth.

Of all the indicators, dental age (dental eruption and dental development) correlates least well with the other developmental indices. Proffit (2007) considers dental age to not be an accurate predictor as it has a correlation of ρ_s =0.7 with chronologic age which provides an almost 50% chance of making an accurate prediction.

Hand-wrist radiograph Index

The most widely used method of evaluating skeletal maturation is the hand-wrist method (Flores-Mir, Nebbe & Major, 2004). Hellman (1928) was one of the first researchers to publish relationships of chronologic age and stature with the ossification and fusion stages of the hand. Greulich and Pyle (1950) created a radiographic atlas of skeletal development of the hand and wrist for various ages, where a patient's hand-wrist radiograph was matched with a corresponding image with an associated in the Atlas.

Based on 1000 hand-wrist radiographs of children, a 20-bone summative score of the short bones, carpal radius and ulna was subsequently developed that added the score from the percentage of total maturation of each bone to predict skeletal maturation scored out of 1000 that was used for many years (Tanner and Whitehouse, 1959; Tanner, Whitehouse and Healey, 1962). A simplified method was developed by Fishman (1982) that followed 11 stages of maturation measuring widening, capping and fusion of the phalanges and distal radial epiphysis and ossification of the adductor sesamoid of the thumb.

Hassel and Farman (1995) found the transition from hand-wrist stage 6 to stage 7 to represent PHV. Correlations of maximal growth velocity of the mandible with hand wrist radiographs have also been reported. Statistically significant correlations found between the onset of the fusion of the distal phalanges in the hand-wrist radiograph with mandibular length, ramus height and body length were found to be r=0.53, r=0.60 and r=0.71 respectively (Tofani, 1972). The correlation with mandibular length and ramus height is considered to be "moderate", while the correlation with body length is regarded as "substantial" (Landis and Koch, 1977).

While correlations do exist, a disadvantage of this index is that the patient needs to be exposed to supplemental X-radiation for a radiograph of their hand that's sole use is to detect the maturational level. When not therapeutically administered, X-radiation exposure predilects individuals to develop cancer (Dainiak, 1997).

Cervical Vertebral Maturation (CVM) Index

Cervical Verterbal Maturation (CVM) can also be used to assess mandibular skeletal maturity (Lamparski, 1972; O'Reilly and Yanniello, 1988). This assessment does not require exposing the patient to additional radiation as the image of the cervical vertebrae is in the cephalometric radiograph that is a routinely obtained for orthodontic diagnosis (Franchi and Baccetti, 2002).

Lamparski (1972) developed a series of standards for assessing CVM and showed them to be as reliable and valid as the hand-wrist method for the assessment of skeletal age, and O'Reilly and Yanniello (1988) found that CVM stages are related to mandibular growth changes during puberty. Reducing radiation exposure further, through allowing for the use of a thyroid protective collar, Hassel and Farman (1995) developed a CVM index using only the bodies of the second, third and fourth cervical vertebrae. They found that the PHV to occur between stages 3 and 4 in their method. Franchi, Baccetti and McNamara (2000) enlarged on Lamparski's (1972) classification of CVM stages and found a significant correlation of CVM with stature and mandibular length in a sample of boys and girls. While they did not report correlation coefficient values, they did report that stages 2 and 3 were before PHV, that the peak occurred between stages 3 and 4 and that there was then decelerated between stages 4 and 5. In their investigation, 100% of boys and 87% of girls underwent their PHV between stages 3 and 4, with the remaining 13% of girls peaking between stages 4 and 5.

In 2002, and further in 2005, Baccetti, Franchi and McNamara modified their previous CVM classification. Following the method of Hassel and Farman (1995), they provided a classification method which utilized only the second, third and fourth cervical vertebrae to decrease radiation exposure through allowing a thyroid collar to be used and still providing the necessary anatomy. They also provided a description of each vertebrae's geometry at each stage.

Sphenoid Synchondroses Formation and the Cranial Base

The cranial base, from foramen magnum to foramen cecum, forms from cartilage continuous with the nasal capsule (Scott, 1958). During the first half of fetal life ossification centres develop within that cartilage forming the basioccipital, basisphenoid and presphenoid bones (Ford, 1958). The sphenoid and occipital bones are two of the bones that form the cranial base. These two bones form from 25 separate ossification centers, 19 of which are found in the sphenoid bone. Through childhood and adolescence, the sphenoid bone consists of 12 synchondroses; most of which fuse by the age of 2 years old (Adem, Lafitte, Jarquin Guillem & Chiras, 1999). After that time, the anterior and posterior cranial base lengths increase due to bony deposition, as well as growth at the spheno-ethmoidal and SOS (Graber, Vanarsdall & Vig, 2012).

Ford (1958) described that each segment of the cranial base has an anterior-posterior growth rate that follows either the general skeletal or neurologic growth rates. He reported that while the portion from the anterior to posterior foramen magnum followed a neurologic growth rate, the segment of the cranial base from Sella Turcica to Basion followed a skeletal growth rate. The cranial base in humans is more flexed than any animal (Scott, 1958). In adult animals, after birth, flattening of the cranial angle occurs to nearly 180 degrees whereas in humans it decreases to 133 degrees (Scott, 1958). In humans, it has been suggested that the centre of rotation of this cranial flexure is at the site of the SOS (Björk, 1955). Scott (1958) on the other hand has indicated that most of this flexure happens during fetal life in the cranial base anterior to the SOS.

The cartilages of the synchondroses grow like an epiphyseal plate with the exception that it grows bipolar in nature (Thilander and Ingervall, 1973). The cartilage has an area of immature proliferation (hyperplasia) in the centre, surrounded by maturing chondrocytes (hypertrophy) in either direction. In the outer layers, these cells undergo endochondral replacement (Proffit, 2007). The position of the maxilla depends on the growth of these two synchondroses (Singh, 2007).

There may be a connection between the cranial base angle and the position of the mandible. While some studies have reported little or no relationship, most studies show that individuals with larger cranial base angles, and/or larger anterior and posterior cranial base lengths, tend to be retrognathic, whereas those with the smaller lengths and angles tend to be prognathic. Growth of the posterior cranial base (i.e. SOS) is directly positively related to inferior and posterior displacements of the glenoid fossa. Consequently, cranial base growth variations can partially explain individual and population differences in antero-posterior skeletal relationships (Graber, Vanarsdall & Vig, 2012).

Another sphenoidal synchondrosis, the spheno-ethmoidal synchondrosis fuses at 6-8 years of age (Ford, 1958; Scott, 1958; Melsen, 1974; Ohtsuki, Mukherjee, Lewis and Roche, 1982; Bishara, 2001; Mitchell, 2007; Graber, Vanarsdall & Vig, 2012). As it loses its cartilaginous phenotype it functions as a suture at which time growth of the anterior cranial base is essentially complete (Graber, Vanarsdall & Vig, 2012).

Closure of the Spheno-occipital Synchondrosis (SOS): orthopaedic implication

The SOS significantly contributes to craniofacial growth, but after 6 years of age its relative contribution is small (Bishara, 2001). Its duration of activity is likely not of major significance in affecting the antero-posterior (AP) position of the maxilla (Long, 1971; Proffit, 2007). While the majority of the anterior-posterior growth of the cranial base may be completed early, restraining forces applied to the maxilla and the underlying sutures and synchondrosis with a headgear attempt to impede the amount of growth expressed at that site (Proffit, 2007). With closure of the SOS the magnitude of orthopedic modification possible may be reduced. Equally, in order to gain boney expansion of the maxilla with RME it would be advantageous to do so prior to the closure of the SOS (Gardner and Kronman, 1971; Leonardi, Cutrera & Barbato, 2010; Silvestrini-Biavati, Angiero, Gambino & Ugolini, 2013).

For some growth modification techniques, like headgear use, other indices of maturation are used to predict when it would be too late to affect the SOS. Rather than through use of a distant maturation indicator, by observing the SOS directly, the patency of the synchondrosis may be assessed.

Closure of the Spheno-occipital Synchondrosis (SOS): an index

Several methods of investigating the SOS have been used in assessing the maturation of this structure. These include conventional radiographic (i.e. laminagraphy), histologic, direct inspection of cadaveric samples, CT images and a combination of direct inspection with any of the other techniques. Further, regions of the body grow at different rates - the SOS is closer in proximity to the facial complex than the cervical vertebrae or the hand-wrist. To that end, the SOS, due to its proximity, would be expected to be more predictable at indicating facial growth potential than hand-wrist or cervical vertebral maturation indicators (Smith, 1980).

Studies have described the pattern of fusion of the spheno-occipital synchondrosis along the midsagittal plane. It fuses from the superior margin in an inferior direction until the inferior margin is fused (Irwin, 1960; Powell and Brodie, 1963; Ingervall and Thilander, 1972). Aside from this pattern observed in the midsagittal plane, there is no available information in the English literature concerning a possible three-dimensional pattern of fusion of this structure. Further, it was not the intention of the present investigation to explore if a possible three-dimensional pattern of fusion of the synchondrosis might exists.

In early radiographs it was hard to discern whether the SOS was open, partially closed or completely closed (Melsen, 1969). The development of CBCT has allowed the possibility of more clearly distinguishing the closure of the SOS. Recently there have been several studies employing CT technology to determine the age of fusion of the SOS (Bassed, Briggs & Drummer, 2010; Bassed, Briggs & Drummer 2011; Can, Ekizoglu, Hocaoglu, Inci, Sayin & Kaya, 2014; Franklin and Flavel, 2014). Table 1 shows the findings and methods of the studies analyzing age of fusion of the SOS.

Table 1 Range of Time of Closure of the Spheno-occipital Synchondrosis (SOS)

	Female Age (Yrs)	Male Age (Yrs)	Method
Scott (1958)	17-20*		Unknown
Irwin (1960)	14-25*		Radiographic
Powell and Brodie (1963)	11-14	13-16	Radiographic
Melsen (1972)	12-16	13-18	Histologic
Thilander and Ingervall (1973)	>16-17	>18-19	Histologic
Williams, Bannister, Berry, Collins, Dyson & Dussek (1995)	18-25*		Unknown
Okamoto, Ito, Tokiguchi, & Furusawa (1996)	12-14	14*	CT
Sahni, Jit, Neelam & Suri (1998)	13-17	15-19	Direct Inspection / CT
Scheuer and Black (2000)	11-13	13-18	Unknown
El-Sheikh and Ramadan (2006)	11-16	12-18	CT
Coqueugniot and Weaver (2007)	13**	18**	Direct Inspection
Akhlaghi, Taghaddosinejad, Sheikhazadi, Valizadeh, Shojaei (2010)	12**	15**	Direct Inspection
Shirley and Jantz (2011)	13-20	16-23	Direct Inspection
Franklin and Flavel (2014)	11.8-25.6	13.4-25	CT

* No sex differentiation was made

** Maximum in range not available

Partial fusion was reported in one investigation to first be seen in females of 12 years old and in males of 13 years old (Sahni, Jit, Neelam & Suri, 1998). Enlow,

(1996) while not mentioning his method of measurement, was of the opinion that there is a difference between the time the SOS became inactive (12-15 years old) and when it fused (20 years old).

A possible source of the variation in the reported values may be due to the method in which studies report closure of the SOS. While some studies rank the SOS as either open or closed, other studies have listed 5 stages of progressive closure (Irwin, 1960; Powell and Brodie, 1963; El-Sheikh and Ramadan, 2006). Authors have also classified 5 stages of progressive closure and then reported values on the closure stage to include the final two stages without differentiating values between the fourth and fifth stages (Bassed, Briggs & Drummer, 2010). Another possible reason for the variation in the age of fusion in females from 11-25 years old in females and 12-25 years old in males reported may be due to the different methods used. Direct macroscopic, histologic, conventional radiograph and multi-slice CT (MSCT) all offer different abilities to detect a closed suture with varied sensitivities (Krishan and Kanchan, 2013). A study by Madeline and Elster (1995) and one by Okamoto, Ito Tokiguchi and Furusawa, (1996) used MSCT and looked at SOS maturation in more than just the midsagittal plane. Madeline and Elster (1995) reported the first ossification of the SOS to occur in only the midline. Okamoto, Ito, Tokiguchi and Furusawa, (1996) found that the initial ossification center of the SOS was found in all subjects in the midline and in some females they noticed additional symmetric parasagittal ossification centers.

SOS Relationship with Other Indicators

Several investigations have analyzed the relationship between SOS fusion and chronologic age. Spearman rank-ordered correlations ranged between ρ_s=0.63 and ρ_s=0.86 for males and ρ_s=0.62 and ρ_s=0.82 for females (Akhlaghi, Taghaddosinejad, Sheikhazadi, Valizadeh & Shojaei, 2010; Shirley and Jantz, 2011; Can, Ekizoglu, Hocaoglu, Inci, Sayin & Kaya, 2014; Franklin and Flavel, 2014). These values are regarded as "substantial" to "almost perfect" (Landis and Koch, 1977). Hence, a positive correlation between SOS fusion and chronologic age has been shown to exist when assessed with non-CBCT methods of analysis.

Contrastingly, Bassed, Briggs and Drummer (2011) used CT images and assessed with regression, dental maturation of the third molar, medial clavicular epiphysis maturation, SOS maturation and age. They used a five-stage maturation scale for the SOS. The 95% confidence interval range for the beta value of the molar was 0.66-0.995 for males and 0.34-0.67 for females, the clavicle was 1.07-1.34 for males and 1.48-1.85 for females and the SOS was -0.026-0.51 for males and -0.28-0.45 for females. The SOS confidence interval beta value passing through zero indicates in both males and females that the SOS does not contribute to the model's validity. Thus, using multiple regression analysis, they found that adding the SOS to the regression analysis provided no increase in predictive value of age and explained that this was likely due to the older age range of their sample.

No research to date in the English literature could be found which has reported on the relationship between SOS closure and dental development of the mandibular canine (DI) or between SOS and the CVM methods.

Reproducibility

An index cannot be relied upon if the same examiner measuring the same image at two different times scores it differently. Likewise, the index would not be very useful if a second examiner measured the same image under the same conditions and was not able to score the maturation at the same stage as the first examiner (Franchi and Baccetti, 2002). Intra-rater and inter-rater reliability is a measure of the amount of agreement between measurements between the same and different observers, respectively. According to Landis and Koch (1977), the strength of agreement by Kappa values are considered: "almost perfect" if 0.81-1, "substantial" if 0.61-0.80, "moderate" if 0.41-0.60, "fair" if "0.21-0.40, "slight" if 0.20 and to have "no agreement" if less than 0

Intra-rater reliability

Dental maturation, as described by the Demirjian, Goldstein and Tanner (1973) method, has been reported to have an intra-rater reliability of 94-95% (Kumar, Singla, Sharma, Virdi, Anupam and Mittal, 2012; Perinetti, Contardo, Gabrieli, Baccetti & Di Lenarda, 2014). Using Fishman's (1982) method of evaluation (previously mentioned), hand-wrist radiographs have had reported intra-rater reliabilities between 93-100% (Küçükkeleş, Acar, Biren and Arun, 1999; Hassel and Farman, 1995).

Intra-rater reliability has most commonly been reported for various CVM methods to range from 89-100% (Hassel and Farman, 1995; Küçükkeleş, Acar, Biren and Arun, 1999; Baccetti, & McNamara, 2005; Flores-Mir, Burgess, Champney, Jensen, Pitcher & Major, 2006; Kumar, Singla, Sharma, Virdi, Anupam and Mittal, 2012; Perinetti, Contardo, Gabrieli, Baccetti & Di Lenarda, 2014). Therefore, most studies find that it is an “almost perfect” test in its ability to be repeated within the same observer.

One study differs notably from the majority of those reporting high intra-rater reliability. Gabriel, Southard, Qian, Marshall, Franciscus and Southard (2009) trained 10 orthodontists, averaging almost 20 years experience each as orthodontists, briefly on how to perform accurate CVM analyses. They found intra-rater reliability to be 62%. They attribute a possible cause for much higher reliability in other studies to the researchers themselves, being very well trained in these techniques, and being the same individuals scoring the images.

Using MSCT imaging, intra-rater reliability of SOS maturation has been reported to be 91% (Bassed, Briggs & Drummer, 2010; Franklin and Flavel, 2014).

Inter-rater reliability

Inter-rater reliability for dental maturation has been reported at 84% (Kumar, Singla, Sharma, Virdi, Anupam and Mittal, 2012) and to range from 94-100% for hand-wrist maturation (Küçükkeleş, Acar, Biren and Arun, 1999; Hassel and Farman, 1995).

Cervical vertebral maturation had a strong inter-rater reliability ranging from 87-99% (Hassel and Farman, 1995; Küçükkeleş, Acar, Biren and Arun, 1999; Uysal, Ramoglu, Basciftci & Sari, 2006; Kumar, Singla, Sharma, Virdi, Anupam and Mittal, 2012). The study by Gabriel, Southard, Qian, Marshall, Franciscus and Southard (2009) described earlier reported inferior inter-rater reliability values (50%) than it did for intra-rater reliability (62%). Therefore, there continues to be some speculation about the ability for those who are not experts to be able to use this measure reliably.

MSCT images of the SOS have been shown to have "substantial" to "almost perfect" inter-rater reliability at 78-87% showing that it can be relied on for its assessment to be reproducible (Bassed, Briggs & Drummer, 2010; Franklin and Flavel, 2014).

In summary, the timing of delivering orthopaedic treatment is of the utmost importance, and the current indicators of when this optimal time would be are less than ideal. Common radiologic methods such as CVM and DI have been used to predict when the optimal time of intervention is for a particular patient. All of these methods have shortcomings. Many orthopaedic treatment techniques apply forces to the skull base. These forces are not exclusively directed at the SOS, however the SOS is often one of the structures targeted. Knowing the patency of the SOS is important since, if the SOS is fused, the effectiveness of the orthopedic treatment is decreased. The timing of the fusion of the SOS has been studied with various techniques. Compared to one another, the studies on the chronologic age at the time of fusion of this structure have reported a wide range of chronologic age in both females (11-25 years old) and males (12-25 years old). This has been attributed to the difference in chronologic age at onset of puberty and the corresponding peak height velocity. While SOS maturation has been investigated with MSCT, it has not been investigated with CBCT used in dentistry (Bassed, Briggs & Drummer, 2010; Can, Ekizoglu, Hocaoglu, Inci, Sayin & Kaya, 2014; Franklin and Flavel, 2014). CBCT offers better spatial resolution than MSCT and has the ability to show patency of the SOS at smaller voxel resolutions than that shown by MSCT studies which could falsely display a more mature SOS than truly exists (Angelopoulos, Scarfe & Farman, 2012). The correlation of SOS with CVM has not been reported prior to this study. Further, intra-rater and inter-rater reliability for assessing the SOS with CBCT has not been previously reported.

CHAPTER II

PURPOSE AND HYPOTHESIS

Purpose

The primary purpose of this study was to evaluate the validity of maturation of the spheno-occipital synchondrosis (SOS) as an indicator of skeletal age in the circum-pubertal growth spurt period of each sex by correlating it to cervical vertebral maturation and dental maturation of the mandibular canine. The second purpose of this study was to describe in both sexes the range of chronologic age and cervical vertebral maturation stage for each level of spheno-occipital synchondrosis maturation. The third purpose of this study was to assess the intra-observer and inter-observer reproducibility of the observations for spheno-occipital synchondrosis, cervical vertebral and dental maturation stages using CBCT.

Study Hypothesis

<u>Hypothesis #1:</u>

Null: There is no statistically significant positive relationship between spheno-occipital synchondrosis maturation and chronologic age, dental maturation and cervical vertebral maturation stages for females or males.

Alternative: There is a statistically significant positive relationship between spheno-occipital synchondrosis maturation and chronologic age, dental maturation and cervical vertebral maturation stages for females or males.

CHAPTER III

MATERIALS AND METHODOLOGY

Ethics

The study was approved by the University of Manitoba Bannatyne Human Research Ethics Board (BHREB) on February 16, 2013 (Ethics #: H2013:071) (Appendix 1).

Sample Groups and Size

The PHV has been reported to be consistent with the timing of pubertal growth spurt (Houston, 1980). The pubertal growth spurt has been reported to occur at 12.0 years old in females and 14.0 years in males with a standard deviation of 1 year however these chronologic ages vary to some degree based on the source (Houston, 1980; Nakamoto, 2000). Six groups were selected to represent both genders before, during and following their peak height velocities as follows:

1) Females prior to their PHV, (<10 years old)
2) Females during their PHV, (11-13 years old)
3) Females following their PHV, (>14 years old)
4) Males prior to their PHV, (<12 years old)
5) Males during their PHV, (13-15 years old)
6) Males following their PHV, (>16 years old)

A sample size of no less than 10 cases in each group was set as the criteria for this study. This number is similar to that found in other high-impact refereed journal publications using cephalometric radiographs to assess cervical vertebral maturation (e.g. O'Reilly and Yanniello, 1988; Hassel and Farman, 1995; Franchi, Baccetti & McNamara, 2000; Baccetti, Franchi & McNamara, 2002; Baccetti, Franchi & McNamara, 2005) and using CBCT to assess the patency of the SOS (e.g. Leonardi, Cutrera Barbato, 2010) with Spearman rank-ordered correlation and reliability testing with Cohen's Kappa statistic.

Collection of Subjects

An Orthodontist (T.C.) (Edmonton, Alberta, Canada) who had been routinely obtaining CBCT images of his patients as part of his standard initial diagnostic records, made his previously collected database available for this retrospective cross-sectional study. The images available from the database were mostly obtained prior to the commencement of patient's orthodontic treatment. However, many were obtained during the middle of orthodontic treatment and following the end of orthodontic and/or orthognathic surgical combined treatment. It was not known how many patients may have been pretreatment, in the middle of treatment or had completed active orthodontic treatment. These images were obtained using a cone beam computed tomography machine (iCAT Next Generation, Imaging Sciences International, Hatfield, PA). The machine was set to record a voxel resolution of 0.3 or 0.4 mm. Each radiograph captured, comprised of either 328, 432, 440 or 576 basis images ($\bar{x}$ =551; σ =60).

At this orthodontist's practice, patients were assigned identification numbers based on when they were first seen by that orthodontic practice; there was no gender or age associated with this number assignment. A report of patients from a practice management software program (Dolphin Management, v.5.0, Dolphin Imaging and Management Solutions, Chatsworth, CA) was exported to a data analysis spreadsheet (Microsoft Excel, Microsoft Corp., Redmond, WA) and became the "master key" for blinding purposes. Five specific data fields were exported to a spreadsheet including:

1. Chart number
2. Number of basis images
3. Gender
4. Date of birth
5. Date of scan.

The master key spreadsheet was opened and a column was created titled "age" in which the chronologic age of the patient at the time of the scan was calculated through subtracting the patient's date of birth from their date of the scan. For consistency, the subject's age was calculated in whole years by always rounding down unless the date of the data acquisition was equivalent to their birthday, not a day earlier. Another method to have calculated age would be to have rounded all those within six months of their next birthday up, and those within six months since their last birthday down. The method ultimately used, of rounding all ages down, maintained the space of a year between groups.

Subjects were randomly identified to see if they were acceptable for use in this study. This was done until all sample groups had at least 16 subjects collected into each of the six sample groups. The goal of selecting 16 subjects in each group was done in order to ensure that there were extra subjects available after exclusion criteria would be applied and leave no group with less than 10 subjects. If less than 10 subjects remained in any particular sample group after exclusions, the master key list was revisited in order to identify more subjects and increase that sample group size to 16 again.

The identified images were opened in the proprietary acquisition software (iCATVision, v.1.9.3.14, Imaging Sciences International, Hatfield, PA) by selecting their chart number and assessing them for their suitability for this study. This was done by launching the proprietary acquisition software, sorting the patient identification chronologically, scrolling the vertical scroll bar to find the identification number correlated to the identified image. If the file type "ct" was listed next to the date of the acquisition of the images, then the image was opened and assessed for exclusion criteria. Definitions of landmarks used for exclusion, orientation and capture in this investigation are shown in Table 2.

Table 2 Topographic Points Used as Landmarks for Image Exclusion, Orientation and Capture (Athanasiou, 1995)

Landmark	**Definition**
Anterior Nasal Spine	The tip of the bony anterior nasal spine
Nasion	The most anterior point of the frontonasal suture in the median plane
Orbitale	The lowest point in the inferior margin of the orbit
Porion	The superior point of the external auditory meatus
Posterior Nasal Spine	The tip of the posterior spine of the palatine bone, at the junction of the hard and soft palates

The exclusion criteria included:

- ✓ Presence of orthodontic brackets, appearing radiopaque on the dentition
- ✓ Subjects who had radiographic indications of having had orthognathic surgery, such as brass wires or metal plates

- ✓ Images that did not completely include:
  - Anterior Nasal Spine
  - The most antero-inferior point on the symphysis of the chin
  - Nasion
  - Porion
  - Posterior Nasal Spine
  - The body of the sphenoid bone
  - The entire spheno-occipital synchondrosis (SOS)
  - The entire bodies of the second, third and fourth cervical vertebrae
- ✓ Obvious anomaly in the vertebral bodies of the second, third or fourth cervical vertebrae
- ✓ At least one congenitally absent, or obviously ectopic, permanent mandibular canine

These exclusions were necessary to ensure the scans would be able to be oriented and captured the essential anatomy for measurements. Subjects with missing permanent teeth, other than mandibular canines, or those with heavily restored teeth were not excluded. This was because agenesis and heavily restored teeth were not expected to interfere with growth and development. Subjects were not excluded for having had completed orthodontic treatment alone. It was not possible to obtain any record of the subject's race. Images were excluded for subjects displaying radiographic indications of having had orthognathic surgery, obvious anomalies in the second, third or fourth vertebral bodies and those displaying congenitally absent or obviously ectopic permanent mandibular canines were necessary. The reason for these exclusions is that they all may represent subjects exhibiting growth and development that is out of the norm and there is potential that their maturational indicators do not represent the average population. Subjects presenting with orthodontic brackets were also excluded from this study. This was done to minimize the possibility of subjects who may have undergone any orthopaedic compressive or tensile forces on the SOS. It is unknown if orthopaedic forces acting on the SOS alter its course or timing of fusion. While such orthopaedic treatment may be initiated concurrently with fixed orthodontics, it often precedes it. In this investigation it was not possible to discern if a subject had undergone any orthodontic or orthopaedic treatment.

If a subject met the requirements, their corresponding image was compressed and exported. This was done by selecting in the menu bar "Tools," then sequentially, "Export DICOM" and "Original Study." The location to save the file was chosen to be on an external hard drive. A detailed description of image acquisition in described in Appendix 2.

Scoring Rubrics

Melsen (1969) wrote that in early radiographs it was hard to discern which of the three-stages of maturation the SOS was in. Irwin, (1960) using film-based tomography had suggested four stages of SOS maturation. Several investigations have described five stages of SOS maturation using laminagraphy (Powell and

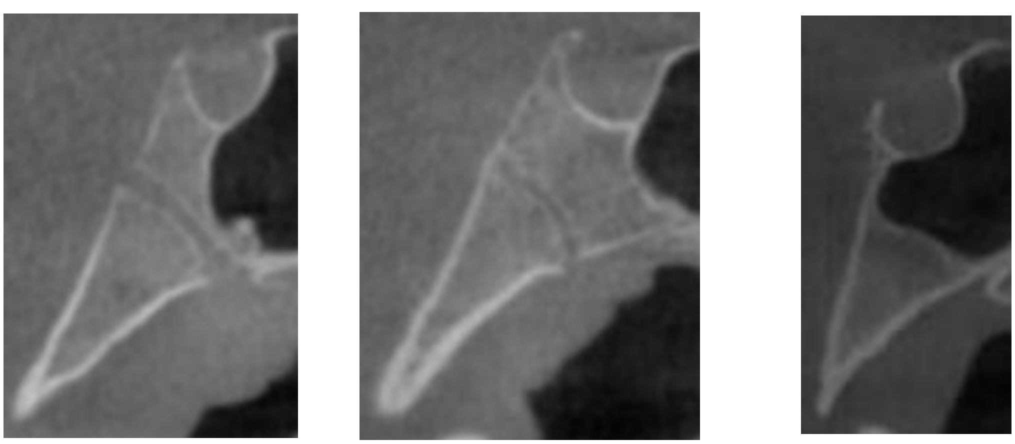
Brodie, 1963) and MSCT (Bassed, Briggs & Drummer, 2010; Can, Ekizoglu, Hocaoglu, Inci, Sayin & Kaya, 2014; Franklin and Flavel, 2014). It is unknown to the authors of this study, how Irwin (1960) or Powell and Brodie (1963) were able to accurately differentiate over 50 years ago, four or five stages of SOS respectively with what is now antiquated technology when it is relatively hard in select cases to discern three stages of SOS with current state-of-the-art technology (CBCT). MSCT offers improved contrast resolution and is therefore likely advantageous at differentiating between 5 stages of maturation over CBCT. However, CBCT allows one to be able to see smaller voxels of patency (spatial resolution) than with MSCT. Further the benefit of obtaining increased contrast resolution of images with MSCT does not outweigh the cost of the significant increased radiation exposure to the highly radiosensitive tissue of the head and neck region in highly sensitive subjects (growing patients) that this technology accompanies in comparison to CBCT. It was not possible to obtain retrospective images from MSCT for this study nor is it a common diagnostic technology used in orthodontics due to the increased radiation (Angelopoulos, Scarfe & Farman, 2012).

Observing human autopsy material, Melsen (1972) described maturation of the SOS in three stages: open, closing or closed. She further defined the classification of closing as occurring when the first osseous bridge between the occipital and sphenoid bones had been established. Sahni, Jit, Neelam and Suri (1998) described three stages of fusion using MSCT imaging of cadavers: unfused, partially fused and completely fused. Coqueugniot and Weaver (2007), looking at skeletal remains, without radiography, described three stages of maturation: open (no fusion), partial union (fusing) and complete union. Other CT studies of SOS maturation have analyzed three-dimensional slices of multiplanar MSCT images (Madeline and Elster, 1995; Okamoto, Ito Tokiguchi & Furusawa, 1996). While Okamoto, Ito Tokiguchi and Furusawa, (1996) found additional symmetric ossification centers parasagittaly in some of the females in their study, they found the first SOS ossification in all of their subjects in the midsagittal plane. These findings supported Madeline and Elster (1995) who had earlier found the first ossification of the SOS to occur in the midline using three-dimensional slices of multiplanar MSCT imaging. Therefore, the midsagittal plane was chosen in the current investigation. The three-stage index used by Melsen (1972) was selected at 1 voxel (0.3 or 0.4 mm) thick as it was already relatively hard in select cases to discern between SOS stages, and the authors did not want to introduce additional sources of error by subdividing the three-stages any further into a four or five stage index. The present investigation used those descriptions as the basis for the rubric used in this radiographic investigation (Table 3 and Figure 1).

Table 3 Spheno-occipital Synchondrosis (SOS) Rubric

Open (no fusion)	Openings at the superior and inferior margins	**no** opaque margin is found on the superior or inferior exterior surface of the sphenoid crossing the synchondrosis
Partial union (fusing)	One, but not both margins are touching each other	a continuous opaque margin is found on the superior **or** inferior exterior surface of the sphenoid crossing the synchondrosis
Complete Union	Both margins are touching each other	continuous opaque margins are found on the superior **and** inferior exterior surfaces of the sphenoid crossing the synchondrosis

Figure 1 Portions of images of subjects demonstrating open (a), partial union (b) and complete union (c) of the spheno-occipital synchondrosis (SOS)



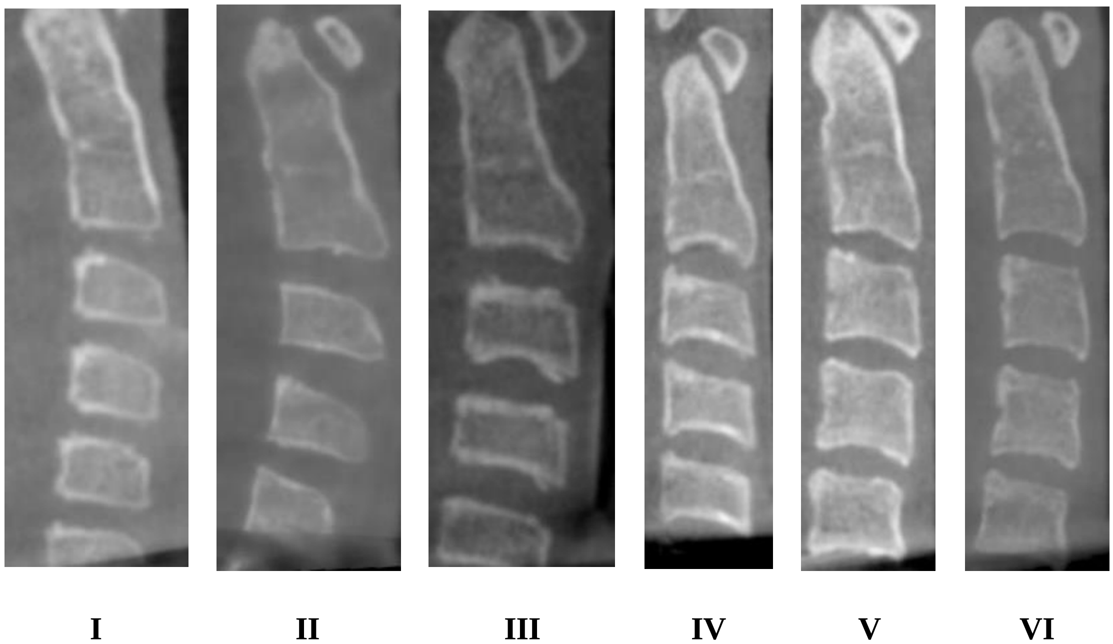
(a) **(b)** **(c)**

There have not been any studies published which could be found in the English literature that assessed cervical vertebral maturation using computed tomography. As such, the method described by Baccetti, Franchi and McNamara (2005) using lateral cephalometric radiographs was used here. The observer began by assessing if a concavity was present at the inferior border of the second, third and fourth cervical vertebrae. If the fourth cervical vertebra was found to have a concavity then the height to width ratio and morphology of the body of third and fourth cervical vertebrae was used to assess whether a vertebral body was horizontal, square or vertical. A transparent ruler was available to be placed against the monitor as an aid in assessing borderline cases. The grading rubric described in Table 4 and shown in Figure 2 was used concurrently to yield an appropriate score.

Table 4 Cervical Vertebral Maturation (CVM) Rubric

Stage	Location of Observation	C2	C3	C4
1	Inferior Border	Flat	Flat	Flat
	Vertebral Body Shape		Wedged	Wedged
2	Inferior Border	Concave	Not Concave	Not Concave
	Vertebral Body Shape		Trapezoid	Trapezoid
3	Inferior Border	Concave	Concave	Not Concave
	Vertebral Body Shape		Trapezoid or Horizontal	Trapezoid or Horizontal
4	Inferior Border	Concave	Concave	Concave
	Vertebral Body Shape		Horizontal	Horizontal
5	Inferior Border	Concave	Concave	Concave
	Vertebral Body Shape		Square > Horizontal	Square > Horizontal
6	Inferior Border	Concave	Concave	Concave
	Vertebral Body Shape		Square > Vertical	Square > Vertical

Figure 2 Portions of images of subjects showing cervical vertebral maturation stages I to VI



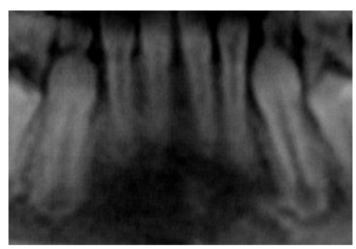
The method described by Coutinho, Buschang and Miranda, (1993) was used to evaluate the dental maturation of the mandibular canines (DI). Where a difference existed between canine developmental stages, the more immature canine observation was recorded (Table 5 and Figure 3).

Table 5 Dental Index (DI) Rubric

Stage	**Description**
E	Crown and root both exist; crown is taller than the height of the root
F	Root is equal or taller than the root in height; an isosceles triangle found at inferior border
G	Root length is complete; the apex is still open; there is an increased periapical radiolucency in the apical region of the periodontal ligament
H	The root is fully formed and the apex is closed

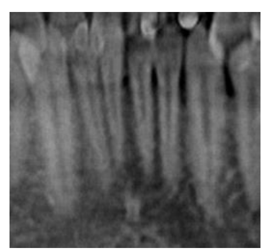
Figure 3 Portions of images of subjects demonstrating the dental index scale used of stages E to H of mandibular canines

(E)



(F)

(G)



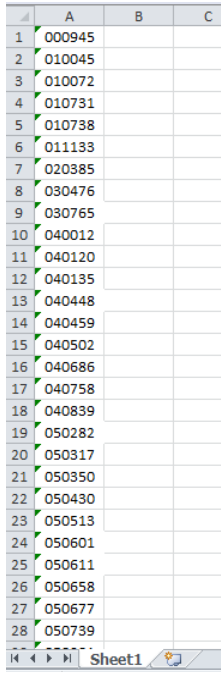
(H)

Recording Observations

Three separate spreadsheet files were created for each DI, CVM and SOS maturation stages, separate from the master key file, for recording the observations of the captured images. This allowed for the observer to remain blind to the association of the patient identification with any chronologic age or gender of the subject. The creation of three separate observational spreadsheets also removed the likelihood of the observer remembering the patient identification number and observations from one type of maturational analysis when they began the next type of maturational observations.

Each of the observational spreadsheets were each created with two columns: Column A for the patient identification number and Column B for the observational stage to be recorded (Figure 4). When creating these observational spreadsheets, patient identification numbers were copied from the master key into Column A of each of these three spreadsheets.

Figure 4 Spheno-occipital synchondrosis (SOS) observation spreadsheet sample



	A	B	C
1	000945		
2	010045		
3	010072		
4	010731		
5	010738		
6	011133		
7	020385		
8	030476		
9	030765		
10	040012		
11	040120		
12	040135		
13	040448		
14	040459		
15	040502		
16	040686		
17	040758		
18	040839		
19	050282		
20	050317		
21	050350		
22	050430		
23	050513		
24	050601		
25	050611		
26	050658		
27	050677		
28	050739		

Sheet1

At the time of making the observations, the data analysis spreadsheet sample was opened and the image that corresponded with the patient identification number in the first column was opened. When the observer decided on the appropriate stage the image was closed and the grade recorded in the spreadsheet accordingly.

Unlike the intra-rater and inter-rater reliability for the CVM and DI that has been well documented in the literature (Hassel and Farman, 1995; Küçükkeleş, Acar, Biren and Arun, 1999; Baccetti, & McNamara, 2005; Flores-Mir, Burgess, Champney, Jensen, Pitcher & Major, 2006; Uysal, Ramoglu, Basciftci & Sari, 2006; Kumar, Singla, Sharma, Virdi, Anupam and Mittal, 2012; Perinetti, Contardo, Gabrieli, Baccetti & Di Lenarda, 2014), there is a void in SOS repeatability testing using CBCT. Measures were taken three times for this maturational index as studies have not reported previously on SOS maturation using CBCT and the most accurate observations of this index were desired, as was done in a study by Moshiri, Scarfe, Hilgers, Scheetz, Silveira and Farman (2007). For initial measurements, the first observations for the spheno-occipital synchondrosis were made for each subject and then “hidden,” with that option in the spreadsheet and the measures were repeated again for each subject. The second set of measurements where hidden and a third set of measurements were made. Following the third set of measurements, all measurements were “unhidden” with that option in the spreadsheet and the average value was rounded to nearest stage, recorded and used for subsequent measurements.

Twelve months later, the first 28 patient identification numbers listed in the grading spreadsheets were selected for inter-rater and intra-rater reliability assessment for the CVM and Dental indices. This provided repeat assessments of 36.4% of the total sample. This amount is substantial and has been used in other research (Wong, Alkhal & Rabie, 2009). The entire sample (n=77) was remeasured three times as was previously performed during the initial measurements.

A second observer was given the following tools to make one independent observation of each image:

1. Corresponding SOS, cervical vertebral and reconstructed panoramic virtual images in three virtual folders
2. Three virtual scoring spreadsheets (Figure 4)
3. A transparent ruler

4. Three sample virtual scoring images and three printed rubrics (Tables 3-5 and Figures 1-3)

These repeat measurements were recorded and compared to the initial observers measures to determine inter-rater reliability.

The pattern of fusion of the SOS is known to progress from the superior to the inferior surface (Irwin, 1960; Melsen, 1972; Scheuer and Black, 2000; Bassed, Briggs & Drummer, 2010). Asides from this pattern, Okamoto, Ito Tokiguchi and Furusawa, (1996) noted that in addition to the midsagittal plane ossifying first in all patients, in some females, a parallel symmetric ossification center had been found parasagitally. No other centers of initial ossification or patterns of SOS maturation could be found in the English literature. Therefore, a review was made by the primary investigator of a subsample of 10 random subjects, in the partial fusion stage of SOS maturation, to assess if other ossification centers of the SOS, or a different pattern of ossification, could be noted. Axial, coronal and sagittal slices were scanned through and observations recorded.

Statistical Analysis

The data collected in the spreadsheets was combined with the information from the master key pertaining to the age of each subject and their respective sample group. This information was imported into the SPSS statistical software (IBM SPSS Statistics, v. 20.0.0, IBM Corp., Armonk, NY). All tests were set at an *á priori* level of significance set at $\alpha \leq 0.05$.

Descriptive analyses were used to highlight the least mature cervical vertebral stage and age grouping found for each sex when the SOS was in the most mature stage. The same was investigated for those found with open spheno-occipital synchondroses.

Bivariate Spearman rank-order correlations were computed to assess any possible relationship between SOS maturation with CVM, chronologic age grouping and DI for each gender separately. Bivariate correlations were made with one-tailed Spearman Rank Order correlation tests that were used for this study with data that fit more with non-parametric statistical analyses. Correlations were calculated for groups 1-6 as well as for groups 2 and 5. Groups 2 and 5 received further analysis in this study, as these are the two age groups where SOS maturation stages varied the most, and the correlations values were considered most clinically relevant. A one-tailed test was selected, as a reasonable prediction of the resultant direction of correlation was expected and all tests were set at an *á priori* level of significance set at $\alpha \leq 0.05$.

Measurements obtained from the second observer were compared to those from the first observer to assess the inter-rater reliability. Reliability was assessed for groups 1-6 and for groups 2 and 5. Particular focus was placed on groups 2 and 5, as these two stages were believed to include the most difficult to discern SOS maturation stages and assessing the reliability of this group was expected to be yield the most clinical relevancy. Subjects that were selected randomly for remeasurement of groups 1-6 that were part of groups 2 and 5 were later used for the remeasurements of groups 2 and 5. combined Due to the ordinal nature of the measured values, Cohen's Kappa statistics were calculated to assess the level of repeatability of observations in this study. According to Dancey and Reidy (2004), the strength of correlation values are considered: "perfect" if 1, "strong" if 0.7-0.9, "moderate" if 0.4-0.6, "weak" if "0.1-0.3 and to have "zero" correlation if 0

CHAPTER IV

RESULTS

Findings of the Sample

The sample was stratified according to sex and age groupings as shown in Table 6, along with average age and sample sizes for each group. Each group began with 16 subjects identified. When exclusion criteria were applied, groups 1, 2, 3 and 5 were reduced to the sample sizes in Table 6. Groups 4 and 6 were reduced to 6 and 9 subjects respectively. Further subjects were sought for these two groups to raise the number of subjects in each group again to 16. When the exclusion criteria were applied again to groups 4 and 6, the remaining sample sizes were above the minimum sample size of at least 10 and their resultant sizes are displays in Table 6. Seventy-seven subjects (42 females and 35 males) between the ages of 9 and 21 years old compromised the final total sample.

Table 6 Group Sample Size and Average Age

Group	Group Definition	Average Age (Years)	Sample Size (n)
1	Females prior to their PHV (<10 years old)	9	11
2	Females during their PHV, (11-13 years old)	12	15
3	Females after their PHV, (>14 years old)	16	16
4	Males prior to their PHV, (<12 years old)	10	10
5	Males during their PHV, (13-15 years old)	14	13
6	Males after their PHV, (>16 years old)	19	12

The corresponding chronologic ages from the master key were copied into the SOS spreadsheet. The distribution for each stage of maturation of the SOS for both sexes at each age is presented in Table 7. The oldest age where an open SOS was found was 12 years old in females, (1 subject) and 13 in males (1 subject). The earliest SOS partial union was found in this sample at the age of 9 years old in females (3 subjects) and 10 in males (2 subjects), whereas complete SOS union was found earlier in females (by 3 years). In the present study, the earliest complete union of the SOS was found in 14 year old males and 11-year-old females. No subjects with an open SOS were in the age groups representing being after their PHV.

Table 7 Actual Number of Individuals in Each Range of Fusion for Females and Males, by Age

	Females (n =42)			**Males (n = 35)**		
Age	Open	Partial Union	Complete Union	Open	Partial Union	Complete Union
9	8	3	0	-	-	-
10	-	-	-	4	2	0
11	1	1	1	2	2	0
12	1	6	5	-	-	-
13	-	-	-	1	0	0
14	-	-	-	0	9	3
15	-	-	-	-	-	-
16	0	0	11	-	-	-
17	0	0	5	-	-	-
18	-	-	-	0	0	3
19	-	-	-	0	0	4
20	-	-	-	0	0	3
21	-	-	-	0	0	2

Table 8 shows the average, minimum and maximum CVM stage found for females and males in each stage of SOS maturation. All females with fused SOS were in CVM stage 3 or later and in the age groups representing being in, or after, their PHV, while all males were in at least CVM stage 4 and in the age groups representing being in, or after, their PHV.

Table 8 Average and Range of CVM and DI Stages for Females and Males with Respect to SOS Maturation Stages

SOS Stage	**Sex**	**Average CVM (Stage)**	**Minimum CVM (stage)**	**Maximum CVM (stage)**	**Average Dental (stage)**	**Minimum Dental (stage)**	**Maximum Dental (stage)**
Open	Female	2	1	4	F	F	G
Partial Union	Female	3	1	5	G	F	H
Complete Union	Female	5	3	6	H	G	H
Open	Male	2	1	5	F	E	H
Partial Union	Male	3	1	4	G	F	H
Complete Union	Male	6	4	6	H	G	H

The average, minimum and maximum range of DI stages for females and males and SOS maturation stages are shown in Table 8. The average DI Stage form males and females with open, partial union and complete union of their SOS was stage F, G and H respectively. With the exception of females in the open SOS stage, DI stage H was found in males and females in all stage of SOS. This indicates that the DI stage varies heavily and may not be a useful indicator of SOS maturation for any one patient if the patient is in DI stage H.

Correlations of Maturational Indices with SOS Maturation

The Spearman Rank-Ordered correlation between SOS maturation findings and each of CVM stages, chronologic age and DI, for both males and females, were assessed for groups 1-6 and groups 2 and 5. For groups 1-6, the maturation of SOS was significantly correlated (one-tailed $p \leq 0.001$) with CVM (0.831 [females] and 0.870 [males]); and with Chronologic age (0.830 [females] and 0.849 [males]). These correlation values demonstrate “almost perfect” positive relationship between both CVM stage and chronologic age with SOS in both sexes. The maturation of SOS was also significantly correlated (one-tailed $p \leq 0.001$) with DI (0.734 [females] and 0.638 [males]). The correlations values observed here demonstrate a strong positive relationship between DI and SOS maturation stages in both sexes. For groups 2 and 5, SOS was significantly correlated (one-tailed $p \leq 0.001$) with CVM (0.612) in males, (one-tailed $p \leq 0.005$) with CVM in females (0.656) and (one-tailed $p \leq 0.05$) in males with chronologic age. These correlations demonstrated “moderate” positive relationships that were not as strong as the "almost perfect" relationships of their equivalents in groups 1-6. Unlike the findings in groups 1-6, there were no statistically significant correlations ($p \leq 0.05$) between SOS maturation stages in groups 2 and 5 with chronologic age in females (0.169), DI in males (-0.200) or DI in females (0.221).

Analysis of Reliability of Measurements

The intra-rater and inter-rater variability of repeated measurements was also assessed with Cohen's Kappa statistic. A p value $\leq$0.05 indicates that the congruence between initial and remeasured values was statistically significant and due to more than that expected by chance alone (Karras, 1997). Results are shown in Tables 9 and 10.

For groups 1-6, according to the Cohen's Kappa statistic, "substantial" agreements for SOS maturation for both intra-rater and inter-rater reliability and for CVM only for intra-rater reliability were found here. The Kappa values for inter-rater reliability of CVM and for both intra-rater and inter-rater reliability of DI are only "moderate." Cohen's Kappa showed "substantial" agreement for intra-rater and inter-rater reliability of SOS and intra-rater reliability. They also show only "fair" and "moderate" reliability respectively for DI as intra-rater and inter rater repeat measures. For inter-rater reliability, CVM was "moderate" when considered by Cohen's Kappa statistic. For groups 2 and 5 combined, the Cohen's Kappa statistic also had "substantial" agreement for intra-rater and inter-rater reliability of SOS maturation and intra-rater reliability of CMV as was found in groups 1-6. Groups 2 and 5 combined also had “moderate” agreement for inter-rater reliability of CVM and DI as was found in groups 1-6. The largest difference for reliability between groups 1-6 in comparison with groups 2 and 5 combined is that there was no statistically significant Cohen’s Kappa statistic for intra-rater reliability in groups 2 and 5 combined of DI.

The subsample review of 10 random patients in the partial fusion state of SOS maturation did not result in any additional centers of ossification, apart from the midsagittal plane, being found. The pattern of ossification was found to be from the superior to inferior margin of the SOS in the midsagittal plane for all (n=10) subsamples reviewed.

Table 9 Cohen's Kappa Statistic for Intra-rater and Inter-rater Reliability for Groups 1-6.

Values shown with significance at $p \leq .05$ are **bolded**

			Intra-rater		Inter-rater	
Parameter	**Remeasured sample size (n)**	**(% of sample)**	**Kappa Value**	**Approx *p***	**Kappa Value**	**Approx *p***
SOS	77	100	.757	**.000**	.750	**.000**
CVM	28	36.4	.646	**.000**	.471	**.000**
DI	28	36.4	.411	**.004**	.492	**.000**

Table 10 Cohen's Kappa Statistic for Intra-rater and Inter-rater Reliability for Groups 2 and 5 combined.

Values shown with significance at $p \leq .05$ are **bolded**

			Intra-rater		**Inter-rater**	
Parameter	**Remeasured sample size (n)**	**(% of sample)**	**Kappa Value**	**Approx *p***	**Kappa Value**	**Approx *p***
SOS	28	100	.610	**.000**	.623	**.000**
CVM	13	46.4	.776	**.000**	.504	**.000**
DI	13	46.4	.204	.340	.480	**.021**

CHAPTER V

DISCUSSION

Relationship of Chronologic age with SOS Fusion

This study found a complete union of the SOS as early as 11 years old in females and 14 years old in males that corresponded with the age groups representing being in their PHV. For females, the present findings paralleled the results of the laminagraphy study of Powell and Brodie (1963) and a CT study by El-Sheikh and Ramadan (2006) who each found females with fused spheno-occipital synchondroses at 11 years old.

There is a large variation in the literature concerning chronologic age with respect to SOS fusion using numerous methodologies. Different methodologies may be responsible for the variation in wide ranges of fusion reported. As CBCT has not been used to report chronologic age of fusion of the SOS, the results of the current investigation are compared to other studies with their respective methodology indicated. The present findings of males first having complete union of their SOS at 14 years old was older than findings of Powell and Brodie (1963) using laminagraphy or the histologic findings of Melsen (1972). It is also older than the CT findings of El-Sheikh and Ramandan (2006). While the difference between findings is one to two years, this time difference can affect when treatment is delivered (i.e., before the peak of facial growth versus delivering after). The findings of the present study are consistent with earlier findings using tomography (Irwin, 1960) and CT (Okamoto, Ito Tokiguchi & Furusawa, 1996; Franklin and Flavel, 2014). The findings in the present study are earlier than the histologic findings of Thilander and Ingervall (1973) and the direct inspection studies of Sahni, Jit, Neelam and Suri (1998), Coqueugniot and Weaver (2007), Akhlaghi, Taghaddosinejad, Sheikhazadi, Valizadeh, Shojaei (2010) and Shirley and Jantz (2011). The variation in findings may be due to various techniques used in measuring the SOS such as direct inspection, histologic, radiologic, advanced radiologic (Krishan and Kanchan, 2013). Krishan and Kanchan (2013) have suggested, without substantiation, that studies using radiologic methods may have better visualization than those using direct inspection of cadavers. The various reported ages from the numerous study methodologies suggest chronologic age may not be a consistent indicator of SOS maturation for comparative purposes.

No subjects with open SOS or partial union of the SOS were in the age groups representing being after their PHV and no subjects with complete union of the SOS were in the age groups representing being prior to their PHV. It can therefore be interpreted from these findings that the age groups corresponding to pre-PHV and some patients in their PHV stage of growth, of either sex, would be likely to experience the desired effect of orthopaedic forces involving the SOS.

The results of a particular sample do not necessarily reflect the effect of a whole population. A randomized clinical trial by Tulloch, Philips and Proffit (2004) found that early orthopaedic treatment provided prior to adolescence, followed by comprehensive orthodontics, is not more clinically successful than the same combined treatments provided during adolescence. While this result is accurate for the population as a whole for the specific sample in their RCT, Tulloch, Philips and Proffit exemplify the considerable variation between individuals. Prior to PHV, in the pre-pubertal growth spurt phase of growth and development, a juvenile acceleration spurt is known to occur, especially in females. The juvenile acceleration spurt occurs one to two years prior to PHV and also accompanies a corresponding increase in jaw growth. In males, if this spurt occurs, it is almost always less intense than their growth, in puberty. In females however, it may equal or even exceed their growth occurring later in puberty (Proffit, 2007). The complete union of the SOS observed in our female population, which is younger than in most previous studies, may be due to this early spurt. Orthodontists should take into account that the SOS may close earlier than previously believed. They must also be vigilant that growth manipulation may not consistently be as successful at some early ages as was previously believed.

The maturation of SOS had a strong and statistically significant (p<0.001) correlation with age group (ρ_s=0.830 for females and ρ_s=0.849 for males) when analyzing groups 1-6. The “strong” Spearman rank-ordered correlation coefficient found here for females, was similar to that reported by Franklin and Flavel (2014) and higher than the “moderate to strong” correlation coefficients found by other studies (Akhlaghi, Taghaddosinejad, Sheikhazadi, Valizadeh & Shojaei, 2010; Shirley and Jantz, 2011; Can, Ekizoglu, Hocaoglu, Inci, Sayin & Kaya, 2014). For males, several studies found “strong” Spearman rank-ordered correlations (Akhlaghi, Taghaddosinejad, Sheikhazadi, Valizadeh & Shojaei, 2010; Shirley and Jantz, 2011; Can, Ekizoglu, Hocaoglu, Inci, Sayin & Kaya, 2014). These values in males were lower than the “strong” correlation coefficients found by Franklin and Flavel (2014) that was similar to the rho value found in this investigation. When considering group 5, males had a “moderate” correlation of chronologic age with SOS and group 2 did not have a statistically significant correlation. Hence, these findings do not support relying on chronologic age to be a good predictor of SOS maturation for females in their PGS. However, for the sample as a whole, the findings of this study support that when using CBCT, as in the current study, or multi-detector CT technology, chronologic age can be a good predictor of SOS maturation.

Relationship of CVM to SOS Fusion

As reported in Chapter II (Cervical Vertebral Maturation (CVM) Index), the CVM has been found to have a statistically significant positive correlation with both mandibular length and stature (Franchi, Baccetti & McNamara, 2000). Hassel and Farman (1995) found PHV to occur, between CVM stage 3 and 4, while Franchi, Baccetti, and McNamara (2000) found that 100% of boys and 87% of girls underwent their PHV between CVM stages 3 and 4, with the remaining 13% of girls peaking between stages 4 and 5. In the current study, all females with complete union of their spheno-occipital synchondroses were in at least CVM stage 3 while all males were in CVM stage 4 or later. The average CVM stage found in subjects with complete union of the SOS was 5 for males and 6 for females. This indicates that for the average patient, the SOS does not completely fuse until later than Franchi, Baccetti and McNamara report peak in statural height (2000) and mandibular growth (2005) to occur. The maturation of the SOS was significantly positively correlated ($p \leq .001$) for groups 1-6, and ($p \leq .005$) for groups 2 and 5, with CVM. The Spearman rank-ordered correlation coefficient was "strong" in females and males for groups 1-6 and "moderate' for groups 2 and 5. Incorporating the findings in this study with those of Hassel and Farman (1995) and Franchi, Baccetti and McNamara (2000), if a clinician was to see that a patient had complete union of their SOS, they could assume that the patient was at least undergoing, or had passed their PHV. No research to date in the English literature could be found that has reported on the correlation between SOS maturation and cervical vertebral maturation. This "strong" correlation coefficient of SOS with CVM for groups 1-6 indicates that the CVM levels of maturation are accurate in their prediction of the maturation of the SOS.

Relationship of DI to SOS Fusion

The results of this study indicate that if the DI of a female or male were in stage E or F, the SOS would not have reached the complete union stage. Subjects with a DI in stage G were found in both sexes to be in all three stages of SOS maturation. Coutinho, Buschang and Miranda, (1993) found stage G of the canine to be 0.4 years after PHV for females, and 1.3 years for males. The results of this investigation do not find stage G to be reliable in indicating any stage of spheno-occipital synchondrosis maturation for either sex as those with mandibular canines in stage G of dental development were found in all six sample groups.

The findings in this study are supported by Proffit (2007) who stated that of all the indicators, dental age (eruption and dental development) correlates least well with the other developmental indices and that dental age has a correlation of 0.7 with chronologic age. In this study, a statistically significant ($p \leq .001$) but weaker Spearman rank-ordered correlation coefficient was found between SOS maturation and DI in females and in males. When considering groups 1-6, these values are considered to be of "moderate to strong" correlative value. No research to date could be found in the English literature that has reported specifically on the relationship between SOS maturation and DI. No statistically significant correlation ($p \leq .05$) was found between SOS maturation and DI when analyzing groups 2 or 5. This may be attributed to a decreased sample size when analyzing each of those individual groups, difficulty in using this index with reconstructed panoramic radiographs or due to the lack of reliability to detect the DI maturation stages in the most critical age groups.

Intra-rater reliability

The present investigation found intra-rater reliability of the SOS maturation stages to be lower than that reported by two studies that used a similar approach, in that they used MSCT images, for their measurements (Bassed, Briggs & Drummer, 2010; Franklin and Flavel, 2014). Both of those studies reported an "almost perfect"

Cohen's Kappa coefficient value that was of higher value than the Cohen's Kappa coefficient value found here. As MSCT provides increased contrast resolution compared to CBCT, the lower values of Cohen's Kappa coefficient found here, while still significant ($p < 0.001$) and of "substantial" value, may be less than MSCT due to the decreased contrast resolution of the CBCT images (Angelopoulos, Scarfe & Farman, 2012).

The intra-rater reliability of CVM observations were found to have a "substantial" Cohen's Kappa coefficient value, with statistical significance. The Kappa coefficient found here was similar to that found by Gabriel, Southard, Qian, Marshall, Franciscus and Southard (2009). However the Kappa coefficient value found here was lower than the "almost perfect" Kappa coefficient values reported by several authors (Hassel and Farman, 1995; Kumar, Singla, Sharma, Virdi, Anupam & Mittal, 2012; Perinetti, Contardo, Gabrieli, Baccetti & Di Lenarda, 2014). Both the primary investigator and the other rater were orthodontic residents. The present findings corroborate those of Gabriel, Southard, Qian, Marshall, Franciscus and Southard (2009) who attributed their lower values of their study compared to other studies due to the level of expertise of the observers; the same lack of expertise could have been a limiting factor.

The intra-rater reliability (as measured by Cohen's Kappa) of DI was the lowest of the three indices with a "moderate" value and statistical significance for groups 1-6. The values found in this investigation were much lower than those reported by a study looking at canines (Perinetti, Contardo, Gabrieli, Baccetti & Di Lenarda, 2014) and a study looking at second molar development (Kumar, Singla, Sharma, Virdi, Anupam & Mittal, 2012) that reported “almost perfect” intra-rater reliability. The intra-rater reliability for groups 2 and 5 combined was not statistically significant. This may be due to the lack of reliability to detect the DI maturation stages in the most critical age groups, the decreased sample size when analyzing each of those individual groups and/or the difficulty in using this index with reconstructed panoramic radiographs. The intra-observer reproducibility of DI levels in this investigation were at best not optimal and decreases the value of this index at making meaningful predictions of PHV and correlations with other maturational indices. This may be due to the use of panoramic image reconstruction from the CBCT image to assess canine discrepancy that was evaluated in other investigations using periapical radiograph technology.

Inter-rater reliability

Inter-rater reliability was tested using Cohen’s Kappa coefficient for all three indices of maturation. Statistical significance, with a p value of less than 0.001, was found for all results in groups 1-6 and for both SOS and CVM in groups 2 and 5 combined. A p value of less than 0.05 was found for DI in groups 2 and 5 combined. Two studies reported inter-rater reliability using MSCT technology (Bassed, Briggs & Drummer, 2010; Franklin and Flavel, 2014). The current study found a “substantial” level of inter-rater reliability for SOS observations similar to that found by Briggs and

Drummer (2010), while Franklin and Flavel (2014) reported “almost perfect” inter-rater reliability.

The inter-rater reliability of CVM observations were found to have “moderate” levels similar again to the study by Gabriel, Southard, Qian, Marshall, Franciscus and Southard (2009). The repeat measurements found here did not have the same reliability as studies reporting “almost perfect” agreement (Hassel and Farman, 1995; Baccetti, Franchi & McNamara, 2005).

The DI in this study had “moderate” Cohen’s Kappa coefficient values for inter-rater reliability. These were much lower than the value reported in the MSCT study of Kumar, Singla, Sharma, Virdi, Anupam and Mittal (2012) of mandibular second molars.

Limitations and Future Studies

This cross-sectional retrospective study was limited to the amount of information available. It would have been advantageous to prospectively compare the change in stature, mandibular size, hand-wrist maturation, menarche and voice changes in comparison with SOS maturation. This longitudinal study design would however require multiple exposures of patients to excess radiation in order to obtain prospective serial CBCT images and would likely not benefit the individual patient with regard to orthodontic treatment when the risk to benefit ratio were analyzed.

It may be of value to conduct a retrospective study to compare CBCT radiographic images to a sample of MSCT images to see if observations made with the different technologies are equivalent. It would be advantageous to know the ethnicity of the subjects, as studies have identified differences between homogenous races (Okamoto, Ito, Tokiguchi, & Furusawa, 1996; Sahni, Jit, Neelam & Suri, 1998). A reasonable limitation to overcome in future studies would be to identify and exclude patients who had received orthopaedic treatment involving forces affecting the SOS, as it is imaginable that the forces applied to this structure may alter its progression of maturation.

This study was not able to obtain records of mandibular length or stature for this sample. Indices, such as CVM were used as a proxy for their relation with these parameters. Future studies assessing the relation between SOS maturation and mandibular length and stature would be advantageous.

In considering the age ranges presented in this study it is important to recall that this study did not seek to classify the various stages of SOS maturation based on chronologic age, but rather on circum-pubertal growth spurt age groups. Not every age in childhood and adolescence was represented in this study and it is possible that, based on earlier findings, the actual age of maturation could have been outside of the range of ages assessed. In future studies it would be advantageous to obtain samples of every chronologic age. Further, while the literature reports the pattern of fusion from superior to inferior in the midsagittal plane in all patients, and additionally in the parasagittal planes in some females, (Okamoto, Ito Tokiguchi & Furusawa, 1996), no other pattern of fusion of the SOS has been reported. It may be worthwhile to review CT images of the SOS in each plane to see if other patterns of fusion exist using higher contrast resolution multi-detector CT images. In that type of an assessment a scale using multiple ossifications could be used. In the proposed scale, having no ossified borders could be recorded as the first stage, 0-10 ossifications as a second stage, 11-20 ossifications as a third stage, etc.. Lastly, the sample size of the study was small and this could have affected the age ranges found for each group by not having enough samples to exclude outliers. In particular, it may be advantageous to repeat this study looking solely at groups 2 and 5 as those are the ages when the most visibly unclear stages of SOS maturation may exist. Our results from looking only at those two specific groups were limited by the sample size. Larger sample size in groups 2 and 5 would be advantageous in future studies.

Null Hypothesis Revisited

In regards to the null hypothesis the following observations are possible:

Null hypothesis #1: There is a statistically significant positive relationship between spheno-occipital synchondrosis maturation and chronologic age, dental maturation and cervical vertebral maturation stages for females or males. **Rejected**

Null hypothesis #1 was rejected because a statistically significant positive relationship was found for both males and females between the spheno-occipital synchondrosis and chronologic age, dental maturation and cervical vertebral maturation when Spearman rank-ordered correlation coefficients were assessed.

CHAPTER VI

CONCLUSIONS

Based on the results of this study on maturation stages, the following conclusions can be drawn:

1. To avoid missing the window of opportunity for early maturing patients, it is prudent to commence orthopaedic forces prior to 11 years old in females and 14 years old in males based on the results in Table 7.

2. The stages of SOS maturation are valid indicators of the remaining growth potential in the skull base and correlate closely with CVM indicators. Orthodontists can be confident that growth modification timing aimed at SOS patency can be reliably predicted with CVM.

3. The results of the intra-observer and inter-observer statistical tests indicate that a three-stage SOS maturation scale using CBCT is accurate and reproducible both within and between observers.

4. The dental maturation stages of the mandibular canine teeth show satisfactory diagnostic performance only for the identification of the pre-PHV growth phases, with no reliable indications for onset of the PHV.

5. The clinical usefulness of the determination of dental maturity using DI of mandibular canines for the assessment of treatment timing for skeletal malocclusion would thus be limited at best.

Clinical Recommendations:

1. Orthodontists can rely on CVM as a tool as it closely matches the SOS ossification.
2. Orthodontists must be vigilant to start orthopaedic treatment before CVM stage 3 in girls and stage 4 in boys prior to potential early fusion of the SOS.
3. In order to achieve a successful orthopaedic outcome, patient's growth indication must be considered individually. Waiting in general, to start orthopaedic treatment until the late mixed dentition stage may be too late to achieve a more successful outcome in select patients.

REFERENCES

Adem C, Lafitte F, Jarquin S, Guillem P, Chiras J. Persistance de la synchondrose sphéno-occipital chez l'adulte. *J Radiol*. 1999;80(8):863-865.

Akhlaghi M, Taghaddosinejad F, Sheikhazadi A, Valizadeh B, Shojaei SM. Age-at-death estimation based on the macroscopic examination of spheno-occipital sutures. *J Forensic Leg Med*. 2010;17:304-308.

Angelopoulos C, Scarfe WC, Farman AG. A comparison of maxillofacial CBCT and medical CT. *Atlas Oral Maxillofac Surg Clin North Am*. 2012;20(1):1-17.

Athanasiou AE. *Orthodontic Cephalometry*. London, England: Mosby-Wolfe; 1995.

Baccetti T, Franchi L, McNamara JA Jr. An improved version of the cervical vertebral maturation (CVM) method for the assessment of mandibular growth. *Angle Orthod*. 2002;72(4):316-323.

Baccetti T, Franchi L, McNamara JA Jr. The cervical vertebral maturation (CVM) method for the assessment of optimal treatment timing in dentofacial orthopedic. *Semin Orthod*. 2005;11:119-129.

Bassed RB, Briggs C, Drummer OH. Analysis of time of closure of the spheno-occipital synchondrosis using computed tomography. *Forensic Sci Int*. 2010;200(1-3):161-164.

Bassed RB, Briggs C, Drummer OH. Age estimation using CT imaging of the third molar tooth, the medial clavicular epiphysis, and the spheno-occipital synchondrosis: a multifactorial approach. *Forensic Sci Int*. 2011;212(1-3):273.e1-273e5.

Bishara SE. *Textbook of Orthodontics*. Philadelphia, PA: WB Saunders Co.; 2001.

Björk A. Facial growth in man, studied with the aid of metallic implants. *Acta Odontol Scand*. 1955;13(1):9-34.

Björk A. Variations in Growth pattern of human mandible: Longitudinal radiographic study by the implant method. *J Dent. Res*. 1963;42:400-411.

Björk A, Helm S. Prediction of the age of maximum pubertal growth in body height. *Angle Orthod*. 1967;37:134-143.

British Columbia Orthopaedic Association. History of the COA and Orthopaedics in Canada. http://www.bcoa.ca/join-bcoa/history-of-the-coa-and-orthopaedics-in-canada/. Published 2014. Accessed August 12, 2014.

Can IO, Ekizoglu O, Hocaoglu E, Inci E, Sayin I, Kaya KH. Forensic age estimation by spheno-occipital synchondrosis fusion degree: computed tomography analysis. *J Craniofac Surg*. 2014;25(4):1212-1216.

Centers for Disease Control and Prevention. Growth Charts. http://www.cdc.gov/growthcharts/clinical_charts.htm. Updated Aug 4, 2009. Accessed August 16, 2014.

Coqueugniot H, Weaver TD. Brief communication: infracranial maturation in the skeletal collection from Coimbra, Portugal: new aging standards for epiphyseal union. *Am J Phys Anthropol*. 2007;134(3):424-437.

Cormack AM. Early two-dimensional reconstruction (CT scanning) and recent topics stemming from it. Nobel lecture, December 8, 1979. *J Comput Assist Tomogr*. 1980;4:658–664.

Coutinho S, Buschang PH, Miranda F. Relationships between mandibular canine calcification stages and skeletal maturity. *Am J Orthod Dentofacial Orthop*. 1993;104:262-268.

Dainiak N. Practical and theoretical issues in 1993 concerning radiation effects on the growth of normal and neoplastic hematopoietic cells. Stem Cells. 1997;15 Suppl 2:75-85.

Dancey C, Reidy J. *Statistics without Maths for Psychology: using SPSS for Windows*. 4th ed. London, England: Prentice Hall; 2004.

Demirjian A, Goldstein H, Tanner JM. A new system of dental age assessment. *Human Biol*. 1973;45:211-227.

Enlow DH, Hans MG. *Essentials of Facial Growth*. Philadelphia, PA: W.B. Saunders Co.; 1996.

El-Sheikh M, Ramadan S. Closure of the spheno-occipital synchondrosis in the Arabian Gulf region. Proceedings of the 58th Annual Meeting of the American Academy of Forensic Sciences; 2006 Feb 16–21; Seattle, WA. Colorado Springs, CO: American Academy of Forensic Sciences, 2006;12:276.

Ericson S, Myrberg N. The morphology of the spheno-occipital synchondrosis at the age of eight evaluated by tomography. *Acta Morphol Neerl Scand*. 1973;11(3):197-208.

Faltin KJ, Faltin RM, Baccetti T, Franchi L, Ghiozzi B, McNamara JA Jr. Long-term effectiveness and treatment timing for Bionator therapy. *Angle Orthod*. 2003;73(3):221-230.

Farman AG. X-radiation: 100 years of progress in dental diagnosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1995;80(5):493-494.

Fishman LS. Chronological versus skeletal age, an evaluation of craniofacial growth. *Angle Orthod*. 1979;49(3):181-189.

Fishman LS. Radiographic evaluation of skeletal maturation. A clinically oriented method based on hand-wrist films. *Angle Orthod*. 1982;52(2):88-112.

Flores-Mir C, Burgess CA, Champney M, Jensen RJ, Pitcher MR, Major PW. Correlation of skeletal maturation stages determined by cervical vertebrae and hand-wrist evaluations. *Angle Orthod*. 2006;76(1):1-5.

Flores-Mir C, Nebbe B, Major PW. Use of Skeletal Maturation Based on Hand-Wrist Radiographic Analysis as a Predictor of Facial Growth: A Systematic Review: *Angle Orthod*. 2004; 74:118-124.

Ford HER. Growth of the human cranial base. *Am J Orthod*. 1958;44:498–506.

Franchi L, Baccetti T. *The use of maturational indices for the identification of optimal treatment timing in dentofacial orthopedics*. In: McNamara JA Jr, Kelly KA eds. *Treatment timing: orthodontics in four dimensions. Craniofacial Growth Series*, Vol 39. Ann Arbor: Center for Human Growth and Development, University of Michigan; 2002.

Franchi L, Baccetti T, McNamara JA Jr. Mandibular growth as related to cervical vertebral maturation and body height. *Am J Orthod Dentofacial Orthop*. 2000;118:335-340.

Franklin D, Flavel A. Brief communication: timing of spheno-occipital closure in modern Western Australians. *Am J Phys Anthropol*. 2014;153(1):132-138.

Fudalej P, Kokich VG, Leroux B. Determining the cessation of vertical growth of the craniofacial structures to facilitate placement of single-tooth implants. *Am J Orthod Dentofacial Orthop*. 2007;131:S59-S67.

Gabriel DB, Southard KA, Qian F, Marshall SD, Franciscus RG, Southard TE. Cervical vertebrae maturation method: poor reproducibility. *Am J Orthod Dentofacial Orthop*. 2009;136:478.e1-478e7.

Gardner GE, Kronman JH. Cranioskeletal displacements caused by rapid palatal expansion in the rhesus monkey. *Am J Orthod*. 1971;59(2):146-155.

Graber LW, Vanarsdall RL, Vig KWL. *Orthodontics Current Principles and Techniques*. 5th ed. Philadelphia, PA: Mosby Inc.; 2012.

Grave KC. Timing of facial growth: a study of relations with stature and ossification in the hand around puberty. *Aust Orthod J.* 1973;3:117–122.

Greulich WW, Pyle SI. *Radiographic atlas of skeletal development of the hand and wrist*. Stanford, CA: Stanford University Press; 1950.

Hägg U, Taranger J. Menarche and voice change as indicators of the pubertal growth spurt. *Acta Odontol Scand*. 1980;38(3):179-186.

Hägg U, Taranger J. Maturation indicators and the pubertal growth spurt. *Am J Orthod*. 1982;82(4):299-309.

Hassel B, Farman AG. Skeletal maturation evaluation using cervical vertebrae. *Am J Orthod Dentofacial Orthop*. 1995;107(1):58-66.

Hellman M. The process of dentition and its effects on occlusion. *Dent Cosmos*. 1923;65:1329-1344.

Hellman M. Ossification of epiphysial cartilage in the hand. *Amer J phys Anthrop*. 1928;11: 223-257.

Henry, HL. *Craniofacial changes induced by "orthopaedic forces" in the Macaca Mulatta rhesus monkey* [thesis]. Winnipeg, MB: University of Manitoba; 1973.

Holberg C, Holberg N, Rudzki-Janson I. Sutural strain in orthopedic headgear therapy: a finite element analysis. *Am J Orthod Dentofacial Orthop*. 2008;134(1):53-59.

Hounsfield GN. Nobel lecture, 8 December 1979. Computed medical imaging. *J Radiol*. 1980;61:459–468.

Houston WJ. Relationships between skeletal maturity estimated from hand-wrist radiographs and the timing of the adolescent growth spurt. *Eur J Orthod*. 1980;2(2):81-93.

Hunter CJ. The correlation of facial growth with body height and skeletal maturation at adolescence. *Angle Orthod*. 1966;36(1):44-54.

Ingervall B, Thilander B. The human spheno-occipital synchondrosis. I. The time of closure appraised macroscopically. *Acta Odont Scand*. 1972; 30: 349-356.

Irwin GL. Roentgen determination of the time of closure of the spheno-occipital synchondrosis. *Radiology*. 1960;75:450-453.

Karras DJ. Statistical Methodology: 11. Reliability and Validity Assessment in Study Design, Part A. *Acad Emerg Med*. 1997;4(1):64-71.

Krishan K, Kanchan T. Evaluation of spheno-occipital synchondrosis: A review of literature and considerations from forensic anthropologic point of view. *J Forensic Dent Sci*. 2013;5(2):72-76.

Krogman, WM: Studies in growth changes in the skull and face of anthropoids. *Amer J Anat*. 1930;46:315–353.

Küçükkeleş N, Acar A, Biren S, Arun T. Comparisons between cervical vertebrae and hand-wrist maturation for the assessment of skeletal maturity. *J Clin Pediatr Dent*. 1999;24(1):47-52.

Kumar S, Singla A, Sharma R, Virdi MS, Anupam A, Mittal B. Skeletal maturation evaluation using mandibular second molar calcification stages. *Angle Orthod*. 2012;82(3):501-506.

Lamparski DG. *Skeletal age assessment utilizing cervical vertebrae (dissertation)*. Pittsburgh, PA: The University of Pittsburgh; 1972.

Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* 1977;33:159–174.

Lavelle CL. Secular trends of the face and stature. *Angle Orthod.* 1972;42(3):221-226.

Leonardi R, Cutrera A, Barbato E. Rapid maxillary expansion affects the spheno-occipital synchondrosis in youngsters. A study with low-dose computed tomography. *Angle Orthod*. 2010;80(1):106-110.

Lewis AB, Garn SM. The relationship between tooth formation and other maturation factors. *Angle Orthod*. 1960;30:70-77.

Lewis AB, Roche AF, Wagner B. Pubertal spurts in cranial base and mandible. Comparisons within individuals. *Angle Orthod*. 1985;55(1):17-30.

Long JJ. A cephalometric study of the closure of the spheno-occipital synchondrosis in a group of subjects exhibiting Class II dentoskeletal relations. *Am J Orthod*. 1971;59(3):301-302.

Madeline LA, Elster AD. Suture closure in the human chondrocranium: CT assessment. *Radiology*. 1995;196(3):747-756.

Melsen B. Time of closure of the spheno-occipital synchondrosis determined on dry skulls: a radiographic craniometric study. *Acta Odont Scand*. 1969;27(1):73–90.

Melsen B. Time and mode of closure of the spheno-occipital synchrondrosis determined on human autopsy material. *Acta Anat*. 1972;83(1):112-118.

Melsen B. The cranial base: the postnatal development of the cranial base studied histologically on human autopsy material. *Acta Orthod Scand Suppl*. 1974;62:1–126.

Mitchell L. *An Introduction to Orthodontics*. 3rd ed. Toronto, ON: Oxford University Press; 2007.

Moshiri M, Scarfe WC, Hilgers ML, Scheetz JP, Silveira AM, Farman AG. Accuracy of linear measurements from imaging plate and lateral cephalometric images derived from cone-beam computed tomography. *Am J Orthod Dentofacial Orthop*. 2007;132(4):550-560.

Nakamoto JM. Myths and variations in normal pubertal development. *West J Med*. 2000;172(3):182-185.

Nolla CM. The development of the permanent teeth. *J Dent Child*. 1960;27:254-266.

Ohtsuki F, Mukherjee D, Lewis AB, Roche AF. Growth of the cranial base and vault dimensions in children. *J Anthop Soc Nippon*. 1982;90:239–258.

Okamoto K, Ito J, Tokiguchi S, Furusawa T. High-resolution CT findings in the development of the spheno-occipital synchondrosis. *Am J Neuroradiol*. 1996;17:117–120.

Okasha M, McCarron P, McEwen J, Smith GD. Age at menarche: secular trends and association with adult anthropometric measures. *Ann Hum Biol*. 2001;28(1):68-78.

O'Reilly M, Yanniello GJ. Mandibular growth changes and maturation of cervical vertebrae: a longitudinal cephalometric study. *Angle Orthod*. 1988;58(2):179-184.

Peck S. A biographical portrait of Edward Hartley Angle, the first specialist in orthodontics, part 1. *Angle Orthod*. 2009;79(6):1021-1027.

Perinetti G, Contardo L, Gabrieli P, Baccetti T, Di Lenarda R. Diagnostic performance of dental maturity for identification of skeletal maturation phase. *Eur J Orthod*. 2012;34(4):487-492.

Powell T, Brodie A. Closure of the spheno-occipital synchondrosis. *Anat Rec*. 1963;147:15–23.

Proffit WR. *Contemporary Orthodontics*. 4th ed. St. Louis, MS: Mosby; 2007.

Proffit WR, Phillips C, Tulloch JF, Medland PH. Surgical versus orthodontic correction of skeletal Class II malocclusion in adolescents: effects and indications. Int J Adult Orthodon Orthognath Surg. 1992;7(4):209-220.

Proffit WR, White RP Jr. Who needs surgical-orthodontic treatment? Int J *Adult Orthodon Orthognath Surg*. 1990;5(2):81-89.

Sahni D, Jit I, Neelam, Suri S. Time of fusion of the basisphenoid with the basilar part of the occipital bone in northwest Indian subjects. Forensic Sci Int. 1998;98:41-45.

Scarfe WC, Farman AG, Sukovic P. Clinical applications of cone-beam computed tomography in dental practice. *J Can Dent Assoc*. 2006;72(1):75-80.

Scheuer L, Black S. *Developmental juvenile osteology*. New York, NY: Academic Press; 2000.

Scott JH. The cranial base. *Am J Phys Anthropol*. 1958;16:319–348.

Singh G. *Textbook of Orthodontics*. 2nd ed. New Delhi, India: Jaypee Brothers Medical Publishers Ltd.; 2007.

Silvestrini-Biavati A, Angiero F, Gambino A, Ugolini A. Do changes in spheno-occipital synchondrosis after rapid maxillary expansion affect the maxillomandibular complex? *Eur J Paediatr Dent*. 2013;14(1):63-67.

Smith RJ. Misuse of hand-wrist radiographs. *Am J Orthod*. 1980;77(1):75-78.

Tanner JM, Whitehouse, RH. *Standards for skeletal maturity. Part I*. Paris: International Children's Centre; 1959.

Tanner JM, Whitehouse RH, Healy MJR, *A new system for estimating skeletal maturity from the hand and wrist, with standards from a study of 2,600 healthy British children. Part II. The scoring system*. Paris: International Children's Centre; 1962.

Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. I. *Arch Dis Child*. 1966a;41(219):454-471.

Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. II. *Arch Dis Child*. 1966b;41(220):613-635.

Thilander B, Ingervall B. The human spheno-occipital synchondrosis. II. A histological and microradiographic study of its growth. Acta Odonto Scand. 1973; 31: 323-334.

Tofani MI. Mandibular growth at puberty. *Am J Orthod*. 1972;62(2):176-195.

Tulloch JF, Phillips C, Proffit WR. Benefit of early Class II treatment: progress report of a two-phase randomized clinical trial. *Am J Orthod Dentofacial Orthop*. 1998;113(1):62-72.

Tulloch JF, Proffit WR, Phillips C. Outcomes in a 2-phase randomized clinical trial of early Class II treatment. *Am J Orthod Dentofacial Orthop*. 2004;125(6):657-667.

Uysal T, Ramoglu SI, Basciftci FA, Sari Z. Chronologic age and skeletal maturation of the cervical vertebrae and hand-wrist: is there a relationship? *Am J Orthod Dentofacial Orthop*. 2006;130(5):622-628.

Vento M. Marie Vento: One Thousand Years of Chinese Footbinding: Its Origins, Popularity and Demise. Fordham University. http://www.fordham.edu/halsall/women/vento.asp. Published Mar 7, 1998. Accessed August 12, 2014.

Vukuzenzele. http://www.vukuzenzele.gov.za/2007/number14/art_12.htm. Published November 2007. Accessed August 12, 2014.

Wahl N. Orthodontics in 3 millennia. Chapter 1: Antiquity to the mid-19th century. *Am J Orthod Dentofacial Orthop*. 2005;127(2):255-259.

Wahl N. Orthodontics in 3 millennia. Chapter 7: Facial analysis before the advent of the cephalometer. *Am J Orthod Dentofacial Orthop*. 2006;129(2):293-298.

Wahl N. Orthodontics in 3 millennia. Chapter 8: The cephalometer takes its place in the orthodontic armamentarium. *Am J Orthod Dentofacial Orthop*. 2006;129(4):574-580.

Wahl N. Orthodontics in 3 millennia. Chapter 9: functional appliances to midcentury. *Am J Orthod Dentofacial Orthop*. 2006;129(6):829-833.

Walker A. New Mandala. http://asiapacific.anu.edu.au/newmandala/2007/05/16/bound-by-tradition/. Published May 16, 2007. Accessed August 12, 2014.

Wetzel NC. The grid technique of evaluating growth and development in infants and children. *Am J Phys Anthropol.* 1946;4:255-256.

Williams PL, Bannister LH, Berry MM, Collins P, Dyson M, Dussek JE, Ferguson MWJ eds. *Gray's Anatomy: the Anatomical Basis of Medicine and Surgery*. 38th ed. New York, NY: Churchill Livingstone; 1995.

Wong RW, Alkhal HA, Rabie AB. Use of cervical vertebral maturation to determine skeletal age. *Am J Orthod Dentofacial Orthop*. 2009;136:484.e1-484.e6.

JOURNAL ARTICLE

SPHENO-OCCIPITAL SYNCHONDROSIS MATURATION AS RELATED TO THE DEVELOPMENT OF CERVICAL VERTEBRAE, MANDIBULAR CANINE AND CHRONOLOGIC AGE: A CONE-BEAM COMPUTED TOMOGRAPHY ANALYSIS

Richard M. Halpern[a], William A.Wiltshire[b] Frank J Hechter[c], Ian Clara[d]

[a] Orthodontic Resident, Department of Preventive Dental Science, Division of Orthodontics, University of Manitoba, Winnipeg, Canada.

[b] Professor, Program Director and Department Head, Department of Preventive Dental Science, Division of Orthodontics, University of Manitoba, Winnipeg, Canada.

[c] Part-time Professor, Department of Preventive Dental Science, Division of Orthodontics, University of Manitoba, Winnipeg, Canada.

[d] Assistant Professor, Department of Community Health Sciences, University of Manitoba, Winnipeg, Canada

ABSTRACT

Objective: To investigate the relationship between maturation of the spheno-occipital synchondrosis (SOS) with cervical vertebrae (CVM), dental development of the mandibular canine (DI), chronologic age and intra-rater / inter-rater reliability.

Materials and Methods: Seventy-seven subjects (42 females and 35 males) were randomly selected into six age groups from retrospective cone-beam computed tomograms: (1) 9 year old females, (2) 11-12 year old females, (3) 16-17 year old females, (4) 10-11 year old males, (5) 13-14 year old males and (6) 18-21 year old males. Spearman correlation coefficients between SOS, CVM, DI, and age group, along with tabulations of stages of SOS, CVM and age were evaluated separately for each gender.

Results: SOS maturation was significantly and positively correlated with CVM and age group in both females and males (all $r > 0.8$). A weaker significant correlation coefficient was found between SOS maturation and DI for both females and males ($r > 0.6$). All males with fused SOS were in CVM stage 4 or later, while all females were in at least CVM stage 3. No subjects with open SOS were in the post-pubertal growth spurt age group and no subjects with closed SOS were in the pre-pubertal growth spurt age group. SOS maturation showed substantial and significant inter-rater and intra-rater reliability (kappa > 0.7).

Conclusion: SOS stages are reliable and valid indicators of potential craniofacial growth and development and correlate with measures such as CVM.

Key Words: Skeletal maturation; Spheno-occipital synchondrosis; Maturation indicators; Age determination; Computed tomography, cone-beam, x-ray; inter-rater reliability

ARTICLE

Introduction

The timing and decisions about treatment modalities are critically dependent upon the accurate assessment of individual growth and development. Predicting the optimal time to begin orthopedic treatment may be discerned by several imperfect methods. The accuracy of maturational indices is limited and has a large error of measurement. A common method of assessing maturation involves the radiographic analysis of the cervical vertebrae (CVM).[1] Strong relationships between CVM, changes in stature and growth spurts of the mandible have been reported.[2] Dental age, however, has the weakest correlations with other developmental indices.[3] Advances in radiological technology have rendered cone beam computed tomography (CBCT) commonplace in orthodontics in certain regions of North America.[4] It has now become possible to discern anatomical structures with increased clarity through images obtained using CBCT.

Some orthopedic treatments such as rapid maxillary expansion and headgear treatment apply forces across the spheno-occipital synchondrosis (SOS).[5,6] Knowing the age of fusion of the SOS, the last synchondrosis in the cranial base to fuse, may alter how the timing of an orthopedic treatment may be initiated. The SOS, which is readily viewed with CBCT, has been investigated for its use as a maturation indicator with direct inspection, histologic analysis and radiographic methods ranging from laminagraphy to multi-slice computed tomography.[7-10] However, a comprehensive review of the literature has revealed a void in the English literature relating the SOS, viewed with CBCT images, with other common maturational indices such as CVM. For an index to be effective it must be accurate and reproducible.[1] For example, CVM assessment is frequently reported to have an intra-rater reliability of at least a 90%[11-13] and an inter-rater reliability of more than 86%.[11,12] The reproducibility of the SOS has been reported using multi-slice CT studies.[10,14] The intra-rater reliability was found to be 91% and inter-rater reliability was 78-87%.[10,14] There is a void in the literature concerning the intra-rater and inter-rater reliability of the SOS using CBCT technology that emits less-radiation and provides lower contrast resolution in comparison to the aforementioned technology.

The aims of this study therefore were to: 1) investigate the relationships between SOS maturation with CVM, circum-pubertal growth spurt age groups and dental maturation of the mandibular canine (DI) in both genders; 2) describe in both genders the range of chronologic age and CVM stage for each level of SOS maturation; 3) evaluate intra-rater and inter-rater reliability of measuring a three-stage SOS maturation scale using images obtained with CBCT technology.

Materials and Methods

This retrospective cross-sectional study obtained ethics approval from the University Human Research Ethics Board. Samples (n=77) were obtained from a private orthodontic practice and consisted of images collected from a CBCT machine (iCAT Next Generation, Imaging Sciences International, Hatfield, PA) that obtained a voxel resolution of 0.3 or 0.4 mm with 328 to 576 basis images. Subjects representing three circum-pubertal growth spurt developmental periods of both genders[15] made up the six sample groups: 1) Females prior to their peak height velocity (PHV), (<10 years old) (n=11); 2); females during their PHV, (11-13 years old) (n=15); 3) females following their PHV, (>14 years old) (n=16); 4) males prior to their PHV, (<12 years old) (n=10); 5) Males during their PHV, (13-15 years old) (n=13); 6) males following their PHV, (>16 years old) (n=12).

Subjects were excluded for being in fixed appliances, having had orthognathic surgery, congenitally absent or ectopic permanent mandibular canines, anomalies of the second, third or fourth cervical vertebra or not completely displaying the necessary images, (anterior and posterior nasal spines, the most anterior inferior point on the chin, nasion, porion, body of the sphenoid, entire SOS, second, third and fourth cervical vertebrae).

Using Dolphin Imaging 3D, (v.11.5.04.34, Dolphin Imaging and Management Solutions, Chatsworth, CA) images were oriented to the Frankfort horizontal plane and rotated to have the midsagittal plane along the anterior and posterior nasal spine. A midsagittal slice, 1 voxel thick, was screen captured and a reconstructed panoramic radiograph was created with focal trough seeds placed at the apex of the mandibular canines and exported. CVM stages were evaluated with the method described by Baccetti *et al*.[16] The method described by Demirjian *et al*.,[17] was used to evaluate the DI of the more immature mandibular canine. A modification of the maturation index of Melsen[8] was used for evaluation of the SOS.

Figure 1 shows the stages of maturation of the SOS used. The SOS was considered open when both the superior and inferior margins of the synchondrosis were without a continuous opaque bridge from the sphenoid to the occipital bone. When only one of the superior or inferior borders across the SOS was continuously opaque, the stage was recorded as a partial union. When there were continuous radiopaque margins across the superior and inferior margins of the SOS, a complete union stage was noted.

The entire sample (n=77) was measured once for CVM and DI and three times for all SOS images. The three SOS measurements were averaged to the nearest stage. The measurements of SOS, CVM, age group and DI were analyzed using statistical software (IBM SPSS Statistics, v. 20.0.0, IBM Corp., Armonk, NY). All tests were set at an *á priori* level of significance set at $\alpha \leq 0.05$. A one-tailed Spearman rank-ordered correlation test was used for each gender to determine the correlation between the SOS and each of CVM stage, age group and DI. Twelve months after initial measurements, intra-rater and inter-rater reliability (Cohen's Kappa) for 28 random samples of CVM and DI as well as triplicate measurements of all SOS maturation images were recorded by two calibrated orthodontic residents using the initially captured and exported images. Intra- and inter-rater reliability was also assessed for those repeat measures made of samples in groups 2 and 5 combined.

Results

The range of stages for CVM and DI for each sample group are reported in Table 1, and the chronologic age distribution for each subject according to chronologic age are shown in Table 2. The oldest age where an open SOS was found was 12 years old in females, and 13 in males. No subjects with an open SOS were in the post-PHV age group. The earliest SOS partial union was found in this sample at the age of 9 years old in females and 10 in males, whereas complete SOS union was found earlier in females (by 1 year). In the present study, the earliest complete union of the SOS was found in an 11 year old female and 14 year old males. All females with fused SOS were in CVM stage 3 or later and in the pubertal growth spurt (PGS) or post-PGS age group, while all males were in at least CVM stage 4 and in the PGS or post-PGS age group. With the exception of females in the open SOS stage, DI stage H was found in males and females in all stages of SOS.

Correlation coefficient for SOS maturation in females was found to be 0.831, 0.830 and 0.734 ($p<0.001$) for groups 1-6 with respect to CVM, age and DI. The only statistically significant correlation of SOS maturation in group 2 was found with CVM 0.656 ($p<0.005$). For males, correlation coefficients of SOS maturation with CVM, age and DI for groups 1-6 were 0.870, 0.849 and 0.638 ($p<0.001$) respectively. For group 5, the SOS maturation had a correlation coefficient ($p<0.05$) of 0.612 and 0.570 with respect to CVM and age. Group 5 did not have a statistically significant correlation of SOS stages with DI. Cohen's Kappa coefficients ($p<0.001$) for intra-rater reliability of 0.757, 0.646 and 0.411 for groups 1-6 and 0.610, 0.776 and no statistical significance for groups 5 and 6 combined were obtained for SOS, CVM and DI respectively. Cohen's Kappa coefficients for inter-rater reliability of groups 1-6 ($p<0.001$) were 0.750, 0.471 and 0.492. The inter-rater reliability for groups 2 and 5 combined were 0.623 ($p<0.001$), 0.504 ($p<0.001$) and 0.480 ($p<0.05$).

Discussion

We used a three-stage index of SOS maturation as described by Melsen.[8] A three-stage index was chosen as at 1 voxel thick it was already relatively hard in select cases to discern between three SOS stages and knowing subdivisions of these stages is not clinically relevant.

We found a complete union of the SOS as early as 11 years old in females and 14 years old in males that corresponded with the PGS age groups in this study. For females, the present findings paralleled the results of the laminagraphy study of Powell and Brodie[7] and a CT study by El-Sheikh and Ramadan[18] who each found females with fused spheno-occipital synchondroses at 11 years old. These findings were notably earlier than the histologic findings of more than 16 to 17 years old.[19]

Our findings for males first having complete union of their SOS at 14 years, was later than studies using laminagraphy, histology and CT images where 12-13 years olds with fused SOS were identified.[7,8,14,18] This is consistent with a tomographic study[20] and a CT study[21] but earlier than the histologic findings and direct inspection studies[9,19] who reported fusion from 15 to over 18 to 19 years in males. The variations may be due to various techniques used in measuring SOS maturation. The various reported ages from the numerous study methodologies suggest chronologic age may not be a consistent indicator of SOS maturation.

Considering the age ranges presented in our study, it is important to note that our study did not seek to classify the various stages of SOS maturation based on chronologic age, but rather on circum-PGS age groups. Hence, not every single age in childhood and adolescence is represented in this study.

No subjects with open SOS or partial union of the SOS were in the post-PGS age group and no subjects with complete union of the SOS were in the pre-PGS age group. It can therefore be interpreted from these findings that pre-PGS and some PGS patients, of either gender, would be likely to benefit from orthopedic forces affecting the SOS.

The results of a randomized clinical trial[22] found that early orthopedic treatment provided prior to adolescence, followed by comprehensive orthodontics, is not more clinically successful than one stage of treatment provided during adolescence. However, our study exemplifies the considerable variation within any given individual. Prior the PHV, in the pre-PGS phase of growth and development, a juvenile acceleration spurt is known to occur, especially in females.[3] The juvenile acceleration spurt occurs one to two years prior to PHV and also accompanies a corresponding increase in jaw growth. In males, if this spurt occurs, it is almost always less intense than their growth in puberty. In females however, it may equal or even exceed their growth, occurring later in puberty.[3] The complete union of the SOS observed in our female population, which is younger than observed in most previous studies, may be due to this early spurt. Orthodontists should take into account that the SOS may close earlier than previously believed and understand that growth manipulation may not consistently be as successful at earlier ages.

The maturation of SOS had a strong and statistically significant correlation (p<0.001) with age for groups 1-6 (ρ_s=0.830 for females and ρ_s=0.849 for males) and a moderate correlation (p<0.050) for group 5 alone (ρ_s=0.570). Group 2 did not have a statistically significant (p<0.05) correlation of SOS maturation with age. No research to date in the English literature has reported on the relationship between SOS and CVM. These strong relationships for groups 1-6 and moderate to strong relationships for groups 2 and 5 of SOS with CVM indicate that the CVM stages could be regarded as being accurate in predicting the levels of SOS fusion.

The results of our study indicate that if the DI were in stage E or F, the SOS would not have reached the complete union stage. Coutinho *et al.*,[23] found stage G of the canine to be 0.4 years after PHV for females, and 1.3 years for males. The results of this investigation did not find stage G to be reliable in indicating any stage of SOS maturation for either gender as those with mandibular canines in stage G of dental development were found in all six sample groups.

The findings in this study are supported by Proffit[3] who stated that of all the indicators, dental age (eruption and dental development) correlates least well with the other developmental indices and that dental age has a correlation of 0.7 with chronologic age. In our study, a statistically significant (p<0.001) but weaker correlation coefficient was found between SOS maturation and DI in females (ρ_s=0.734) and in males (ρ_s=0.638) for groups 1-6. These values are considered to be of moderate to strong correlative value. No research in the English literature has reported on the relationship between SOS closure and the DI.

Intra-rater reliability

The present investigation found intra-rater reliability of the SOS maturation stages to be lower than that reported by two studies that used a similar approach, in that they used CT images, for their measurements.[10,14] The lower value of Cohen's Kappa coefficient found here, while still significant ($p<0.001$) and a "substantial" value, may be lower due to the decreased resolution of the CBCT images obtained in this study, which provides decreased contrast resolution, compared to multi-slice CT. The intra-rater reliability of CVM was found to be similar to that found by Gabriel *et al.*,[24] and weaker than reported by several authors.[11-13] Gabriel *et al.*,[24] suggested their values were likely lower than other studies due to the increased expertise of the observers in the studies they compared their results to. Orthodontic residents obtained all measurements made in this study. The intra-rater reliability of DI had the lowest reliability of the three indices. The findings in this study were much lower than that reported by a study looking at canines and a study looking at second molar development.[12,13] The intra-rater reproducibility of DI levels is at best not optimal and decreases the value of this index at making meaningful predictions.

Inter-rater reliability

Inter-rater reliability was tested using Cohen's Kappa coefficient for all three indices of maturation and statistical significance was found for all results. Two studies reported coefficient values of the SOS using multi-slice CT technology.[10,14] Bassed *et al.*,[10] reported similar agreement to the findings here that were much less reliable than the finding of Franklin and Flavel.[14] The inter-rater reliability of CVM was found here to be much lower than reliability of other studies[11,16] but similar again to the study by Gabriel *et al*.[24] The inter-rater reliability of DI in this study was much lower than that reported in a multi-slice CT study of mandibular second molars.[12]

Conclusions

1. To avoid missing the window of opportunity for orthopaedics in early maturing patients, it is prudent to commence orthopaedic forces prior to 11 years in females and 14 years in males, based on SOS maturation.

2. The stages of SOS maturation are valid indicators of the remaining growth potential and correlate closely with CVM indicators.
3. Orthodontists can be confident that growth modification timing aimed at SOS patency can be reliably predicted with CVM.
4. Intra-observer and inter-observer statistical tests indicate that a three-stage SOS maturation scale using CBCT is accurate and reproducible both within and between observers.
5. The dental maturation stages of the mandibular canine teeth show satisfactory diagnostic performance only for identification of the pre-PHV, with no reliable indications for onset of the PHV.
6. The clinical usefulness of the determination of dental maturity using DI of mandibular canines for the assessment of treatment timing for skeletal malocclusion is limited.

Address for Correspondence

Dr. Richard M. Halpern, Department of Preventive Dental Science, Division of Orthodontics, University of Manitoba, D341 Dental Building, 780 Bannatyne Ave., Winnipeg, Manitoba, Canada R3E 0Z2 (email: [redacted])

Acknowledgments

Dr. Terry Carlyle for use of CBCT images from his orthodontic office.

References

1. Franchi L, Baccetti T. *The use of maturational indices for the identification of optimal treatment timing in dentofacial orthopedics*. In: McNamara JA Jr, Kelly KA eds. *Treatment timing: orthodontics in four dimensions. Craniofacial Growth Series,* Vol 39. Ann Arbor: Center for Human Growth and Development, University of Michigan; 2002.
2. Franchi L, Baccetti T, McNamara JA Jr. Mandibular growth as related to cervical vertebral maturation and body height. *Am J Orthod Dentofacial Orthop*. 2000;118:335-340.
3. Proffit WR. *Contemporary Orthodontics*. 4^{th} ed. St. Louis, MS: Mosby; 2007.
4. Scarfe WC, Farman AG, Sukovic P. Clinical applications of cone-beam computed tomography in dental practice. *J Can Dent Assoc*. 2006;72:75-80.
5. Holberg C, Holberg N, Rudzki-Janson I. Sutural strain in orthopedic headgear therapy: a finite element analysis. *Am J Orthod Dentofacial Orthop*. 2008;134:53-59.

6. Leonardi R, Cutrera A, Barbato E. Rapid maxillary expansion affects the spheno-occipital synchondrosis in youngsters. A study with low-dose computed tomography. *Angle Orthod*. 2010;80:106-110.
7. Powell T, Brodie A. Closure of the spheno-occipital synchondrosis. *Anat Rec*. 1963;147:15–23.
8. Melsen B. Time and mode of closure of the spheno-occipital synchrondrosis determined on human autopsy material. *Acta Anat*. 1972;83:112-118.
9. Sahni D, Jit I, Neelam, Suri S. Time of fusion of the basisphenoid with the basilar part of the occipital bone in northwest Indian subjects. Forensic Sci Int. 1998;98:41-45.
10. Bassed RB, Briggs C, Drummer OH. Analysis of time of closure of the spheno-occipital synchondrosis using computed tomography. *Forensic Sci Int*. 2010;200:161-164.
11. Hassel B, Farman AG. Skeletal maturation evaluation using cervical vertebrae. *Am J Orthod Dentofacial Orthop*. 1995;107:58-66.
12. Kumar S, Singla A, Sharma R, Virdi MS, Anupam A, Mittal B. Skeletal maturation evaluation using mandibular second molar calcification stages. *Angle Orthod*. 2012;82:501-506.
13. Perinetti G, Contardo L, Gabrieli P, Baccetti T, Di Lenarda R. Diagnostic performance of dental maturity for identification of skeletal maturation phase. *Eur J Orthod*. 2012;34:487-492.

14. Franklin D, Flavel A. Brief communication: timing of spheno-occipital closure in modern Western Australians. *Am J Phys Anthropol*. 2014;153:132-138.

15. Houston WJ. Relationships between skeletal maturity estimated from hand-wrist radiographs and the timing of the adolescent growth spurt. *Eur J Orthod*. 1980;2:81-93.

16. Baccetti T, Franchi L, McNamara JA Jr. The cervical vertebral maturation (CVM) method for the assessment of optimal treatment timing in dentofacial orthopedic. *Semin Orthod*. 2005;11:119-129.

17. Demirjian A, Goldstein H, Tanner JM. A new system of dental age assessment. *Human Biol*. 1973;45:211-227.

18. El-Sheikh M, Ramadan S. Closure of the spheno-occipital synchondrosis in the Arabian Gulf region. Proceedings of the 58th Annual Meeting of the American Academy of Forensic Sciences; 2006 Feb 16–21; Seattle, WA. Colorado Springs, CO: American Academy of Forensic Sciences, 2006;12:276.

19. Thilander B, Ingervall B. The human spheno-occipital synchondrosis. II. A histological and microradiographic study of its growth. Acta Odonto Scand. 1973; 31: 323-334.

20. Irwin GL. Roentgen determination of the time of closure of the spheno-occipital synchondrosis. *Radiology*. 1960;75:450-453.

21. Okamoto K, Ito J, Tokiguchi S, Furusawa T. High-resolution CT findings in the development of the spheno-occipital synchondrosis. *Am J Neuroradiol*. 1996;17:117–120.

22. Tulloch JF, Proffit WR, Phillips C. Outcomes in a 2-phase randomized clinical trial of early Class II treatment. *Am J Orthod Dentofacial Orthop*. 2004;125:657-667.

23. Coutinho S, Buschang PH, Miranda F. Relationships between mandibular canine calcification stages and skeletal maturity. *Am J Orthod Dentofacial Orthop*. 1993;104:262-268.

24. Gabriel DB, Southard KA, Qian F, Marshall SD, Franciscus RG, Southard TE. Cervical vertebrae maturation method: poor reproducibility. *Am J Orthod Dentofacial Orthop*. 2009;136:478.e1-478e7.

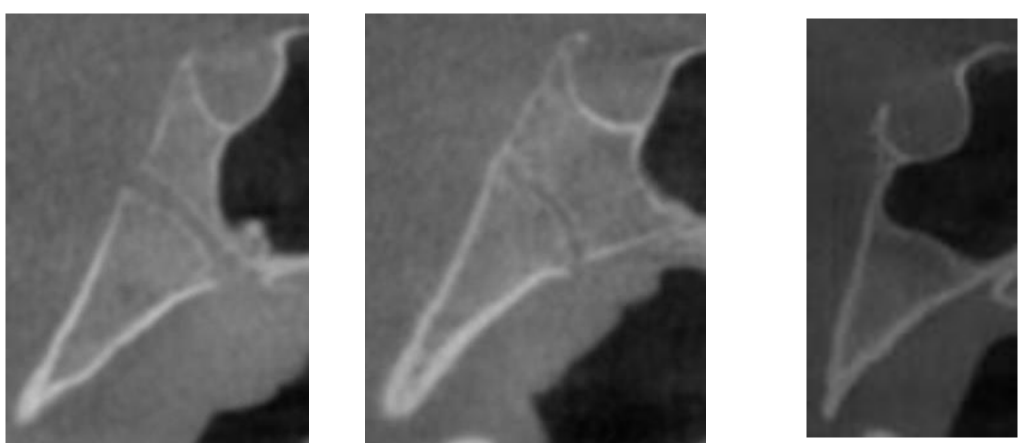
Table 1 Average and Range of CVM and DI Stages for Females and Males with Respect to SOS Maturation Stages

SOS Stage	**Gender**	**Average CVM (Stage)**	**Minimum CVM (stage)**	**Maximum CVM (stage)**	**Average Dental (stage)**	**Minimum Dental (stage)**	**Maximum Dental (stage)**
Open	Female	2	1	4	F	F	G
Partial Union	Female	3	1	5	G	F	H
Complete Union	Female	5	3	6	H	G	H
Open	Male	2	1	5	F	E	H
Partial Union	Male	3	1	4	G	F	H
Complete Union	Male	6	4	6	H	G	H

Table 2 Actual number of individuals in each range of fusion for females and males, by age

	Females (n =42)			Males (n = 35)		
Age	Open	Partial Union	Complete Union	Open	Partial Union	Complete Union
9	8	3	0	-	-	-
10	-	-	-	4	2	0
11	1	1	1	2	2	0
12	1	6	5	-	-	-
13	-	-	-	1	0	0
14	-	-	-	0	9	3
15	-	-	-	-	-	-
16	0	0	11	-	-	-
17	0	0	5	-	-	-
18	-	-	-	0	0	3
19	-	-	-	0	0	4
20	-	-	-	0	0	3
21	-	-	-	0	0	2

Figure 1 Portions of images of subjects demonstrating open (a), partial union (b) and complete union (c) of the spheno-occipital synchondrosis (SOS)



(a) **(b)** **(c)**

APPENDICES

Appendix 1: Approval of Protocol by University of Manitoba Health Research Ethics Board (HREB)

P126 - 770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Telephone 204-789-3255
Fax 204-789-3414

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS
Research Ethics Boards

HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

PRINCIPAL INVESTIGATOR:	**INSTITUTION/DEPARTMENT:**	**ETHICS #:**
Dr. R. Halpern	UofM / Preventive Dental Sciences	H2013:071
APPROVAL DATE: February 16, 2013	**EXPIRY DATE:** February 16, 2014	
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):		

PROTOCOL NUMBER:	**PROJECT OR PROTOCOL TITLE;**
NA	Skeletal Maturation Evaluation Using Spheno-Occipital Synchondrosis: A Cone-Beam Computed Tomography Analysis
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: NA	

Submission Date of Investigator Documents:	**HREB Receipt Date of Documents:**
February 6, 2013	February 6, 2013

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	**Version(if applicable)**	**Date**

Protocol:

Proposal received February 6, 2013

Consent and Assent Form(s):

Other:

Data Capture Sheet received February 6, 2013

CERTIFICATION
The above named research study/project has been reviewed in a ***delegated manner*** by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION
The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

- 1 -

www.umanitoba.ca/faculties/medicine/ethics

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of annual approval.** **A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

John Arnett, PhD., C. Pysch.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone**: (204) 789-3255/ **Fax:** (204) 789-3414

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS
Research Ethics Board

P126 - 770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Telephone 204-789-3255
Fax 204-789-3414

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF ANNUAL APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Dr. R. Halpern	U of M / Dentistry	H2013:071
HREB MEETING DATE (If applicable):	**APPROVAL DATE:** March 19, 2014	**EXPIRY DATE:** February 16, 2015
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
NA	Skeletal Maturation Evaluation Using Spheno-Occipital Synchondrosis: A Cone-Beam Computed Tomography Analysis
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: NA	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
March 18, 2014	March 19, 2014

REVIEW CATEGORY OF ANNUAL REVIEW: **Full Board Review** ☐ **Delegated Review** ☒

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name(if applicable)	Version(if applicable)	Date

Annual approval

*Annual approval implies that the most recent **HREB approved** versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc. are approved.*

Consent and Assent Form(s):

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the annual study status report for the research study/project named on this ***Certificate of Annual Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. Annual approval was granted by the Chair or Acting Chair, UM HREB, per the response to the conditions of approval outlined during the initial review (full board or delegated) of the annual study status report.

HREB ATTESTATION

The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE

The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

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The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:
1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
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5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

John Arnett, PhD. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

- 2 -

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone**: (204) 789-3255/ **Fax:** (204) 789-3414

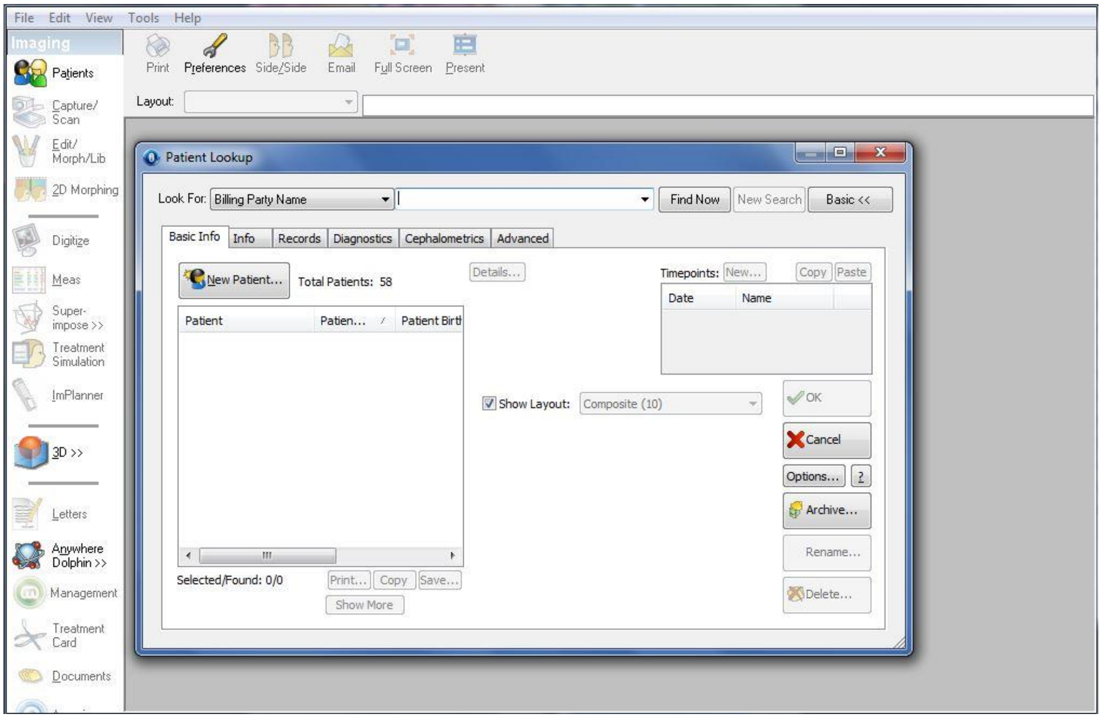
Appendix 2: Description of Image Acquisition.

Collection of Images

The external hard drive was connected to a computer that had a proprietary orthodontic analysis software program (Dolphin Imaging 3D, v.11.5.04.34, Dolphin Imaging and Management Solutions, Chatsworth, CA). One examiner (R.H) performed all manipulations of the images in the collection of images. Selected images were imported into Dolphin Imaging 3D, (Dolphin) with a new subject entry.

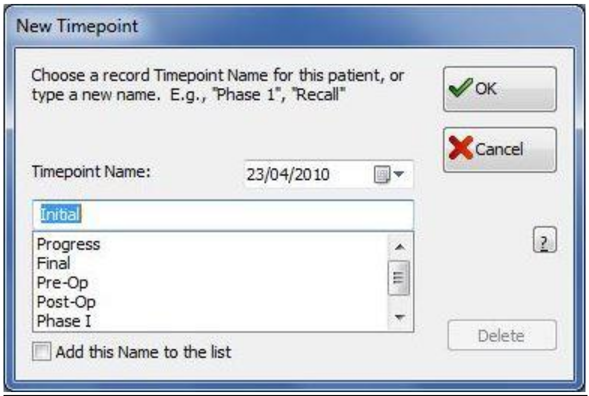
The Dolphin program was opened, the "Patients button selected (Figure 5). In the patient look up window that would then open the, "New Patient" button was chosen. and a menu would appear. The, "New Patient From DICOM" option was selected from the menu. A new window titled, "Open" popped-up where the desired DICOM file was selected and the, "Open" button selected. A complete description of how the images were obtained can be found in Appendix 2.

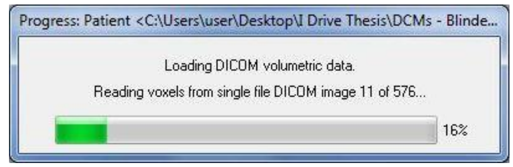
Figure 5 Screen capture of Dolphin Imaging 3D demonstrating opening screen for uploading patient



The “New Timepoint” window popped-up, the ”Initial” timepoint name was selected and the OK button selected (Figure 6a). The Progress window popped-up while the progress window popped-up while the DICOM volumetric data uploaded (Figure 6b).

Figure 6 Screen capture of segment of Dolphin Imaging 3D display demonstrating creation of timepoint (a) and subsequent loading verification screen (b)



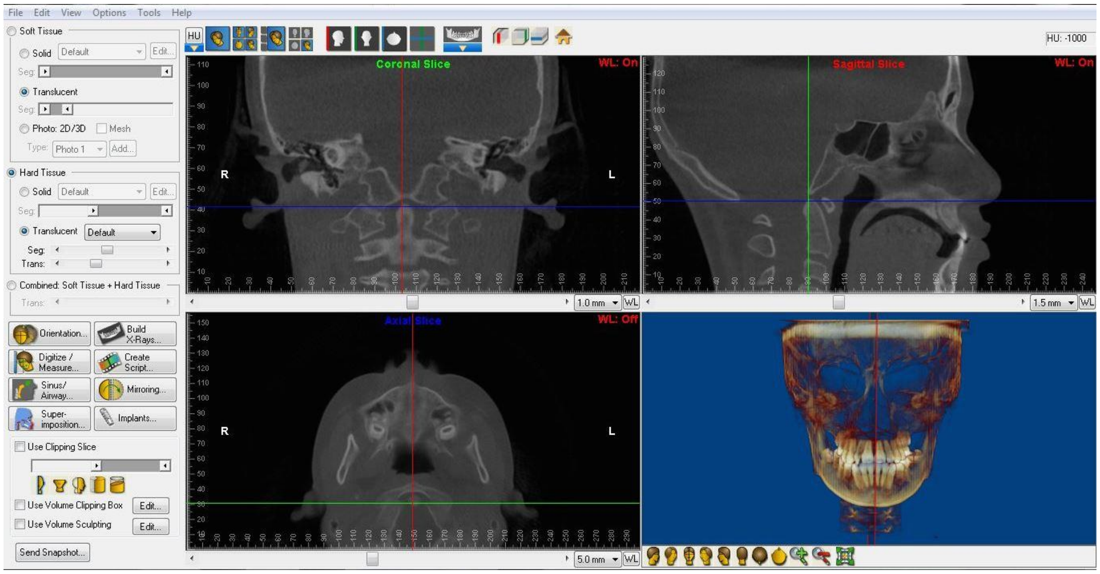


(a) **(b)**

<u>Manipulation of reconstructed spheno-occipital synchondrosis (SOS) and cervical vertebral maturation (CVM) images</u>

When the image was uploaded, the 3D rendered image was displayed. The "Orientation in 4-Equal Layout" view was selected. To begin orienting the image, the horizontal crosshair in the sagittal window was moved to the palate. The images in the sagittal and axial view windows were both rotated to ensure the horizontal and vertical crosshairs respectively went through both the subject's anterior and posterior nasal spines to represent the midsagittal plane (Ericson and Myrberg, 1973) (Figure 7).

Figure 7 Screen capture of Dolphin Image 3D demonstrating 4-equal view display, crosshairs and orientation along the line from anterior to posterior nasal spines

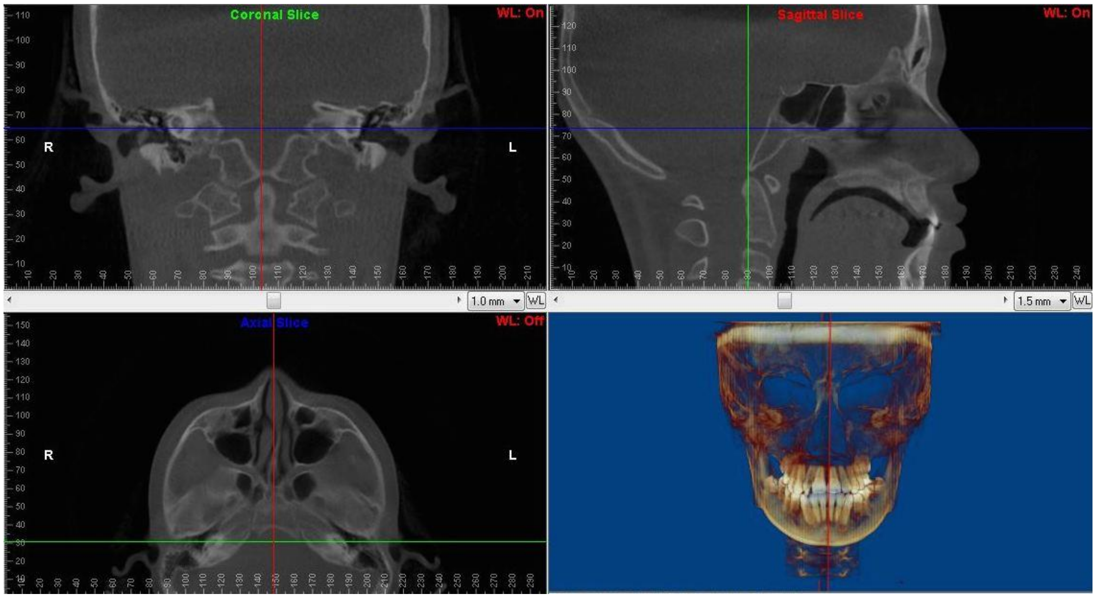


In the coronal slice window, the slice indicator scroll bar directly below that image was moved left and right to display the slice with the most:

1. confluent auditory meati bilaterally such that minimal to no radiopacity lay within the meati
2. superiorly lying external auditory meati

The coronal slice's horizontal crosshair was then raised so that it would pass through both porions bilaterally. The coronal image was rotated to facilitate this (Figure 8).

Figure 8 Orientation along line from anterior to posterior nasal spines



The coronal, sagittal and axial slices were set by adjusting their respective drop down lists below their images to display and image of 1 voxel thick. The “Show/Hide Crosshairs on the Slice Views” button was selected to remove crosshairs. The view was switched from the “4-Equal Layout” to fill the majority of the screen with the “Sagittal” view display.

Bassed, Briggs and Drummer (2010) in their multi-slice CT study of SOS maturation suggested using slices of 1 mm in thickness to measure the SOS. In that study the thinnest slices they were able to obtain with that technology would have been of 1 mm in thickness. Hence, the present study used the thinnest slices available with CBCT technology that was 1 voxel thick; in this study that was equivalent to 0.3 or 0.4 mm thick. This maximized the present investigation’s usage of the advantage of the superior spatial resolution CBCT offers over MSCT. Thicker slices average the radiopacity/radiolucency of adjacent voxels. If patency exists, it would be more advantageous to observe the radiolucency than observe an averaged radiopacity. Thickening the viewed slice from 1 voxel (0.3 or 0.4 mm) to 3 voxels (0.9 or 1.2 mm) thick results in slices similar to those of MSCT while lacking the superior contrast resolution MSCT offers.

The brightness was adjusted by holding the depressed left mouse button while moving the mouse horizontally for contrast, left to decrease contrast and right to increase it. The mouse, with the depressed left mouse button was moved vertically to adjust brightness, up to decrease brightness and down to increase it. The mouse button was then released. These parameters were adjusted to create the clearest image to the observer for the SOS and the cervical vertebrae.

To change the magnification of the sagittal image, with the mouse pointer located anywhere in the image, the control key on the keypad was depressed and held as was the left mouse button. The mouse was moved up and/or to the right to enlarge the image or down and/or to the left to decrease the enlargement. The control key and mouse button were then released.

To reframe the image, with the mouse pointer located anywhere in the sagittal image, the shift key was depressed as was the left mouse button. As the mouse was moved the image would be reframed following the mouse pointer. The shift key and mouse button were then released.

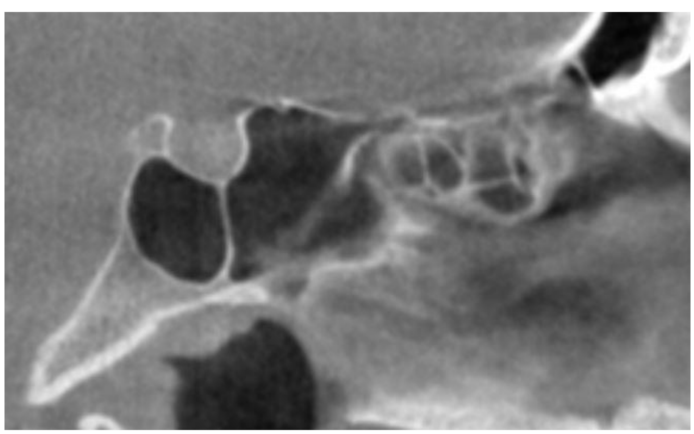
The SOS image was obtained by enlarging and centering an image as large as possible while allowing some clearance around the:

- foramen magnum in the bottom left corner
- nasion in the upper right corner of the display

All images were obtained from Dolphin using a screen capture software (Snipping Tool in Microsoft Windows 7 Home Premium™ 64 bit, Microsoft Corp., Redmond, WA) with the Dolphin window maximized to fill the entire display screen.

The SOS image was screen captured to include the entire displayed reconstructed image and saved in a folder titled SOS a JPEG image with the file name of the initial patient identification number (Figure 9).

Figure 9 Screen capture of spheno-occipital synchondrosis (SOS) image saved



In order to obtain the desired image for the cervical vertebra, the image was magnified as large as possible and reframed to include at minimum some clearance around:

- the most inferior aspect of the most inferiorly imaged cervical spine
- the superior aspect of the first and second cervical spine's bodies
- the most posterior cervical spinous process and
- some slight portion of the anterior laryngeal wall

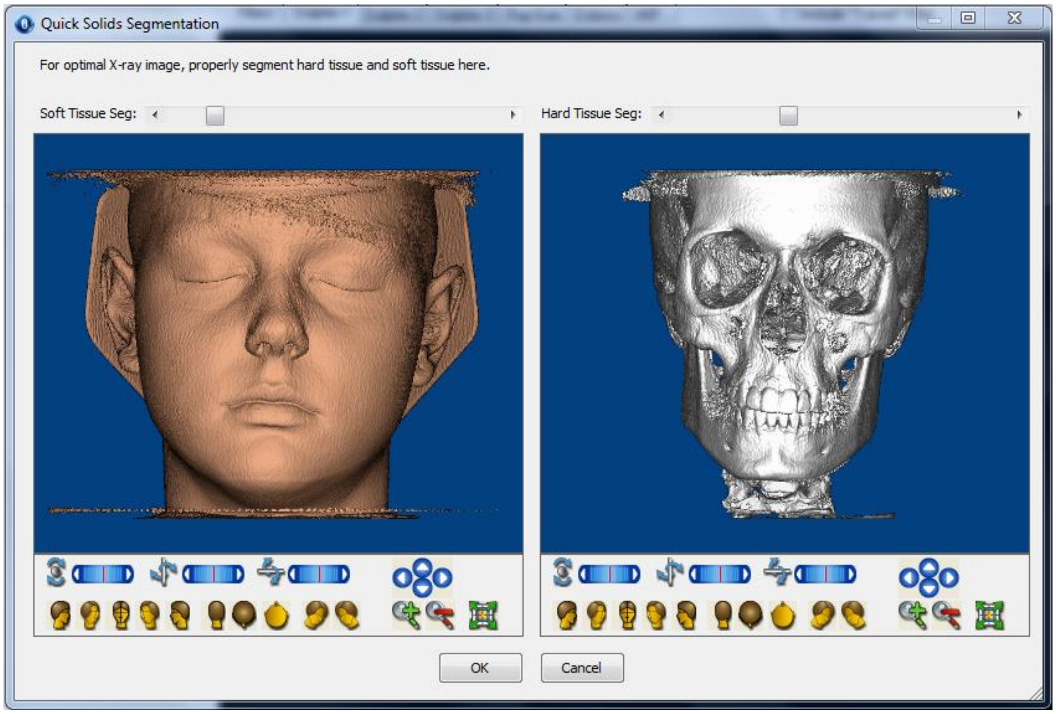
The cervical vertebral image was then also screen captured to include the entire displayed reconstructed image and saved in a folder titled CVM as a JPEG image with the file name of the initial patient identification number (Figure 10).

Figure 10 Screen capture of cervical vertebral image

Manipulation of panoramic reconstructed for obtaining the dental development of the mandibular canine image

In order to obtain a reconstructed panoramic image, the “Build X-Rays” button was selected (Figure 7). A “Radiograph Reconstruction” window opened with an overlying, ”Quick Solids Segmentation” window immediately opening-up over it. The “Quick Solids Segmentation” windows comprised two smaller inset windows inside; a reconstructed external 3D frontal view of the soft tissue of the subject appeared in the inset window on the left, and of the hard tissue on the right (Figure 11). Above each was a respective tissue segmentation scroll bar. Each of the scroll bars increased the sensitivity of the rendered image as it was moved right and decreased the sensitivity as it was moved left. The scroll bars were moved so that the sensitivity of the rendered image included a balance between minimal artefacts, (radiographic “noise”) without removing confluence in the surface appearance of the representative image of the skin or boney skeleton. The “OK” button at the bottom of that window was then selected.

Figure 11 Screen capture of "Quick Solids Segmentation" window



After the OK button was selected in the, "Quick Solids Segmentation" window the, "Radiograph Reconstruction" window remained. The view selected drop-down list at the top was set at the selection of, "Panoramic" (Figure 12). The, "Uniform Thickness" option below the inset lower right axial view window was set at 12 mm. The filters tab at the top of the reconstructed image was set at its default of the, "Dolphin 1" view. The, "Dolphin 1 Level" drop-down list below the reconstructed image was also set at its default level of, "0."

In the inset collimation window in the top left corner was a 3D rendered view of the subjects' right skeletal profile. This image required mild rotation for orientation purposes. By depressing the left mouse button, moving the mouse to rotate the image and then releasing the mouse button the 3D rendered imaged oriented. The rotations were done to overlap the posterior and inferior borders of the left and right mandibular rami and sigmoid notches such that none of the left ramus could be seen in this view.

Two white horizontally positioned parallel crosshairs existed in the inset collimation window. These two crosshairs were used to identify the desired upper and lower limits to be captured for the reconstruction. The upper crosshair was set slightly above the temporomandibular joint. The lower crosshair was set slightly below the lowest part of the chin anteriorly. A third horizontally positioned crosshair, red in colour, was used to identify the desired focal trough. This was set at the occlusal plane.

In the lower left corner a smaller inset axial view display was found. This image was magnified as needed and the same manner as was done in capturing the SOS and cervical vertebrae images described previously.

Red focal trough seeds were sequentially placed in the axial window in the bottom right corner of the screen. The first two seeds were placed:

- ✓ slightly behind and laterally to the most posterior border of the left mandible
- ✓ in the centre of the left first mandibular molar

The focal trough crosshair in the collimation window was then moved inferiorly to overly the roots of the mandibular anterior teeth. Three further focal trough seeds were placed:

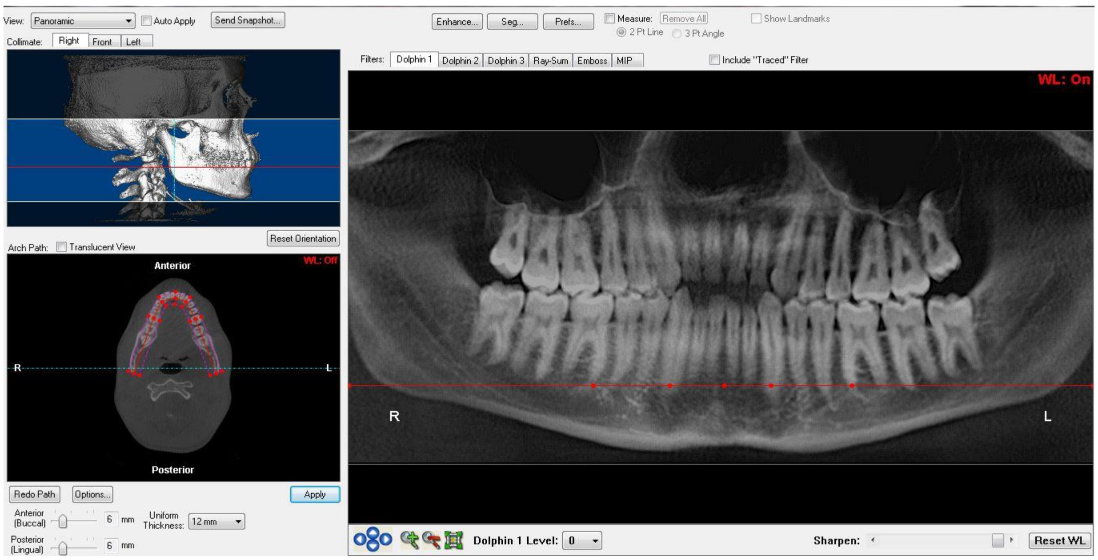
- ✓ in the centre of the mandibular left canine
- ✓ at the anterior cortical border of the alveolar bone between the mandibular central incisors
- ✓ in the centre of the mandibular right canine

The focal trough crosshair in the collimation window was then returned superiorly to overly the occlusal plane. The remaining two focal trough seeds were placed:

- ✓ in the centre of the right first mandibular molar
- ✓ slightly behind and externally to the most posterior border of the right mandible

At the placement of the last focal trough seed, the mouse was double clicked and the focal trough capture was completed. For ideal image reconstruction in the lower anterior region, the seed between the mandibular central incisors was then moved to create a relatively straight line from one mandibular canine seed to the other. This was done by depressing the left mouse on the midline scene, scrolling the mouse to the desired position, and releasing the mouse button. The, “Apply” button was selected below the axial image window and a Panoramic image was constructed. The sharpen scroll bar was moved to the far right for sharpest image and the, “Apply” button was selected again (Figure 12).

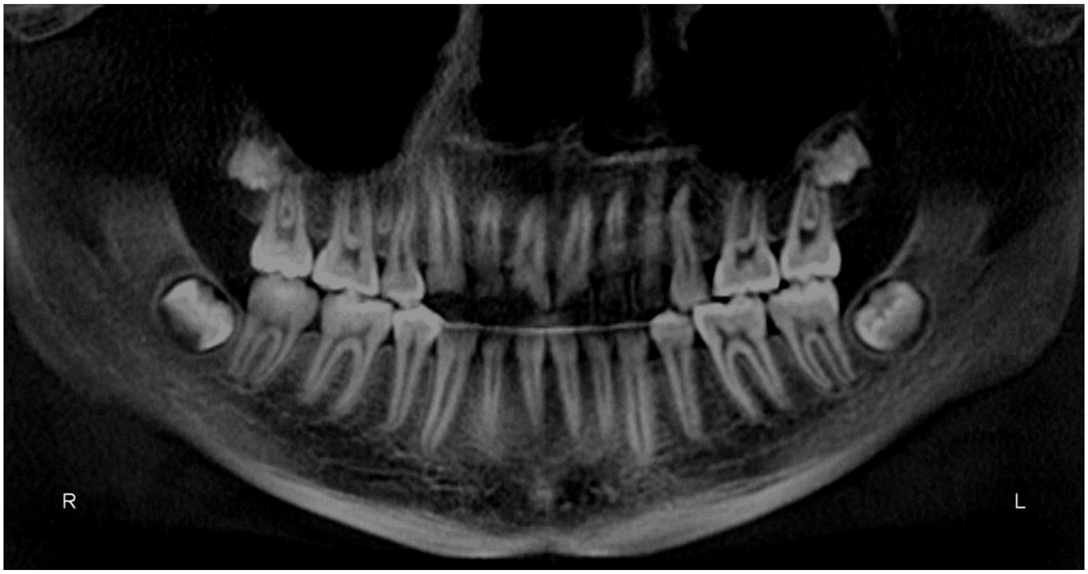
Figure 12 Screen capture of the reconstruction window of Dolphin Imaging 3D displaying orientation, collimation, seed points, uniform thickness selection, sharpness adjustment and image reconstruction



Brightness and contrast were adjusted for best contrast of apex of mandibular canines in the same fashion as was previously described for the image creation of the SOS and cervical vertebral images. This image was not magnified.

The right button on the mouse was clicked with the cursor anywhere in the reconstructed image. The, “Export this image to file option” was selected and this image was saved as a 24-bit JPEG file with the name of the patient identification number in a folder named “Dental” (Figure 13).

Figure 13 Exported panoramic reconstruction



Appendix 3: Journal Article Submission Approval

THE ANGLE ORTHODONTIST

ONLINE MANUSCRIPT SUBMISSION AND PEER REVIEW

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Detailed Status Information

Manuscript #	112614-845
Current Revision #	0
Submission Date	2014-11-26 02:20:40
Current Stage	Initial QC Started
Title	SPHENO-OCCIPITAL SYNCHONDROSIS MATURATION AS RELATED TO THE DEVELOPMENT OF CERVICAL VERTEBRAE, MANDIBULAR CANINE AND CHRONOLOGIC AGE: A CONE-BEAM COMPUTED TOMOGRAPHY ANALYSIS
Running Title	S-O SYNCHONDROSIS MATURATION AND CVM, DI AND AGE
Manuscript Type	Original Article
Special Section	N/A
Corresponding Author	Richard Halpern (University of Manitoba)
Contributing Authors	William Wiltshire , Frank Hechter , Ian Clara
Financial Disclosure	I have no relevant financial interests in this manuscript.
Abstract	Objective: To investigate the relationship between maturation of the spheno-occipital synchondrosis (SOS) with cervical vertebrae (CVM), dental development of the mandibular canine (DI), chronologic age and intra-rater / inter-rater reliability. Materials and Methods: Seventy-seven subjects (42 females and 35 males) were randomly selected into six age groups from retrospective cone-beam computed tomograms: (1) 9 year old females, (2) 11-12 year old females, (3) 16-17 year old females, (4) 10-11 year old males, (5) 13-14 year old males and (6) 18-21 year old males. Spearman correlation coefficients between SOS, CVM, DI, and age group, along with tabulations of stages of SOS, CVM and age were evaluated separately for each gender. Results: SOS maturation was significantly and positively correlated with CVM and age group in both females and males (all r > 0.8). A weaker significant correlation coefficient was found between SOS maturation and DI for both females and males (r > 0.6). All males with fused SOS were in CVM stage 4 or later, while all females were in at least CVM stage 3. No subjects with open SOS were in the post-pubertal growth spurt age group and no subjects with closed SOS were in the pre-pubertal growth spurt age group. SOS maturation showed substantial and significant inter-rater and intra-rater reliability (kappa > 0.7). Conclusion: SOS stages are reliable and valid indicators of potential craniofacial growth and development and correlate with measures such as CVM.

Assistant Editor	Not Assigned
Key Words	Skeletal maturation, Spheno-occipital synchondrosis, Maturation indicators, Computed tomography, cone-beam, inter-rater reliability
Conflict of Interest	**I have no conflict of interest that I should disclose.**

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