

A Systematic Review of Methods to Determine Skeletal Maturation Based on Cervical Vertebrae

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Introduction: Since the determination of skeletal maturation by surveying concavity on lower surface of cervical vertebrae and evaluating shape of vertebrae is a subjective and quantitative study, this systematic review was performed to evaluate new quantitative and objective methods by using cervical vertebrae for determining skeletal maturation. **Material and Methods:** Related keywords were searched in Pubmed and Cochran database in order to find studies that were published in English from January 2000 to January 2019 and evaluated skeletal maturation based on cervical vertebrae by modern methods. Also, the references of the included studies were search for other related studies. **Results:** From overall 1371 titles, 27 were selected by initial screening. Evaluation of the full texts resulted in inclusion of 13 articles. Among articles included in this review, three studies used CBCT images and another studies used lateral cephalogram. One study performed evaluation cervical vertebrae in the axial view of CBCT images while another evaluation was on sagittal view. Most of the studies used a regression model in order to determine bone age of vertebrae and then compared it with skeletal age obtained from hand wrist radiography. **Conclusion:** As the methods and measurements were different in the included studies it was not possible to reach a decisive conclusion regarding method for determining skeletal age based on cervical vertebrae. It is suggested to use a combination of maturation signs along with development stages of cervical vertebrae in order to determine skeletal maturation until a quantitative and valid method is presented.

Keywords: Bone age; Cervical vertebrae; Skeletal age; Skeletal maturation.

Introduction

Evaluation of craniofacial development is a basic part of diagnosis in orthodontics, especially when growth modification or orthognathic surgery are considered as treatment plans (1). Use of an effective appliance for dentofacial structures is one of the most important treatment modalities for treatment of skeletal anomalies. Mechanism of orthopedic therapies mostly depends on maxillary and mandible growth and effectiveness of these devices depends on growth stage of the patient (2). Determination of a suitable time for treatment onset is as important as selection of treatment protocol. By beginning the treatment in the specific growth stage of each individual, it is expected to have the most suitable response in anterior-posterior, transversal and vertical dimensions with the least complications (3). The proper time for beginning orthopedic treatments has a close relationship with accelerated growth times. The best time for treatment of mandibular deficiency, is reported to be during pubertal growth spurt, while the suitable time for treatment of maxillary deficiency is considered before pubertal growth spurt (3, 4).

Secondary sexual characteristics, chronological age, dental development, height and weight are the most common items which are used for determining growth stages (5). Dental development markers are not valid predictor to determine maturity stage (7, 6). Because time could cause diversity among individuals and also because of individual differences in growth rate, time and duration, chronological age usually is not a good index for determining growth condition of one person (8). Including these indices in order to estimate time of puberty growth spurt needs more data. So usage of a valid biological index for determining maturity development in order to check possible orthopedic treatments are of great importance (9).

By using skeletal age instead of chronological age and other individual characteristics, one can decrease the effect of time on diversity and of environmental factors and personal variations on incidence of sexual characteristics. There are different methods for evaluation of the skeletal age and each of them involves different parts of skeleton; for example, some methods use hip bone, knee, hand wrist and cervical vertebrae for determining skeletal age (10).

Evaluating palm bones by hand wrist radiography and cervical vertebral maturation (CVM) by lateral cephalogram are the most common methods (11). According to study of Hagg and Taranger, there is a time correlation between different events in hand wrist bone and puberty growth spurt (12).

Cervical vertebrae are ossified and reshaped from onset of embryo and their transformation continues until the adulthood, so we can observe maturity changes of cervical vertebrae during this period (13). Told and Pyle (14), Lainer (15) and Taylor (16) measured dimensional changes of cervical vertebrae on lateral cephalogram during growth. Lamparski primary researches reported separate standards for cervical vertebral maturity in women and men that were observed by chronological age and skeletal maturity and was related to hand and wrist radiography. Shape and size changes of second to sixth cervical vertebrae were analyzed in this method (13). Hassel and Farman combined their observations from changes in skeletal maturity in radiographic images of the wrist and cervical vertebrae and summarized eleven groups of sesamoid maturation index (SMI) to six cervical vertebral maturation index (CVMI) (5). Franchi *et al.*, Confirmed six-stage CVM as index for evaluating mandibular growth in 24 patients with no history of orthodontics treatment (17). Baccetti *et al.*, introduced an advanced method for considering cervical vertebrae growth (9). Their study involved fewer cervical vertebrae (C2, C3, and C4) which are observable in commonly used lateral cephalometric radiography. In this visual analysis, growth stages of cervical vertebrae were assessed on this basis of the existence of concavity on the inferior margin of the second, the third and the fourth vertebrae and four trapezoidal, horizontal rectangles, vertical rectangle and square shapes of third and fourth vertebrae. Many researchers confirmed CVM as a valid and beneficial method for clinical assessments. This method makes clinicians abler to find the best time for growth modification in the patients. The most advantage of this method is that there is no need for extra radiation exposure since cervical vertebrae can be surveyed during Lateral cephalometric assessment (11, 18).

Based on systematic review done by Santiago *et al.* Application of CVMI for skeletal maturation assessment and evaluation of mandible growth maturation stage is a valid and precise method (19). However, evaluation of the concavity on cervical vertebrae inferior border and assessment of cervical vertebrae shape is mostly qualitative and subjective, and is prone to error. Gabriel *et al.* reported weak reliability of the method %50> inter-examiner agreement and about %62 intra-examiner agreement. Recently, some methods have been introduced to assess CVM by quantitative and methods. The purpose of this study was to find

the best and the most reliable methods for skeletal age assessment by systematically reviewing these quantitative methods.

Materials and Methods

Study design

This study was performed as systematic review of articles based on PRISMA 2010 to evaluate studies assessing skeletal age using modern methods of studying cervical vertebrae. This study included clinical studies that presented a quantitative, objective, practical and non-invasive method. Studies that evaluated skeletal age on the basis of qualitative characteristics or in people with certain conditions, such as metabolic and skeletal diseases, using growth-on-effective drugs and trauma to cervical vertebrae were excluded. Also the studies that introduced a quantitative method in order to evaluate maturation stages of a craniofacial component such as mandible or performed cervical vertebrae assessment by special software, excluded from the study. In vivo studies and case report study were also excluded from this systematic review.

Search Strategy

Electronic search was performed in PubMed and Cochran database, using following keywords:

("Cervical vertebral" or "cervical vertebrae") AND ("skeletal maturation" or "skeletal age" or "bone age") AND ("morphology" or "dimension" or "volume" or "new method" or "new version" or "formula" or "quantitative")

This search was performed in January-2019 and limited to studies published from January 2000 to January 2019 written in English. Finally, references of included articles were reviewed and each study that introduced a new method for evaluating cervical vertebrae skeletal age, was included in this review.

Study selection and data extraction

Two reviewer performed the review independently, disagreements were solved by discussion. After a complete search throughout databases, at first, preliminary screening was performed based on title and abstracts of articles, then full text of selected articles based on including and excluding criteria were investigated. Finally, new methods introduced for skeletal age assessment for orthopedic treatments based on cervical vertebrae were collected and considered.

The following have been extracted from the studies:

Purpose of study, population studied, age and number of cases, method, reviewed parameters, radiography modality and conclusion.

The methods presented in these studies were not compared to each other and were simply described in a qualitative manner

Table 1. Summary of the included studies

Author	Measuring instruments	Population	Number of participants	Age	Methodology	Selected parameters	Modality of radiology	Outcome
Mito <i>et al.</i> 2002	Assessment of skeletal maturation by lateral cephalogram	Japan	176 girls 66 girls	7-14.9 years old 8-13.9 years old	To find correlation between bone age of wrist and cervical vertebral bone age	Dimensions of third and fourth CV	Lateral cephalogram / Hand wrist radiography	CV skeletal age is as valid as bone age of wrist bones
Roman <i>et al.</i> 2002	Assessment of skeletal maturation by lateral cephalogram	Spain	530 girls 428 boys	11.5 years old 11.6 years old	Measuring wrist skeletal age and cervical vertebral bone age using shape and height of vertebrae	Shape and dimensions of all cervical vertebrae	Lateral cephalogram / Hand wrist radiography	There is an exact correlation between CV growth stage classification and skeletal age of wrist
Caldas <i>et al.</i> 2007	Estimation of skeletal age using the Cervical Vertebral dimensions	Brazil	183 women 164 men	7-15.9 Years old	Measuring wrist skeletal age and cervical vertebral bone age using dimensions of vertebrae	Dimensions of second and third CV	Lateral cephalogram/ Hand wrist radiography	Skeletal age measured by vertebrae had no Significant difference with bone age of hand wrist in both genders
Caldas <i>et al.</i> 2007	Assessment of validity of Mitto's formula	Brazil	128 girls 110 boys	7-15.9 years old	Measuring cervical vertebral skeletal age and comparing it by bone hand wrist bone age and chronological age	Dimensions of third and fourth CV	Lateral cephalogram/ Hand wrist radiography	The formula is useful only for assessment of girls' skeletal maturation a
Chen <i>et al.</i> 2008	Assessment of skeletal maturation by lateral cephalogram	China	55 girls 32 boys	8-18 years old	Samples were classified to 11 growth groups on fish man's skeletal maturation index. Morphology cervical vertebral were analyzed in 11 groups.	Dimensions of second third and fourth CV	Lateral cephalogram/ Hand wrist radiography	four growth stages of cervical vertebral were achieved using dimensions of vertebrae
Chatzigianni <i>et al.</i> 2009	To find correlation of cervical vertebrae shape and hand wrist bone age	Greece	58 women 40 men	-17.7 8.1 Years old	Shape pattern of cervical vertebral were evaluated for predicating skeletal maturation.	Shape of first four cervical vertebral	Lateral cephalogram/ Hand wrist radiography	The shape of cervical vertebral cannot estimate skeletal age better than chronological age.
Alhadlaq <i>et al.</i> 2012	To assess validity of statistical model for estimating skeletal age in the growing boys	Saudi Arabia	122 boy	10-15 years old	To find correlation between bone age of wrist and cervical vertebral bone age.	Dimensions of second, third, fourth CV	Lateral cephalogram/ Hand wrist radiography	There was high correlation between cervical vertebral skeletal age and hand wrist bone age.
Beit <i>et al.</i> 2013	To assess agreement	Swiss	378 women 352 men	6-18 years old	To find correlation among bone age of wrist	Dimensions of third and	Lateral cephalogram/	There was a moderate

	between skeletal age of wrist and skeletal age of CV				, cervical vertebral bone age and chronological age before and after growth mutation of maturation	fourth CV	Hand wrist radiography	correlation among skeletal ages in both genders which was weaker than relationship between chronological age and hand wrist bone age.
Yang et al. 2014	To Introduce a model to estimate skeletal age by Axial cervical vertebrae	Korea	74 women 47 men	14/6 Years Old 14 years Old	Considering different sections of CV in axial view and several regression models were introduced: each of them was assessed toward skeletal age of wrist and the most valid model was introduced.	Axial cervical vertebrae (ACV) dimensions of CV in axial view	CBCT Hand wrist radiography	ACV is a biological strong marker for assessing skeletal maturation
Byun et al. 2015	To assess correlation of skeletal maturation with parameters from spinous process and a second, third and fourth CV body	Korea	74 girls	6-18 years old	To Determine parameters in Cervical vertebrae and odontoid process for introducing regression formula	Dimensions of second, third, fourth Cervical vertebrae odontoid process	CBCT/ Hand wrist radiography	six parameters can be used to calculate multiple regression models with high correlation
Choi et al. 2016	To determine correlation of volumetric parameters of second, third, fourth CV with skeletal maturation	Japan	54 girls 48 boy	5-18 years old	To calculate correlation between bone age of wrist and cervical vertebral bone age.	Volumetric parameters of 2 nd , 3 rd and 4 th Cervical Vertebrae	CBCT/ Hand wrist radiography	Volumetric parameters of Cervical vertebrae have high correlation with bone age of wrist.
Kamar et al. 2016	To assess reliability and validity of formula introduced by Mitto in cases of north India	North India	30 men 30 women	8-16 years old	Measuring bone age by wrist bones and comparing with skeletal age of CV from Mitto formula	Dimensions of second, third, fourth CV	Lateral cephalogram/ Hand wrist radiography	Mitto's formula is valid only for women in north India and for estimating skeletal age of men
Turkoz et al. 2017	To introduce a formula to measure skeletal age of Cervical Vertebrae	Turkey	167 women 157 men	17.2 7.3 years old	To find correlation between bone age of wrist and cervical vertebral bone age.	Dimensions of third and fourth Cervical Vertebrae	Lateral cephalogram Hand wrist radiography	The skeletal age calculated based on Cervical Vertebrae was valid for woman and men

Results

Search flowchart is shown in Figure 1. During electronic search, 1371 article titles were found that decreased to 27 after studying abstract and title. Finally, considering including and excluding criteria 10 articles were admitted to the study (1, 20- 24, 27- 29, 31). After reviewing references of selected articles, 3 more articles were eligible for study (29-31). So 13 articles were selected in order to assess skeletal age for this systematic review. In all studies a formula has been introduced by doing the regression analysis on the various dimensions of cervical vertebrae. The age which is calculated by this formula has been compared with hand wrist bone age and their correlation has been evaluated. The method used in all studies is almost the same, with only some minor differences. These differences are the use of various dimensions, different cervical vertebrae and different views of radiographic images. These details are shown in Table 1 and discussed in discussion. Three studies (1, 21, 24) used CBCT in order to survey cervical vertebrae dimensions and other studies performed this assessment on lateral cephalogram. The samples of two studies (21,29) were only girls and one study (23) was only boys. Only one study (22) did not find any correlation between hand wrist bone age and skeletal age. Yang and colleagues' study (1) was the only one that used axial dimensions of cervical vertebrae for determining skeletal maturation. Other studies assessed cervical vertebrae in lateral view.

Discussion

Many methods were described and assessed for determining skeletal age of bone. Hand wrist radiography is considered as gold standard method to determine skeletal age for orthopedic treatments (32-33). Because additional exposure is imposed to patient by hand wrist radiography, different methods have been introduced to assess skeletal age using cervical vertebrae. This method is popular because cervical vertebrae assessment can be done on lateral cephalogram which is used routinely in diagnosis process of orthodontics treatment (9). Recently, studies introduce new versions of cervical vertebral evaluation for objective assessment of skeletal age. In all studies an attempt has been made to find a formula based on various dimensions of vertebrae which can estimate skeletal age. So cannot call these ways as separate methods but they are different uses of one general method. These different ways are discussed under several subheadings.

A-conical-beam CT in lateral view

Three articles (1, 21, 24) that were included in to this review used conical-beam CT scan for assessing cervical vertebrae dimensions. This is because growth changes happen in all three dimensions in human while lateral cephalogram is a two-dimensional image and it can be misleading to estimate skeletal age. These studies could find a regression model for determining skeletal age. Byun *et al.*, (21) proposed a model for determining skeletal maturation using second, third and fourth cervical vertebrae. This is the only study that has used odontoid process for skeletal age assessment. This process can only be detected in 3D images and finding a suitable cross-section for observing and measuring dimensions of Odontoid process accurately is time-consuming. Another disadvantage of this study is that this model is limited only to girls.

Disadvantage of using CBCT images only for skeletal age assessment is additional radiation on patient that violates ALARA (as low as reasonably achievable) principle. If this radiography is provided as low dose and be the only radiography for patient and include panoramic and lateral cephalometric view, it is proposed to use this method for estimating skeletal age. Also when CBCT is prescribed for patients with impacted tooth or craniofacial deformity, skeletal age of cervical vertebrae is determined by this method.

B-conical-beam CT in axial view

In one study (1), certain dimensions of cervical vertebrae were assessed in axial view of CBCT.

Based on these dimensions and using regression analysis, a formula was presented to calculate cervical bone age. Although, the results of this study point to strong correlation between skeletal age obtained from this formula and skeletal age of wrist bones, but this method is complex and time-consuming and it is difficult to find suitable region of interest to find suitable parameters. It seems studying skeletal maturation by this method is no better than studying lateral view of cervical vertebrae and there is no logical reason for using this method in clinical cases. Because the lateral view is shown on lateral cephalometry and did not need additional radiography, but the axial view needs CBCT images. Even though the skeletal age estimation on lateral view can be useful, the extra radiography is not rational.

C-Lateral cephalogram

Lateral cephalogram is commonly used in studies (20, 22, 23, 27-31).



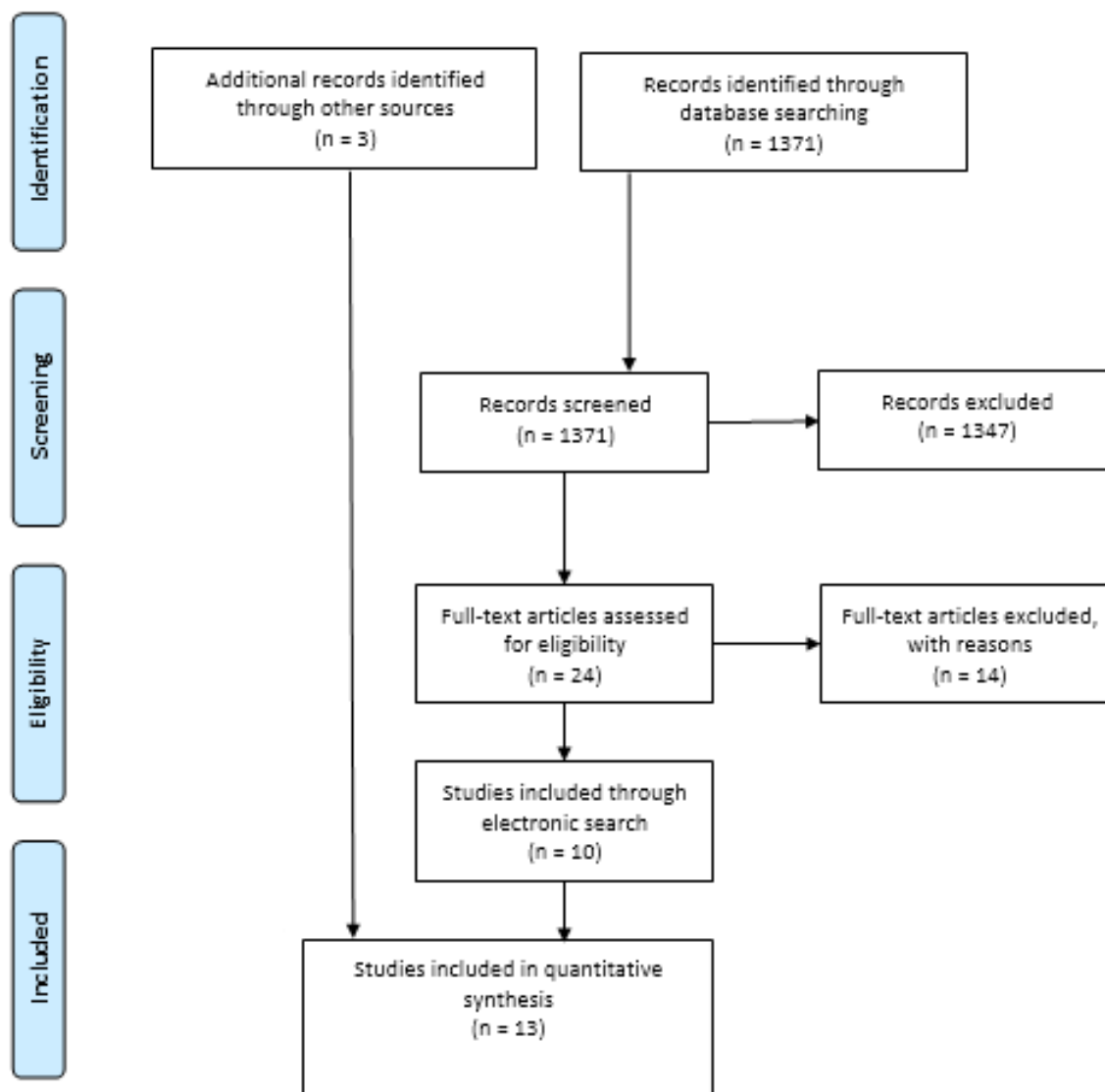


Figure 1. Search strategy

Mito *et al.*, (29) succeeded in making a model for determining skeletal maturation using certain dimension of second, third and fourth cervical vertebrae. He found that cervical vertebral skeletal age from this model is as valid as bone age of wrist bones. Calculating the dimensions of the vertebrae on lateral cephalometry is relatively simple and accurate. It seems that this formula can be used to determine the skeletal maturation in the Japanese population.

Kumar *et al.* considered validity of formula introduced in the study of Mito *et al.* (29) and used it for determining skeletal age of women and men in an Indian population. Although Mito's

formula has been achieved from a different race, but it can be used for skeletal age estimation of women in north India. This can prove that lateral dimension of cervical vertebrae are the same between different races in one gender but there is no similarity between the two genders and more studies are needed for a regression model for men.

Various dimensions of different vertebrae

The anterior height and anterior-posterior length of third and fourth cervical vertebrae were used for introducing regression model in two studies (23-31). While Mito *et al.* (29) used posterior height of forth cervical vertebrae in order to present

formula, other study (25) used chronological age and height of third and fourth cervical vertebrae in the regression model. One advantage of this study is that it's easier to calculate skeletal age based on formula introduced. Computing height of third and fourth cervical vertebrae is easier than other dimensions of cervical vertebrae. Since skeletal age obtained from formula of these studies has acceptable high correlation with skeletal age of wrist, therefore usage of fewer parameter formulas that are computed easily is better for clinical work. This reduced the probability of measuring errors and increase in speed of skeletal age determination.

Roman *et al.* (30) used growth stages of cervical vertebrae on basis of height, shape and concavity of lower border instead of exact dimensions of cervical vertebrae in regression formula. One disadvantage of this method is that it is dependent on complete knowledge of three classifications of cervical vertebrae in former studies for computing skeletal age from this formula. On the other hand, determining growth stages of cervical vertebrae on height, shape and lower border concavity is a subjective and qualitative judgment that has repeatability. This subject can cause a doubt about accuracy of number obtained from estimation formula of skeletal age. In one study (27), concavity degree of second cervical vertebrae is used in regression model for determining skeletal age in addition to anterior-posterior height and length of fourth cervical vertebrae and anterior-posterior height of third cervical vertebrae. Unlike the rest, this study presented only one gender-free formula and defined one four- stage classification for cervical vertebrae growth on basis of numbers obtained from this formula. One advantage of this study is its longitudinal nature: this means that annual Radiography of lateral cephalometry and hand wrist of cases were provided for six years. This increases accuracy of formula that this study introduced.

Conclusion

Introducing different methods and formulas on dissimilar parameters in studies prevent chance of decisive conclusion about one method for determining skeletal age on cervical vertebrae. Although these methods are interesting but their reliability and validity should be tested. Due to different growth characteristics between different races and so between two genders, performing studies with adequate sample size and using simple parameters on conventional radiographic images for orthodontic treatment is required for each community.

It is suggested to use maturation markers such as height spurt, appearance of sexual characteristics and qualitative assessment of cervical vertebrae until a valid, practical and repeatable method is introduced in order to determine skeletal maturation.

Conflict of Interest: 'None declared'.

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