

# Evaluation and development of a bone age assessment method in patients with Down syndrome

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## ABSTRACT

The objective of this paper was to evaluate the applicability of the method developed by Caldas to measure the vertebral bone age of Brazilians suffering from Down syndrome. A database comprised of 57 case records of individuals with this syndrome, both male and female, with ages ranging between 5 and 18 years, was used for this purpose. These records had lateral cephalometric radiographs and radiographs of hand and wrist, all of which had been obtained on the same date. There were 48 other records of individuals who did not suffer from Down syndrome. The Tanner and Whitehouse (TW3) method was used to perform the hand and wrist radiographs for obtaining bone age. The Caldas method was employed on the lateral cephalometric radiographs in order to obtain the vertebral bone age. From the information acquired on bone age, vertebral bone age and chronological age, it could be concluded that there is a statistically significant difference between the three ages for both the male and the female control group and for the female Down syndrome group. Therefore, this method was employed only on male Down syndrome individuals. Based on the results, a formula was devel-

oped to obtain the bone age for Down syndrome individuals.

## DESCRIPTORS

Down syndrome. Bone development. Cervical vertebrae. Growth. Radiology.

The Down syndrome is characterized by mental deficiency and innumerable physical anomalies caused by chromosome 21 trissomy. In 1866, Langdon Down first described the characteristics of individuals with chromosome 21 trissomy and named the individuals with this anomaly, Mongolian idiots. This term soon came into disuse, following a recommendation by the World Health Organization (WHO). It was later renamed Down Syndrome.<sup>3</sup>

In his study, Santos (2007) used 85 X-rays of 52 males and 33 females, all of them suffering from Down syndrome.<sup>6</sup> He evaluated the Greulich and Pyle (1959), the Eklöf and Ringertz (1967) and the Tanner and Whitehouse (1983) methods in order to evaluate how accurate they were in determining chronological age in Down syndrome individuals aged between 61 and 180 months. Evaluations were made using hand

and wrist X-rays.<sup>4,7,9</sup> According to the research conducted by Santos, the TW3 and the Greulich and Pyle methods came closest to determining chronological ages, followed by the Eklöf and Ringertz approach.

Mito *et al.* (2002) also devised a new method to evaluate bone maturation specifically, using lateral cephalometric X-rays.<sup>5</sup> They stated that the correlation between the bone age obtained by the hand and wrist radiograms and the cervical vertebrae maturation was statistically significant. The difference between the bone ages was small and statistically insignificant, when compared with chronological age. It was concluded that, if the objective is to obtain bone age through the cervical vertebrae, a study analyzing details of cephalometric X-rays is viable.

Caldas (2007) evaluated the applicability of the bone age analysis method of the cervical vertebrae developed by Mito *et al.* (2002) in females of Japanese descent in the Brazilian population.<sup>1</sup> He also devised two new methods for Brazilian girls and boys, designed to determine bone maturation of the cervical vertebrae in a straightforward manner in lateral cephalometric X-rays. Bone age was used as the gold standard to determine the reliability of the Mito method. The results showed that there was a statistically significant difference between the vertebral and the chronological age and between the bone age and the chronological age for the female population. The devising of a formula for Brazilian boys and girls derived from an objective analysis of the bone maturation of the cervical vertebrae revealed that there is no statistical difference between the bone age of the cervical vertebrae, bone age and chronological age. Therefore, it was concluded that the Mito method can be applied only to Brazilian girls. In addition, the derived formulas for objective evaluation of the bone age of the cervical vertebrae can be applied to Brazilian boys and girls in an efficient manner.

## MATERIAL AND METHOD

After approval by the Research Ethics Committee, under number 018/2007-PH/CEP, 105 cases were selected for study from the files of the Discipline of Radiology of the Department of Diagnosis and Surgery of the São José dos Campos School of Dentistry, Universidade Estadual Paulista "Júlio de Mesquita Filho"-UNESP. These cases were divided into 2 groups:

- Down Group: 57 cases of Down syndrome, 23 females and 34 males.
- Control Group: 48 cases of non-Down syndrome, 24 females and 24 males.

Both groups were comprised of individuals with ages ranging from 5 to 18 years who had lateral cephalometric X-rays and hand and wrist X-rays obtained on the same dates.

Lateral cephalometric X-rays were used to analyze the vertebral bone age of the individuals according to the method proposed by Caldas, used on both female and male Brazilian individuals, who did not suffer from Down syndrome.

This method consists of applying one formula for the male and another one for the female group, both of which use the mathematical ratio obtained by measuring the variables of the bodies of cervical vertebrae C3 and C4 for obtaining the bone vertebral age of each individual.

- Female vertebral bone age =  $1.3523 + 6.7691 \times \text{AH3/AP3} + 8.6408 \times \text{AH4/AP4}$
- Male vertebral bone age =  $1.4892 + 11.3736 \times \text{AH3/AP3} + 4.8726 \times \text{H4/AP4}$

The following variables were obtained for both cervical vertebrae:

- (AH) anterior height of the vertebral body,
- (AP) lateral anterior-posterior of the vertebral body and
- (H) the height of the vertebral body,
- (PH) posterior height of the vertebral body.

These variables were named AH3, AP3, H3, PH 3 when referring to the cervical vertebra C3, and AH4, AP4, H4, PH 4 when referring to cervical vertebra C4 (Figure 1).

The C3 and C4 vertebral segments were scratched manually and measured by a millimeter ruler and a digital caliper. Two repetitions of the scratch were made after at least a week and in a random manner. The intention was to obtain an average between the measurements made in each radiographic incidence. The segments were called vertebral age 1 and 2 for the Down syndrome individuals. The method proposed by Tanner and Whitehouse (2003), TW3, was used to obtain bone age using hand and wrist X-rays of the same individuals.<sup>10</sup> All the measurements were made by only one examiner, previously trained and author of this paper.

## RESULTS

In this study, the authors chose non-parametric statistical tests. These tests do not compare groups by the average but by the position of the data. Even though this method was not used to make the com-

parisons, descriptive statistics was used to allow us to understand the results, which can be seen in non-Down syndrome individuals. In this group, we observed that there were significant statistical differences for both male and female individuals, among the different ages in overall manner. We used the Wilcoxon test to compare all the ages in pairs in order to discover precisely where the difference occurred (Table 1).

Regarding the p-values comparatively, a significant statistical difference was observed between vertebral bone age, bone age, and chronological age. In the sample studied, the vertebral bone age for both male and female individuals presented higher values than the other ages.

Below, we will show the results for the comparison made among all the ages for the group of Down syndrome individuals. In this group, significant statistical differences could be noticed among the ages for the female individuals (Table 2).

According to the p-values observed, the differences occurring between vertebral age 2 and vertebral

age 1 were revealed. Vertebral age 2 was that which had the highest values when compared to the other ages. Thus, in this sample of the female group of Down syndrome individuals, the formula designed by Caldas was not applied (Figures 2 and 3).

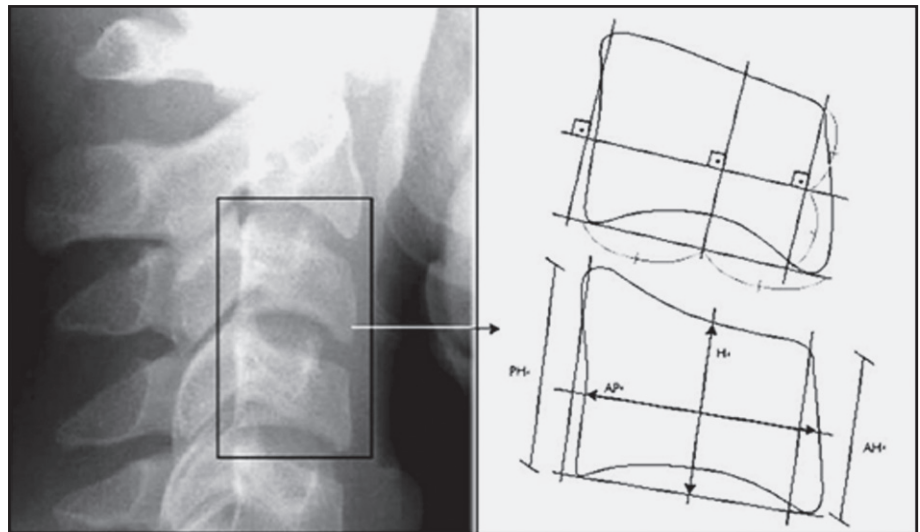
Significant statistical differences among the ages were not observed for the Down syndrome individuals of the male group, thus allowing the formula by Caldas to be applied.

Based on these results, we can formulate a description of the method for bone age in Down syndrome individuals.

- Female vertebral bone age =  $\text{Óssea} = -2.364 + 1.441 - H3/R^2 = 84.2\%$
- Male vertebral bone age =  $\text{Óssea} = -1.004 + 0.759 \times H3 + 0.580 \times AH4/R^2 = 84.1\%$

The results obtained made it possible to prove that the Caldas<sup>1</sup> formula created for Brazilian boys and girls cannot be applied to the female Down syndrome individuals of the studied sample. Thus, two new formulas were devised using the statistical method, one for women and another for men.

**Figure 1** - Body of cervical vertebrae C3 and C4 measured by means of lateral cephalometric X-rays: (AH) anterior height of the vertebral body, (AP) lateral anterior-posterior of the vertebral body and (H) height of the vertebral body, (PH) posterior height of the vertebral body.

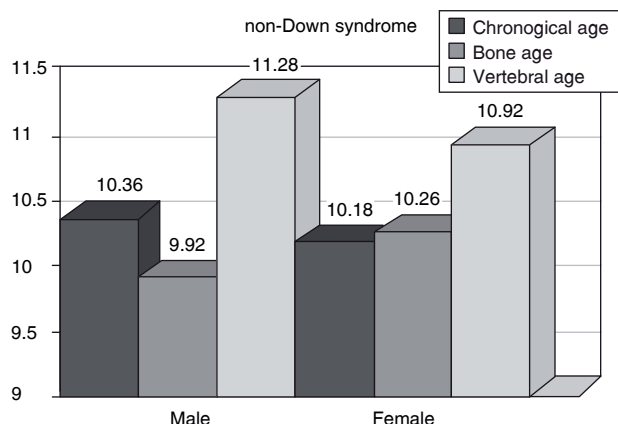


**Table 1** - p-values for non-Down syndrome individuals, chronological, bone and vertebral age for male and female.

	Non-Down Syndrome	Chronological	Bone
Male	Bone	0.367	
	Vertebral	0.042	< 0.001
Female	Bone	0.788	
	Vertebral	0.048	0.037

**Table 2** - p-values for Down syndrome individuals, chronological, bone, vertebral, and vertebral 1 age for female individuals.

	Down Syndrome	Chronological	Bone	Vertebral 1
Female	Bone	0.308		
	Vertebral	0.287	0.114	
	Vertebral	0.073	0.039	0.046



**Figure 2** - Comparison of the chronological, vertebral bone and bone age for male and female non-Down syndrome individuals.

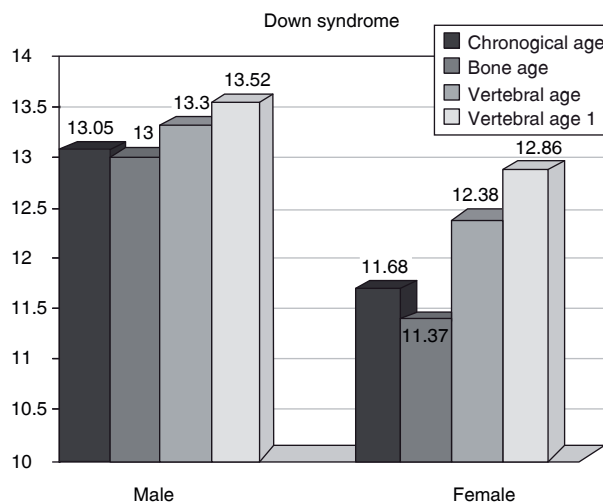
We determined that both models were significant and very explanatory. This means that they were well correlated with reference to the value of  $R^2$ . We determined that the model is applicable, because there is no significant statistical difference between the bone age value (obtained by TW3) and the final bone age calculated through the model developed in this study.

In this context, it is worth mentioning that there is a difference between the final bone ages and the vertebral bone age only for the female group. There is no specific method for determining the bone age index of Down syndrome individuals.

## DISCUSSION

After applying three methods to estimate the bone age of Down syndrome individuals, Santos (2007) noticed that there were statistical differences only using the Eklöf and Ringertz method, in referring to sex and chronological age.<sup>6</sup> The TW3<sup>1</sup> and the Greulich and Pyle methods were statistically the same. In relation to the Eklöf and Ringertz method in Down syndrome individuals, Sannomiya *et al.* (1998) made the same observation, but did not find significant statistical differences among the sexes.<sup>8</sup>

Calles *et al.* (2004) observed that the Greulich and Pyle method is used for Down syndrome individuals, but it is not recommended to determine chronological ages between 10 and 13 years old for the female group and between 13 and 15 years old for the male group.<sup>2</sup> They concluded that there was a significant statistical difference in these age groups, when analyzing the chronological and bone ages. Sannomiya *et*



**Figure 3** - Comparison of the chronological, vertebral bone 1 and bone 1 age in male and female Down syndrome individuals.

*al.* (2005) came to the same conclusion. This is why the authors preferred to adopt the TW3 method in this study, and also because it is more updated.<sup>7</sup>

Mito *et al.* (2002) created a formula using lateral cephalometric X-rays of Japanese people with the measurements of vertebral bodies C3 and C4.. The formula obtains bone age according to the cervical vertebrae of these individuals.<sup>5</sup> They concluded that this result is reliable when compared to those obtained by hand and wrists X-rays using the TW2 method. In 2007, Caldas applied the Mito *et al.* (2002) formula in female and male Brazilians, and observed that it was only applicable to Brazilian girls.<sup>1</sup> With this in mind, he created a formula to analyze the skeleton maturation of the cervical vertebrae in Brazilian boys and girls.

In this study, the authors applied the Caldas formula created for female and male Brazilians to non-Down syndrome individuals, and the result was different from the author's, because the formula created was not statistically significant for the sample studied. Moreover, when applied to the Down syndrome individuals sample, it was statistically significant only for the male but not for the female group.

## CONCLUDING REMARKS

Based on the findings of this study, some important considerations can be made:

- The method proposed by Caldas, when applied to our samples of female and male non-Down syndrome individuals, showed results with a statistically significant difference between bone, vertebral bone, and chronological age.

- Thus, a similar method of evaluation was developed for bone and vertebral bone age for both male and female Down syndrome individuals.

## RESUMO

### Avaliação e desenvolvimento de um método de avaliação de idade óssea em portadores de síndrome de Down

O objetivo deste trabalho foi avaliar a aplicabilidade do método desenvolvido por Caldas para medir a idade óssea vertebral em brasileiros, quando empregado em indivíduos portadores da síndrome de Down. Foram estudados 57 prontuários de indivíduos com síndrome de Down, de ambos os sexos, com idades variando entre 5 e 18 anos. Esses prontuários continham radiografias cefalométricas laterais e radiografias de mão e punho, obtidas no mesmo dia, e também foram avaliados 48 prontuários de indivíduos não portadores de síndrome de Down. Para as radiografias de mão e punho, o método de Tanner e Whitehouse (TW3) foi usado para que pudéssemos obter a idade óssea. O método de Caldas foi empregado nas radiografias cefalométricas laterais, e assim obtivemos a idade óssea vertebral. A partir das informações sobre a idade óssea, idade óssea vertebral e idade cronológica, foi verificada uma diferença estatisticamente significativa entre as três faixas etárias para ambos os sexos do grupo controle e grupo com síndrome de Down do sexo feminino. Portanto, este método foi aplicável apenas em indivíduos do sexo masculino portadores da síndrome de Down. Com base nos resultados, uma fórmula para obtenção da idade óssea de indivíduos com síndrome de Down foi desenvolvida.

## DESCRIPTORES

Síndrome de Down. Desenvolvimento ósseo. Vértebras cervicais. Crescimento. Radiologia. ■

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