An Evaluation of the Effects of Elevated Body Mass Index on Skeletal Age

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Research Article

Keywords: chronological age (CA), pediatric patients, BMI, skeletal age (SA)

Posted Date: September 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-888046/v1

Abstract

Background

Many treatment decisions in children's Orthopaedics are based on age. This study determined whether a discrepancy between chronological age (CA) and skeletal age (SA) is dependent on BMI and if overweight or obese children would have an advanced SA.

Materials and Methods

120 children between ages 8-17 with an adequate hand radiograph and a correlating BMI were enrolled by retrospective chart review. Stratification based on age, sex, ethnicity, and BMI percentile was performed. For each age group, 6 males and 6 females were selected with 50% of each group having an elevated BMI. Two blinded physicians independently evaluated hand radiographs and recorded the SA. Statistical analyses evaluated inter-rater reliability and any discrepancy between groups.

Results

The final statistical analysis included 96 children. The Intraclass Correlation Coefficient for SA determined by the two reviewers was excellent at 0.95. A difference of 13 months was found between CA and SA in the elevated BMI cohort versus the non-elevated BMI cohort, ($p<0.001$). No significant difference was seen between CA and SA for the non-elevated cohort ($p=0.72$), while matching for age and sex.

Conclusion

Chronological age and skeletal age are not always equivalent especially in pediatric patients who are overweight or obese.

Introduction

The prevalence of children above the established normal or healthy weight has risen since the 1980's, resulting in worldwide health challenges in low, medium, and high-income countries[1–3]. In the United States, the Centers for Disease Control and Prevention have established the following guidelines for determining appropriate body mass index (BMI) in the pediatric population: underweight – less than 5th percentile, normal weight – 5th to less than 85th percentile, overweight – at the 85th percentile to below the 95th percentile, obese – 95th percentile or greater when compared to the child's peers based on sex and age[4]. Obesity is not only a well-established risk factor for multiple metabolic diseases but also a proven risk factor for pathologies encountered in pediatric orthopaedics such as Blount disease, slipped capital femoral epiphysis, fracture, knee pain, mobility impairments, and lower extremity malalignment[5–8]. Furthermore, when caring for children with orthopedic conditions, treatment decisions are frequently based on the child's chronological and skeletal age[5,9–10]. Surgical treatment for correction of coronal

plane limb deformity is one such example. Despite extensive research and review on the topics of childhood obesity, there is a paucity of orthopaedic literature describing the effects of an elevated body mass index (BMI) on skeletal age.

In the United States, over three-fourths of pediatric radiologists and endocrinologists prefer using the Greulich and Pyle method to assess bone age for purposes of assessing growth in children and their future height potential[11]. The purpose of this study was to determine if a discrepancy between chronological age (CA) and skeletal age (SA) exists when comparing hand radiographs between children with an elevated BMI and non-elevated BMI. We hypothesized that children with both overweight and obese children would have an advanced SA compared to children with a non-elevated BMI, a normal, healthy weight.

Materials And Methods

Prior to the initiation of this study, the Institutional Review Board of Children's Hospital of Orange County reviewed this study and waived ethical approval and need of informed consent due to the retrospective nature of the study. All methods were carried out in accordance with relevant guidelines and regulations.

A retrospective chart review of children between the ages of 8–17 who were seen at our institution was performed. Children were enrolled and stratified based on age, sex, race, and body mass index (BMI) percentile. Eligible children were identified by searching for all patients in the hospital's picture archiving and communication system (PACS) with a complete left-hand radiograph for each included age group. BMI for children with adequate hand radiographs were then acquired from the electronic medical record. Children were included if the recorded BMI was within 5 months of the hand radiograph study date. Evidence of the complete hand with distal forearm epiphyses was necessary for inclusion. The medical record was then reviewed for any diagnosis of developmental pathology and/or prescribed medications that affect bone development. If found, those children were excluded from the study. In addition, children with inadequate radiographs due to quality or hand deformities that prevented accurate aging were excluded.

Beginning with the most recent radiograph, all hand radiographs were reviewed until a child in each group had been identified according to the selection criteria. BMI percentile, weight in kg, and height in centimeters was tabulated under a de-identified, pre-assigned, random subject number. Twelve patients per age group, 6 males and 6 females, were identified. Each of these groups were divided by BMI, 3 patients with a BMI of < 85th percentile (normal BMI) and 3 patients of a BMI of ≥ 85th percentile (elevated BMI) (Fig. 1). In incomplete groups, a patient meeting the above criteria with an adequate right-hand radiograph were used. In the blinded analysis, a mirror image of the right-hand radiograph (n = 12, 10%) was used as has been supported in prior publication[12].

Hand radiographs were evaluated by 2 blinded physicians, a fellowship-trained pediatric orthopaedic surgeon and a fellowship-trained pediatric radiologist. Each physician independently determined the

skeletal age of each hand radiograph utilizing the Greulich and Pyle atlas (Fig. 2). The skeletal age values from each film reader were averaged and subtracted from the child's chronological age.

Reliability of SA assessment by the 2 raters was analyzed utilizing intraclass correlation coefficient (ICC) with a two-way random, single measure, absolute agreement model. The mean absolute error (MAE) and the standard error of measurement (SEM) were also calculated. Repeated measures ANOVA with the between subjects factor of BMI group (elevated BMI vs normal BMI) was utilized to compare average SA versus CA. This was followed by within subjects analysis to evaluate the difference between SA and CA for each BMI group. Repeated measures ANOVA was also utilized to evaluate differences between SA and CA with the between subjects' factor of ethnicity. Data was checked for normality and homogeneity of variance assumptions prior to performing the ANOVA. Alpha was set at $p < 0.05$ to declare significance. Statistical analysis was performed using SPSS v.25.

Code availability

IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

Results

120 children were enrolled with an Intraclass Correlation Coefficient (ICC) of 0.904. Children whose estimated SA by the physicians varied by greater than one year were excluded from the analysis (N = 24), raising the ICC to 0.95 (95% confidence interval, 0.916 to 0.972). The mean absolute error was 0.8 with a standard error of measurement of 0.58.

The average SA for the remaining children (N = 96) was used in the analysis. The difference between CA and SA in the elevated BMI versus normal BMI cohort was significantly different (Table 1, $p < 0.001$). Overweight children were found to have an advanced SA of 13 months ($p < 0.001$).

Table 1
Average and standard deviation of CA and SA based on BMI group. Significance (p-value < 0.05) for the between subjects analysis (discrepancy of CA vs SA between the BMI groups) and within subjects analysis (discrepancy of CA vs SA within each BMI group) are presented

	Normal BMI (n = 44)	Elevated BMI (n = 52)	Between subjects p-value
CA	12.9 ± 3	12.8 ± 3	< 0.001
SA	13.1 ± 3	14.2 ± 3	
Within subjects p- value	0.72	< 0.001	

There was no significant difference seen between CA and SA for the non-overweight cohort ($p = 0.72$). No significant difference was seen based on sex (Fig. 3).

No significant difference was seen based on ethnicity; however, as this was not a primary focus of the study, we find it underpowered to draw any sound conclusions based on ethnicity.

Discussion

In recent years, there has been some controversy regarding the use of BMI as an indicator of good or poor health. BMI is obtained using measurable objectives, weight and height. In some persons, BMI may be an inadequate measure of health as it does not always accurately measure body composition. However, BMI can be used as a measure of excess weight, and it has been noted that children with an elevated BMI are at risk of obesity in adulthood and various metabolic diseases. Unlike adult BMI, children's BMI is conveyed over wide percentile ranges for each age and sex because a child's height and weight are not changing proportionally during the various growth stages[13]. Oh et al. studied various factors affecting bone age and found that children with increased waist circumference also had advanced skeletal age[14]. Another large-scale study reported that increased BMI (greater than or equal to 85th percentile) had a high association with increased body fat percentage rather than lean mass in the pediatric population compared to those with a lower BMI, and therefore, BMI could be a useful screening tool for obesity, which in turn can affect skeletal age[15].

From a current consecutive cohort of orthopaedic patients at our facility we report a significantly greater discrepancy (average 13 months) between CA and SA in overweight and obese children when compared to non-overweight children of the same age and sex (no discrepancy) when evaluating hand radiographs with the Greulich and Pyle Atlas. Skeletal age discrepancy decreased as chronological age increased for overweight females, as noted in a previous study[16].

In a retrospective study, Mack et al. examined skeletal maturation in orthodontic patients via analysis of cervical radiographs and dental age as a function of BMI percentile. Interestingly, they found both cervical vertebral stage and dental age to be more advanced (relative to chronological age) in subjects with increased BMI percentile[9]. In a similarly designed study, Akridge et al. reported a trend in accelerated SA in obese children as compared to age-matched cohorts. They found no overall statistically significant difference[16]. Of note, Akridge et al. utilized a single observer with Fishman's hand-wrist analysis, contrary to our use of two blinded observers using the Greulich and Pyle method. There have been other case reports of advanced skeletal age in obese children, one in particular by Caffey in 1978, of a 2-year-old obese boy with a SA approximately three times his CA[17].

A discrepancy between CA and SA has been seen among particular ethnicities. In a design similar to this current study, Ontell et al. found SA to be statistically significantly more advanced than CA in African American girls, Hispanic girls, Asian boys, and Hispanic boys. Of interest, this relationship was the most profound in late childhood to adolescence[18]. The authors however did not control for BMI, a potentially confounding variable in the study.

Another factor that may be taken into consideration when studying the variations between CA and SA is growth velocity. In a study done by De Simone et al, results showed that growth velocity varies between obese and non-obese children during the various pubertal stages. Obese children presented with increased SA earlier in life[19].

A defined biochemical pathway establishing between obesity and advanced SA has not yet been identified, however a generalized pathway has been proposed. Klein et al. found leptin levels in obese children with advanced SA to be correlated. Further, this level of leptin was significantly higher in the obese children than in the non-obese children. The authors go on to suggest that leptin may be responsible for the earlier onset of puberty and advanced skeletal age in obese children. They propose that leptin may affect the hypothalamic-pituitary axis by increasing LH and FSH directly at the pituitary, or possibly influencing the axis upstream at the hypothalamus[10]. Both in vitro and in vivo studies indicated that leptin can also have direct effect on osteoblast proliferation and differentiation and inhibit osteoclast formation which can account for increased bone growth and growth plate maturation[20–21]. Elevated levels of insulin are also thought to be implicated with advanced SA in obese children. In a cohort of 74 overweight and obese children 4 to 13 years evaluated by Pinhas-Hamiel et al., hyperinsulinemia was associated with a 6.8-fold increased risk for advanced SA, independent of the degree of obesity[22]. Oh et al. also found that obese children with metabolic syndrome were more likely to have advanced skeletal age compared to obese children without metabolic syndrome further indicating hormonal implications on bone maturation[14].

Despite present literature, the exact relationship between a child's advanced SA and overweight or obese status is thoroughly complex and involves many factors that are still not completely understood.

In this study, both right- and left-hand radiographs were used. Considering that the Greulich and Pyle method of bone age evaluation is performed using left-handed radiographs, it is possible that our use of both right- and left-hand radiographs may have decreased the reliability of our findings. This is unlikely however, considering that differences between right- and left-hand maturation levels (using the Greulich and Pyle method) have been found to be insignificant in relation to the estimation of the maturational stages of the skeleton as a whole[12].

Other methods of calculating bone age include the Tanner-Whitehouse methods, which was not utilized in this study. Previous studies have suggested that the Greulich and Pyle method of bone evaluation may show greater intra-observer variability than the Tanner-Whitehouse method but is a faster and preferred method for assessing bone age in pediatric radiologists and endocrinologists[11, 23–24]. Also, the study done by Chaimotre et al., which included a large multi-ethnic sample, found that the Greulich and Pyle method produces excellent correlation between skeletal age and chronological age and is still a reliable source for assessing bone age accurately[25]. Alshamrani and Offiah also demonstrated the accuracy of the GP method in a mutli-ethnic sample by comparing the method to BoneXpert and found no statistically significant difference between the two methods[26]. Future studies may attempt to utilize other forms of

bone age evaluation and the effects of obesity or elevated BMI on skeletal age. The precision of our results using the GP method to compare relative differences in skeletal age between elevated and normal body mass index is evidence of the effects of elevated BMI on accelerated bone age.

Although our sample size was small, the ICC indicated that we had sufficient subject variability reflective of the average pediatric population and was still able to achieve excellent rater reliability. Comparing our results to similar studies that looked at other factors, such as waist circumference, we can conclude that being overweight or obese does impact skeletal maturation; therefore, the pediatric population cannot be treated for orthopaedic conditions based solely on chronological age.

Based on our cohort, children with weight above normal must be approached with the expectation of significantly earlier skeletal maturity when providing orthopaedic, or other age relative care. Although BMI used for this study was obtained at only one point in time, the increased SA observed is indicative that increased weight can have its implications on orthopaedic care in children because increased SA may not be a transient or acute issue but rather one that has been occurring over time due to physiological responses of chronic increased weight rather than acute weight changes. Expected fracture patterns and treatment options can vary based on age. Pogorelic et al described surgical indications for flexible intramedullary nails for proximal humerus fractures to be based on varying degrees of intolerable translation and angulation, and/or open physis depending on age. Generally, children < 10 years that do not meet criteria for surgery are treated conservatively given the bone has good remodeling potential[27]. Nguyen et al demonstrated differing scaphoid fracture patterns depending on age with distal scaphoid fractures occurring more often in a younger cohort compared to proximal fractures in an older cohort[28]. Casting duration for lower leg fractures is generally 8 weeks for patients 11–17 years and 6 weeks for patients 5–10 years[29]. Since many orthopaedic treatment recommendations are based on chronological age, one should carefully determine the skeletal age of overweight or obese patients before deciding definitive treatment.

While the conclusions of the study are highly translational for this population, there still exists limited orthopedic literature on skeletal age effects in children with an elevated BMI. Further studies should ideally include a multicenter cohort, with an emphasis on obtaining a racially diverse patient population to further explore ethnicity as an effect modifier on skeletal age in the children with elevated BMI.

Conclusion

Our study highlighted that skeletal age of a pediatric patient is not always equivalent to chronological age especially in patients who are overweight or obese. The differences in skeletal age and chronological age must be considered when recognizing fracture patterns and making treatment decisions.

Declarations

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Additional Information

Contributions

J.A.S. supervised this study. M.H.F. and J.A.S. were involved in the conceptualization of the study. M.H.F., J.A.S., and W.N.H. were involved in the methodology of the study. M.H.F., M.S.K., W.N.H., and J.A.S. were involved in the investigation of the study. M.H.F. wrote the original draft of the manuscript. All authors were involved in data curation and reviewing and editing the manuscript.

Conflicts of Interest/Competing Interests

John A. Schlechter, DO is a speaker for Arthrex Inc. All other authors declare that they have no conflict of interest.

Ethics Declaration

This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the Institutional Review Board (IRB) of Children's Hospital of Orange County who determined that our study did not need ethical approval and informed consent due to the retrospective nature of the study. An IRB official waiver of ethical approval was granted from the IRB of Children's Hospital of Orange County.

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Figures

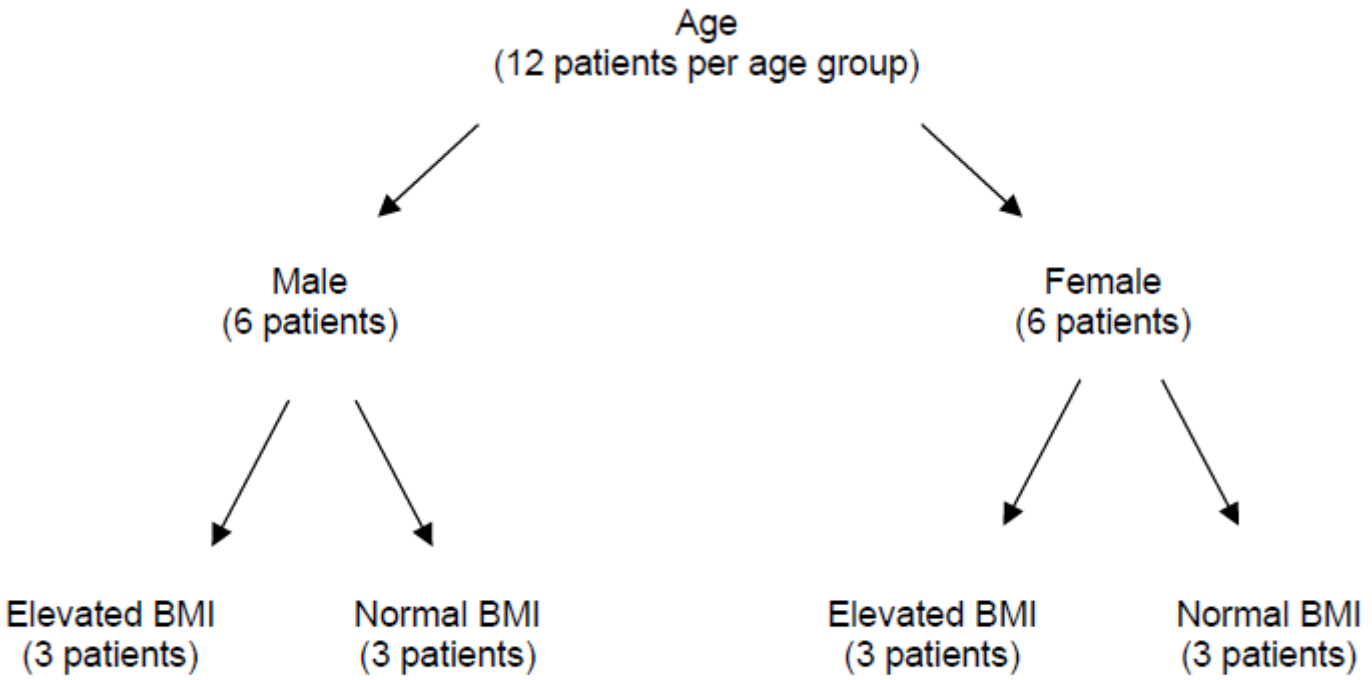

Figure 1

Diagram of the patient selection process.

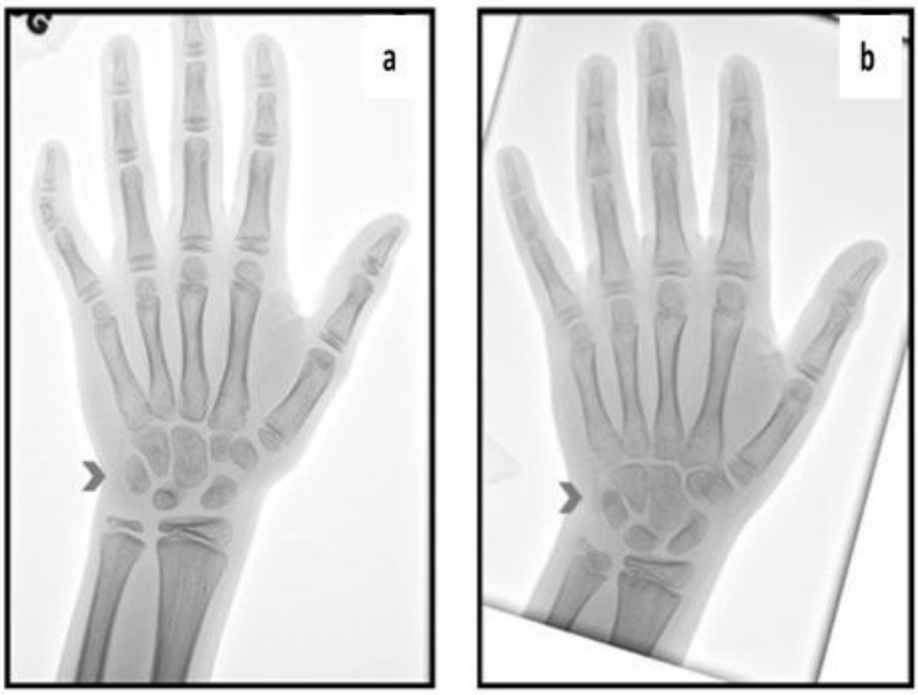

Figure 2

Hand Radiographs of 2 CA matched study subjects. Note the advanced ossification of the pisiform (arrowhead) in (b) the 10-year-old Hispanic male with elevated BMI of 92.09% (skeletal age of 11.5 years), compared with (a) a race and age matched 10-year-old Hispanic male of normal weight with BMI of 11.61% (skeletal age of 10 years)

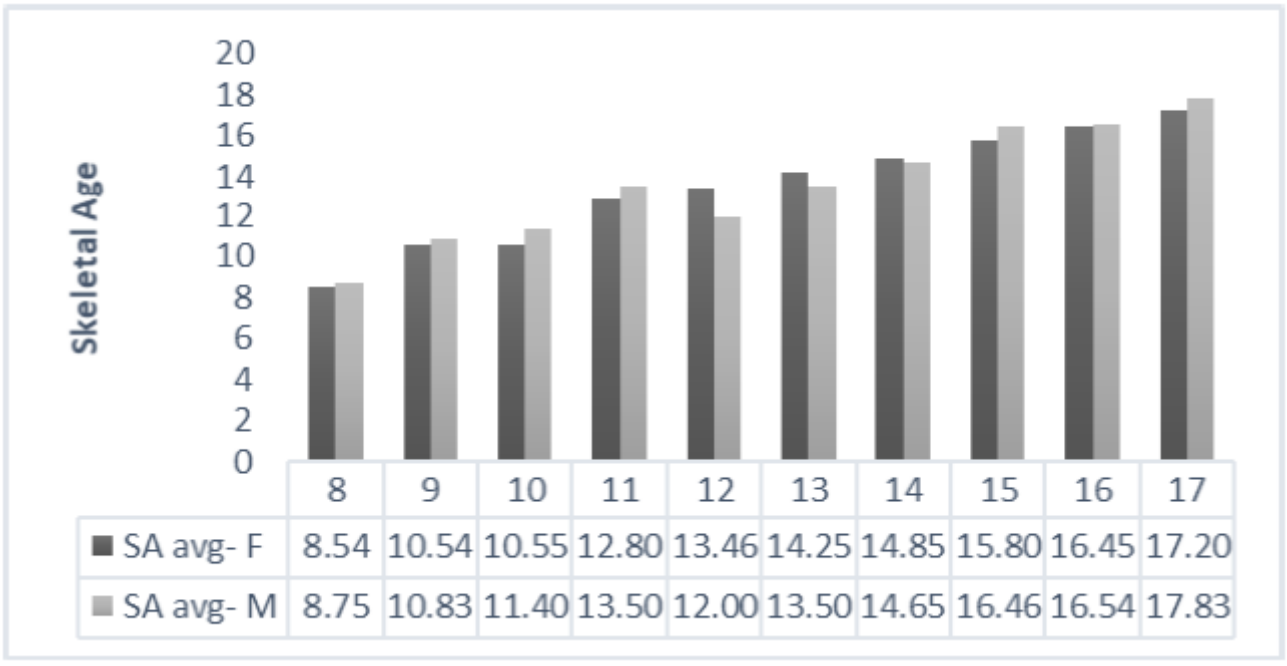

Figure 3

Chronological Age versus Skeletal Age (SA) among females (F) and males (M).