Check for updates

ORIGINAL REPORT: EPIDEMIOLOGIC RESEARCH

Sleep-Disordered Breathing Is Associated with Reduced Mandibular Cortical Width in Children

H. Eimar[1], M.A.Q. Al-Saleh[1,2], A.R.G. Cortes[3], D. Gozal[4], D. Graf[1], and C. Flores-Mir[1]

Abstract: ***Introduction:*** *Evidence from the adult population suggests that sleep-disordered breathing (SDB) (i.e., obstructive sleep apnea [OSA]) is negatively associated with bone mineral density. Whether a similar association exists in children with SDB has not been investigated. Using the mandibular cortical width (MCW) as a proxy for skeletal bone density, we investigated if children at risk of SDB or diagnosed with OSA have a reduced mandibular cortical width compared to children without SDB.*

Methods: *Two retrospective cross-sectional studies were performed. The first study included comparison of MCW between 24 children with polysomnographically (PSG) diagnosed OSA and 72 age- and sex-matched control children. The second study included a cohort of children in which SDB was suggested by the Pediatric Sleep Questionnaire (PSQ) (n = 101). MCW was measured from panoramic radiographs.*

Results: *Multiple-predictors regression analysis from the first study indicated that in children with a severe form of SDB, as induced by OSA severity, there was a negative association with MCW (β = –0.290, P = 0.049). Moreover, PSG-diagnosed OSA children had thinner MCW (2.9. ± 0.6mm) compared to healthy children (3.5 ± 0.6 mm; P = 0.002). These findings were further supported by the second study illustrating that PSQ total scores were negatively associated with MCW (β = –0.391, P < 0.001).*

Conclusions: *Findings suggest that children at risk for or diagnosed with SDB exhibit reduced mandibular cortical width that purportedly may reflect alterations in bone homeostasis.*

Knowledge Transfer Statement: *We report that sleep-disordered breathing (including its severe form, obstructive sleep apnea) in children is associated with reduced mandibular cortical width. This association might be a direct consequence of reduced bone health to sleep-disordered breathing or a reflection that reduced bone formation underlies the development of sleep-disordered breathing. Our findings suggest that mandibular cortical width can be used as an adjunct diagnostic parameter for the diagnosis of sleep-disordered breathing.*

Keywords: sleep apnea syndromes, mandible, cortical bone, dental, cone-beam computed tomography, child

Introduction

Sleep-disordered breathing (SDB) is a common condition, with a wide spectrum of severity ranging from habitual snoring to obstructive sleep apnea (OSA) affecting approximately 10% to 12% of children and up to 35% of the adult population (Young et al. 2009; Heinzer et al. 2015). The more severe form of SDB (i.e., OSA) is characterized by repetitive episodes of upper airway narrowing or collapse during sleep,

DOI: 10.1177/2380084418776906. [1]School of Dentistry, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada; [2]College of Dentistry, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [3]Department of Stomatology, School of Dentistry, University of São Paulo, São Paulo, Brazil; [4]Department of Pediatrics, Pritzker School of Medicine, Biological Sciences Division, The University of Chicago, Chicago, IL, USA. Corresponding author: H. Eimar, School of Dentistry, Faculty of Medicine and Dentistry, University of Alberta, 11405-87 Ave, Edmonton, Alberta, T6G 1C9, Canada. Email: Eimar@ualberta.ca

A supplemental appendix to this article is available online.

© International & American Associations for Dental Research 2018

leading to either reductions or cessation of airflow (hypopnea and apnea, respectively), resulting in intermittently low oxygen levels (hypoxia), episodic hypercapnia, and disrupted sleep due to recurrent arousals. SDB has been identified as contributing to a large number of morbidities involving the cardiovascular, endocrine, metabolic, autonomic, and central nervous systems as well as behavioral problems at home and school (Gozal 1998; Jennum et al. 2013). In addition, pediatric SDB has been associated with increased health care utilization and costs with the frequency of recurrent respiratory problems being particularly prominent (Tarasiuk et al. 2007).

Several studies conducted in adult populations have suggested that patients with poor sleep quality, such as in SDB patients, may be at higher risk for reduced bone density (such as osteopenia and osteoporosis) as well as increased frequency of bone fractures (Chen, Weng, et al. 2014; Yen et al. 2014; Hamada et al. 2016; Liguori et al. 2016). Similarly, poor sleep quality is also observed in a significant proportion of children, especially those with enlarged tonsils and/or adenoids, a deviated nasal septum as well as asymmetric nasal turbinates (Hannon et al. 2012). Although there are major differences in the etiology, symptoms, and even treatment options of SDB between children and adults, it has not been investigated whether children with SDB (including OSA) are similarly characterized by reduced bone density.

Bone density can be appraised using indices measured from dental panoramic radiographs. Among all the radiographic indices, the mandibular cortical width (MCW) demonstrates the highest sensitivity and specificity for detection of reduced bone density (Calciolari et al. 2015), with MCW being designated as the width of the inferior border of the mandible below the mental foramen.

Based on aforementioned considerations, we hypothesized that children diagnosed with or at risk of SDB, particularly OSA, show reduced bone density estimated by MCW. OSA diagnosis was obtained using polysomnography (PSG). Risk assessment for SDB was performed using the Pediatric Sleep Questionnaire (PSQ), a validated screening tool used to identify patients at high risk of SDB. PSQ scores ≥8 are indicative of high SDB risk and prompt referral to ear, nose, and throat (ENT) specialists for further investigation (Chervin et al. 2000).

Methods

Participants

After obtaining the approval from the ethics board of the University of Alberta (Pro00063547), records of any patient with potential symptoms suggestive of SDB were retrieved from a database of all patients who were orthodontically treated at the University of Alberta–Orthodontics Clinics before April 30, 2016. In total, 202 patients with potential symptoms suggestive of SDB were identified. Out of those, 24 patients had an OSA diagnosis based on PSG, 101 patients had an SDB risk assessment done through PSQ, and 77 patients with reported symptoms had not been assessed by either methods and thus were excluded. None of the 202 children were assessed by both methods. Therefore, 2 separate retrospective cross-sectional studies were performed to assess the potential association of OSA and SDB with reduced bone density. The reports were prepared in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement. For both studies, subjects were included in the study only if the complete set of records was available: demographic data (age <18 years, sex, weight, height, body mass index [BMI]), no known genetic or syndromic conditions, and craniofacial imaging (including full-view cone beam computed tomography [CBCT]) as part of the orthodontics diagnostic record. CBCT imaging would have been prescribed to provide a 3-dimensional (3D) visualization of the craniofacial skeleton (such as jaw asymmetry), a 3D evaluation of impacted tooth position, or assessment of the temporomandibular joint complex, among other reasons. Children diagnosed with conditions known to substantially affect bone metabolism or who used medications known to affect bone metabolism were excluded. Moreover, children with no radiographic images or radiographic images of substandard quality were excluded.

First Study

The first study consisted of all children (out of the 202 patients with potential symptoms suggestive of SDB) who underwent a clinical examination by ENT specialists and underwent a full overnight PSG evaluation in a sleep laboratory. The following sleep-related measures were retrieved from the PSG: total sleep time (TST), stages of sleep time (rapid eye movement [REM] stage and non–REM [NREM] stages 1 to 3, reported as percentage of TST), arousal index, and apnea-hypopnea index (AHI) for assessment of the severity of apnea. Children with symptoms compatible with the presence of sleep disorders but without PSG confirmation were excluded.

For each child with PSG-diagnosed OSA, 3 children with no history or physical findings compatible with SDB (controls) were randomly selected from the patient database of the University of Alberta–Orthodontics Clinics and matched for age and sex. Moreover, CBCT evaluation was a prerequisite, and the same exclusion criteria that were applied to patients with OSA were also applied to controls.

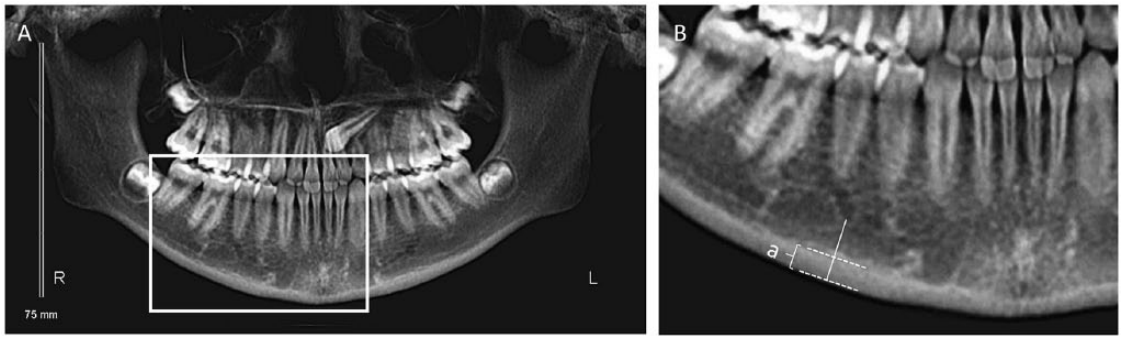
Second Study

The second sample included all children (out of the 202 patients with potential symptoms suggestive of SDB) who were evaluated using the PSQ and who met the study defined inclusion and exclusion criteria.

Data Collection from the Craniofacial Radiographic Images for Both Studies

CBCT scans (ICAT, Imaging Science International) were obtained following a standardized protocol consisting of 0.3-mm voxel, 120 kVp, 18.54 mA,

Figure. Cortical bone assessment in children: (**A**) a panoramic image and (**B**) a higher magnification of the region shown in panel (A), illustrating the following measurements: the distance between the lower border of the mandible to the superior margin of the mandibular cortex "a." The "a" distance, in millimeters, represents the mandibular cortical width.



exposure time of 8.5 s, and field of view of 16 cm in diameter and 6 cm in height, allowing for a low effective radiation dose (approximately 35 microsieverts) (Roberts et al. 2009). Three-dimensional airway volume, dental, and skeletal measurements were performed. Cephalometric and panoramic radiographic images were reconstructed and stored using Dolphin 3D software (Dolphin Imaging & Management Solutions).

Three-Dimensional Airway Volume Measurements

The nasopharynx, oropharynx, and total airway (nasopharynx and oropharynx) volume were reported for each subject using the Dolphin 3D software. The boundaries of the nasopharynx and oropharynx airway spaces were defined as previously described (Chen et al. 2015). For the nasopharynx, the airway space was reconstructed from the intersection of the following lines extending from the sella turcica, tip of the odontoid process, and the posterior nasal spine. For the oropharynx, the airway space was reconstructed from the intersection of the following lines extending from the posterior nasal spine, tip of the odontoid process, superior border of the fourth cervical vertebra, and base of the epiglottis.

Cephalometric Radiographic Analysis

Prior to the reconstruction process, the skull was lined up, with the orbits parallel to the horizontal plane and with a corrected head's rotation. Cephalometric images were obtained from the right side of the patients. The following data were obtained from analysis of the cephalometric images: mandible growth direction and maxilla-mandibular anterior-posterior relationship. Mandible growth direction was recorded using the angular measurement between the Frankfort plane (from porion to orbitale) and the mandibular plane (from menton to gonion) (Tweed 1946). The anterior-posterior jaw relationship was determined using an angular measurement from Steiner analysis (A – nasion –B).

Panoramic Radiographic Analysis

Panoramic images were reconstructed from CBCT scans by selecting a custom focal trough that passed through the lingual cusps of the maxillary teeth and extended posterior to the condyles. Focal trough width was varied to ensure it encompassed the entire length and height of the maxillary dentition. Axial serial slices were reviewed to ensure the focal trough encompassed all teeth regardless of their angulation and with the center of the custom focal trough bisecting as close to the center of the long axis of the teeth as possible.

TIFF-format panoramic images from all individuals were analyzed using the ImageJ software v1.47 (National Institutes of Health). MCW was determined at the side of better visualization. The mental foramen was identified. A line passing perpendicular to the tangent to the lower border of the mandible and through the center of the mental foramen was drawn. The distance, in millimeters, between the lower border of the mandible to the superior margin of the mandible cortex represents the MCW (Fig.).

Validation of MCW Measurements from Panoramic Images Reconstructed from CBCT

Briefly, 10 well-preserved, dry human skull specimens were exposed to standard dental panoramic and CBCT imaging using a standardized protocol. MCW measurements were conducted twice on the panoramic images (either from the standard dental panoramic imaging machine or those constructed from the CBCT scanning machine) by the same observer and once by a second observer using ImageJ 1.47v software (Appendix Fig. 1).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 23.0v for Windows (SPSS, Inc.) was used for statistical analyses. In all experiments, a value of $P < 0.05$ was considered as statistically significant. Continuous variables were reported as mean and standard deviation (SD), whereas categorical variables were summarized as percentages. For both cross-sectional studies, all measurements in CBCT (including the MCW distance)

were performed in a random order by 2 trained observers (i.e., dentists with expertise in oral radiology). Both observers performed their measurements twice, at intervals of 2 wk, to eliminate the memory bias and were assessed for consistency (intrarater reliability) and agreement (interrater reliability) using intraclass correlation coefficient (ICC) statistical tests. ICC values were interpreted by the general guidelines presented by Portney and Watkins (2009).

For the first cross-sectional study, single-predictor regression analysis was performed using a general linear model to determine which factors were statistically associated with MCW. Unstandardized coefficients (B), standard of error (SE), and standardized coefficients (β) were reported for each variable. All factors with a *P* less than 0.25 on the single-predictor analysis were included into the multiple-predictor model. Multiple-predictor regression analysis using a general linear model was performed to determine the factors, which were independently associated with MCW. All included variables were checked for collinearity using variance inflation factor (VIF) and Pearson correlation analysis. Variables that showed multicollinearity issues were excluded from the final model. Furthermore, differences in participants' characteristics between the 2 groups (OSA children vs. controls) were assessed using multivariate analysis of variance (MANOVA) with Tukey's post hoc pairwise comparisons. After checking the normality and homoscedasticity, analysis of covariance (ANCOVA) was performed to assess the differences in MCW between the 2 groups, with age, weight, height, body mass index (BMI), mandibular growth direction, relationship between jaws, and nasopharynx and oropharynx airway volumes as covariates. Post hoc power analyses to evaluate the level of confidence were also calculated with type I error set at 0.05. For the second study, the same statistical approaches were used as described above.

Results

Validation of MCW Measurements from Panoramic Images Reconstructed from CBCT

Measurements of the MCW have only been validated on standard dental panoramic radiographs but not on panoramic images reconstructed from CBCT. Our findings from the ex vivo experiments showed that MCW measurements from CBCT had an excellent intraobserver reliability and interobserver agreement compared to standard panoramic images (Appendix Table). Furthermore, MCW readings performed on panoramic images constructed from CBCT were similar to those readings performed on standard panoramic images (Appendix Fig. 2). Accordingly, MCW performed on panoramic radiographic images constructed from CBCT was deemed valid as a screening tool to evaluate the cortical width of the mandible and has been used in both studies presented below.

First Study

Of 202 patients with potential symptoms suggestive of SDB, only 24 children with PSG-diagnosed OSA were identified. Those patients were matched with 72 children with no reported symptoms or physical findings suggestive of SDB. The general characteristics for both study groups are reported in Table 1. As MCW values did not differ between different sexes ($F = 0.18$, $P = 0.673$), they were not considered separately for subsequent analyses.

As reported in Table 1, PSG-diagnosed OSA children had a more vertical direction of mandibular growth (28.4 ± 8.2 degrees) relative to controls (24.1 ± 5.4 degrees, $P = 0.004$). In addition, OSA children had a significantly smaller nasopharynx airway volume (3,325 ± 1,233 mm^3) in comparison to controls (4,658 ± 1,676 mm^3; $P = 0.004$). The oropharynx airway space was also smaller in OSA children (8,952 ± 2,077 mm^3) compared to controls (12,961 ± 6,209 mm^3) but did not reach statistical significance ($P = 0.162$). Of note, the severity of OSA in 24 children, represented by the AHI, did not correlate with the nasopharynx and oropharynx airway volumes as derived from CBCT scans ($\beta = -0.262$, $P = 0.309$ and $\beta = -0.068$, $P = 0.796$, respectively).

Significant differences between OSA children and controls emerged in the MCW measurements ($F(1, 108) = 11.74$, $P < 0.001$) after adjusting for age, mandibular growth direction, relationship between jaws, and nasopharynx and oropharynx airway volumes. MCW values were significantly lower in OSA children (MCW = 2.9 ± 0.6 mm) compared to control children (MCW = 3.5 ± 0.6 mm; $P = 0.002$; post hoc power analysis = 98%; Table 1).

Table 2 shows the findings for single-predictor and multiple-predictor regression analyses among all the variables that could be associated with MCW in OSA children. Results from single-predictor analyses showed that MCW was positively associated with age of the OSA children ($\beta = 0.74$, $P < 0.01$) and negatively with the severity of OSA, represented by the AHI ($\beta = -0.475$, $P = 0.026$). Weight, height, BMI, anteroposterior jaw relationship, and nasopharynx and oropharynx airway volumes were not significantly associated with MCW ($P > 0.25$) and thus were excluded from the final model. When multiple-predictors analysis was performed, including age and AHI only, the regression linear model predicted MCW, $F = 17.410$, $P < 0.001$, $R^2 = 0.463$. Both age ($\beta = -0.674$, $P < 0.001$) and AHI ($\beta = -0.290$, $P = 0.049$) were significantly associated with MCW.

Second Study

A total of 101 patients (out of 202 patients with potential symptoms suggestive of SDB), who had their SDB assessed by PSQ and fulfilled all of the inclusion and exclusion criteria, were included in the second study. Results of single- and multiple-predictor analyses for all the variables that could be associated with MCW are shown in Table 3. Results from single-predictor analyses

Table 1.
Clinical Characteristics of Children with OSA and Matched Controls.

Characteristics	Controls (n = 72), Girls/Boys (n = 39/33), Mean ± SD	OSA (n = 24), Girls/Boys (n = 13/11), Mean ± SD	P Value[a]
Age, y	11.4 ± 2.8	11.4 ± 2.9	0.938
Mandible growth direction, deg	24.1 ± 5.4	28.4 ± 8.2	0.004
Anteroposterior jaw relationship, deg	2.3 ± 3.2	1.5 ± 3.3	0.189
Nasopharynx airway volume, mm^3	4,658 ± 1,676	3,325 ± 1,233	0.004
Oropharynx airway volume, mm^3	12,961 ± 6,209	8,952 ± 2,077	0.162
TST, min		384.1 ± 116.9	
REM sleep stage, % of TST		15.5 ± 6.7	
N1 sleep stage, % of TST		3.7 ± 0.5	
N2 sleep stage, % of TST		50.5 ± 10.5	
N3 sleep stage, % of TST		30.5 ± 12.2	
Arousal index, /h		12.2 ± 7.9	
AHI, /h		6.9 ± 12.4	
MCW, mm	3.5 ± 0.6	2.9 ± 0.6	0.002

AHI, apnea-hypopnea index; N1 to N3, no REM stages 1 to 3; MCW: mandibular cortical width; OSA, obstructive sleep apnea; REM, rapid eye movement; TST, total sleep time.
[a]P value calculated using multivariate analysis of variance with Tukey's post hoc pairwise comparisons.

Table 2.
Factors Associated with MCW in OSA Children: Single-Predictor and Multiple-Predictor Analyses.

	Single-Predictor Analysis			Multiple-Predictor Analysis	
Variable	β	P Value	R^2	β	P Value
Age	0.742	<0.001	0.529	0.674	<0.001
Weight	0.215	0.326[a]	0.046		
Height	0.276	0.364[a]	0.043		
BMI	0.290	0.626[a]	0.026		
Mandible growth direction	0.168	0.443[a]	0.028		
Anteroposterior jaw relationship	–0.217	0.319[a]	0.047		
Nasopharynx	0.294	0.298[a]	0.050		
Oropharynx	0.216	0.382[a]	0.043		
AHI	–0.475	0.026	0.225	–0.290	0.049

Adjusted R^2 for the multiple linear model = 0.647, $P < 0.001$.
AHI, apnea-hypopnea index; BMI, body mass index; MCW, mandibular cortical width; OSA, obstructive sleep apnea; R^2, adjusted R^2 (percentage of the variance in the dependent variable explained by the independents); β, standardized regression coefficient.
[a]Excluded from multiple-predictor analysis as the $P > 0.25$.

Table 3.
Factors Associated with MCW: Single-Predictor and Multiple-Predictor Analyses.

Variable	Single-Predictor Analysis			Multiple-Predictor Analysis	
	β	*P* Value	R^2	β	*P* Value
Age	0.457	<0.001	0.201	0.327	<0.001
Weight[a]	0.379	0.001	0.132		
Height[a]	0.524	<0.001	0.265		
BMI[a]	0.177	0.126	0.018		
Mandible growth direction	–0.014	0.890[b]	0.010		
Anteroposterior jaw relationship	–0.171	0.087	0.020	–0.037	0.659
Nasopharynx	0.231	0.020	0.044	0.105	0.235
Oropharynx	0.230	0.021	0.043	0.132	0.122
PSQ	–0.455	<0.001	0.199	–0.391	<0.001

Adjusted R^2 for the multiple linear model = 0.364, $P < 0.001$.
BMI, body mass index; MCW, mandibular cortical width; OSA, obstructive sleep apnea; PSQ, Pediatric Sleep Questionnaire; R^2, adjusted R^2 (percentage of the variance in the dependent variable explained by the independents); β, standardized regression coefficient.
[a]Excluded from multiple-predictor analysis due to the presence of multicollinearity with age (variance inflation factor [VIF] was more than 5).
[b]Excluded from multiple-predictor analysis as the $P > 0.25$.

showed that all the variables—age, weight, height, and nasopharynx and oropharynx airway volumes and total PSQ scores—were significantly ($P < 0.05$) associated with MCW.

The aforementioned statistically significant variables ($P < 0.05$)—age, nasopharynx and oropharynx airway volumes, and total PSQ scores, plus anteroposterior jaw relationship (*P* values for both were <0.25)—were included in the final multiple-predictor linear model. Weight, height, and BMI variables were excluded from the final model due to their multicollinearity with age. Table 3 (right section) shows the results from the multiple-predictor analysis. The regression model predicted MCW, $F = 12.319$, $P < 0.001$, $R^2 = 0.364$. However, only age ($\beta = 0.327$, $P < 0.001$) and the global PSQ score ($\beta = –0.391$, $P < 0.001$) were significantly associated with MCW, whereas anteroposterior jaw relationship and nasopharynx and oropharynx airway volumes were not.

When the participants were divided into 2 groups based on PSQ total score cutoff value of 8, a significant difference between children with a PSQ <8 and children with a PSQ ≥8 emerged in the MCW measurements ($F(1, 101) = 9.54$, $P = 0.003$), even after adjusting for age, weight, height, BMI, mandibular growth direction, relationship between jaws, and nasopharynx and oropharynx airway volumes. MCW values were significantly lower when PSQ scores were ≥8 (2.8 ± 0.4 mm) versus PSQ values <8 (3.2 ± 0.5 mm; $P = 0.003$; post hoc power analysis = 99%; Table 4). However, no significant differences emerged between the 2 PSQ score groups in age, height, weight, BMI, mandible growth direction, anteroposterior jaw relationship, and nasopharynx and oropharynx airway volumes (Table 4). Of note, the PSQ score of 101 children did not reveal significant associations with nasopharynx and oropharynx airway volumes as obtained from CBCT imaging ($\beta = –0.135$, $P = 0.177$ and $\beta = –0.044$, $P = 0.665$, respectively).

Discussion

The present study shows that children diagnosed with OSA or who are at risk for SDB based on PSQ have a decreased MCW. In the case of children diagnosed with OSA by PSG, the MCW was inversely correlated with AHI, an indicator of disease severity. If MCW is used as a proxy for bone density, these data suggest that SDB in children may be associated with reduced bone health.

The most reliable method for assessment of altered bone density (such as osteoporosis) is derived from dual-energy X-ray absorptiometry (DXA), a noninvasive imaging method that estimates bone density from the radio-opacity of mineralized structures. However, the reduction of bone density can also be detected by other methods, including quantitative tomography, quantitative ultrasound, and magnetic resonance imaging (Gluer et al. 1997). The MCW determined from panoramic radiographs can also be used to reliably estimate bone density. According to a recent systematic review and meta-analysis (Calciolari et al. 2015), this measurement provides robust sensitivity (0.602; 95% confidence interval [CI], 0.398 to 0.775) and specificity (0.708; 95%

Table 4.
Clinical Characteristics of Participants with PSQ <8 and Patients with PSQ ≥8.

Characteristics	PSQ <8 (*n* = 46), Girls/Boys (*n* = 20/46), Mean ± SD	PSQ ≥8 (*n* = 55), Girls/Boys (*n* = 23/55), Mean ± SD	*P* Value
Age, y	10.7 ± 3.2	10.2 ± 2.5	0.309
Height, m	1.5 ± 0.2	1.5 ± 0.2	0.891
Weight, kg	43.9 ± 21.5	50.5 ± 25.1	0.236
BMI, kg/m^2	19.4 ± 5.4	22.1 ± 6.7	0.061
Mandible growth direction, deg	27.8 ± 6.2	27.6 ± 6.9	0.905
Anteroposterior jaw relationship, deg	3.0 ± 2.9	3.5 ± 2.9	0.389
Nasopharynx volume, mm^3	3,045 ± 2,394	2,823 ± 1,540	0.576
Oropharynx volume, mm^3	9,353 ± 4,141	8,779 ± 4,688	0.523
MCW, mm	3.2 ± 0.5	2.8 ± 0.4	0.003

P value was calculated using multivariate analysis of variance with Tukey's post hoc pairwise comparisons.
BMI, body mass index; MCW, mandibular cortical width; PSQ, Pediatric Sleep Questionnaire.

CI, 0.568 to 0.817) to detect changes in bone density in adults. The MCW value has been successfully applied in pediatric studies to correlate bone mass with different systematic diseases (Apolinario et al. 2015; Paulsson-Bjornsson et al. 2015). However, future studies will have to be conducted to determine the validity of using MCW as a marker for bone density in growing children and how its value was affected during the preadolescence, adolescence, and postadolescence growth periods. These studies would have to compare the MCW readings to those obtained from the clinical accepted tools to evaluate the bone mass such as DXA. Nevertheless, results from a retrospective study conducted in children by Apolinario et al. (2015) demonstrated the close correlation between mandibular cortical width and bone density, as measured by DXA (r = 0.64, $P < 0.05$), which provides support for the validity of our current results.

The use of the MCW was established on panoramic radiographs, which are frequently obtained during routine dental checkups. CBCT is a relatively newer diagnostic imaging tool that is being increasingly used by dentists in their clinical practices. The suitability of panoramic images extracted from CBCT scan data rather than panoramic radiographs for the assessment of the MCW mandibular bone density had not been critically ascertained. We therefore validated this approach by comparing images obtained by either way from dry skull specimens. Thus, we used the MCW measured from panoramic radiographic images reconstructed from the CBCT scanning for our cross-sectional studies. It should be added that as with panoramic radiographs, a consistent and reliable MCW requires CBCT images of high resolution and proper observer training in identifying the landmarks of the measured distance.

In both cross-sectional studies, the MCW readings did not differ between boys and girls, as previously reported (Apolinario et al. 2015). Thus, there was no need for sex-based adjustments in data analyses. This is in contrast to adults, in whom sex-related differences in bone density are possibly related to discrepant aging trajectories mediated by hormonal variations (e.g., growth hormone and estrogen), body size, bone size, and geometry (Parfitt et al. 2000; Seeman 2003). Similarly, the MCW readings increased with age in both studies as reported (Apolinario et al. 2015), suggesting a developmental increase in bone density in growing children (Boot et al. 1997).

The first cross-sectional study revealed differences in MCW among PSG-diagnosed OSA children and control children. These findings are in agreement with results from a recent study, whereby children with OSA had retarded skeletal maturity (assessed by hand and wrist radiographs) and lower serum levels of osteocalcin (biomarker for bone formation) compared with healthy controls, and the osteocalcin levels returned to normal levels following 24 months of the surgical removal of the tonsils and adenoids (adenotonsillectomy) of the OSA children (Zhang et al. 2017). Of interest, these findings were reciprocated in the second cross-sectional study. Significantly thinner MCW measurements were detected in children with PSQ scores ≥8 compared to children with PSQ scores <8. The cutoff value of 8 for the PSQ is based on previous studies, which showed that a value of 8 and higher correlated with an increased risk of OSA and justified referral to ENT specialists (Chervin et al.

2000). Thus, reduced bone density was observed in both studies in children at risk of or diagnosed with OSA.

Interestingly, the overall PSQ score was associated with predictive ability of the MCW, based on our multipredictor regression analysis. This indicates that SDB risk as assessed by the PSQ in children may reflect alterations in sleep that are of relevance to bone morphology (e.g., growth hormone–related pathways), since pulsatile growth hormone release and activity are tightly related to sleep homeostasis and potentially adversely affected by hypoxia (Kim et al. 2015). Our findings are remarkably similar to recently published studies in adult populations, whereby sleep quality as indicated by the Pittsburgh Sleep Quality Index (PSQI) was associated with a reduced bone stiffness index of the calcaneus bone or cortical bone width of the radius, assessed by an ultrasound bone densitometer (Sasaki et al. 2016; Kuriyama et al. 2017). However, results from the published literature on the associations between sleep quantity and bone mass have been somewhat inconsistent. Some studies have shown that low bone mass is associated with short sleep duration (Cunningham and Di Pace 2015; Kuriyama et al. 2017) or long sleep duration (Kobayashi et al. 2012; Tian et al. 2015) or exhibits a U-shape relationship (Chen, Chen, et al. 2014). Since the PSQ does not directly evaluate sleep quality, we cannot specifically infer the degree of sleep disruption or overall magnitude of insufficient sleep in our study. However, it is likely that children at high risk for SDB will also have poor sleep quality driven by increased frequency of respiratory-related arousals during sleep (Tauman et al. 2004).

When appraising the association between the severity of OSA (represented by the AHI) and bone density (represented by bone density [g/cm^2] or T-score) in adults, inconsistent findings have been reported. On the one hand, the severity of OSA was negatively associated with bone density (Eimar et al. 2017), whereas on the other hand, a positive association between the severity of OSA and bone density was reported (Sforza et al. 2013). Also, other investigators have reported no significant associations between the severity of OSA and bone density (Mariani et al. 2012).

A recent review described in great detail possible links between sleep breathing disturbances and bone mass (Swanson et al. 2015). In addition to sleep disruption, intermittent hypoxia events, a major constitutive characteristic of OSA, may also directly impose negative effects on bone cells, thus accelerating bone mass loss (Swanson et al. 2015). In addition, OSA could also facilitate bone loss through indirect physiological mechanisms—namely, elevations in sympathetic nervous system activity (Narkiewicz and Somers 1997), disruption in the secretion of the circadian rhythm hormone melatonin (Luyster et al. 2012), and reductions in serum levels of 25-OH vitamin D (Liguori et al. 2015). However, it might also be hypothesized that growth retardation in the formation of the craniofacial bones (e.g., deviated nasal septum, midfacial hypoplasia, and/or mandibular hypoplasia) (Oishi et al. 2016) or those that fail to reach peak skeletal mass (Swanson et al. 2015) may result in smaller nasal nasopharynx and oropharynx airway chambers, which may result in SDB, including sleep apnea. This chicken-and-egg dilemma is far from being solved. Therefore, future research will have to be conducted to address these hypotheses.

An interesting and as of yet scarcely explored issue is the fact that children with OSA (or children who scored high on PSQ) exhibited smaller nasopharynx airway space volumes, as measured from CBCT imaging, compared to controls. Even if regression analysis did not reveal a significant association with the severity of OSA, the potential usefulness of CBCT imaging for SDB evaluation is currently being explored (Alsufyani et al. 2017), and as such, our findings will need to be prospectively corroborated by other studies.

Several limitations of the present study deserve mention. First, our study was retrospective, such that bone density readings from DXA could not be collected. In addition, control children did not undergo PSG evaluation to ascertain the absence of OSA or any other sleep disturbances; however, we can only infer that confirmatory studies on the absence of OSA in controls would only further enhance the observed differences in MCW reported herein. A third limitation in this study is that the duration of OSA is nearly impossible to determine since symptoms may go unrecognized for several months to years prior to PSG diagnosis. Thus, prospective larger scale studies should be contemplated to corroborate current results.

Conclusion

Findings suggest that children at risk for or diagnosed with SDB exhibit reduced mandibular cortical width that purportedly may reflect alterations in bone homeostasis.

Author Contributions

H. Eimar, contributed to conception, design, and data analysis, drafted the manuscript; M.A.Q. Al-Saleh, contributed to data analysis, critically revised the manuscript; A.R.G. Cortes, D. Gozal, D. Graf, C. Flores-Mir, contributed to conception and design, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

Acknowledgments

This work was supported by the operating grant from the Alberta Innovates—Health Solutions (AIHS; grant RES0027174) and a studentship to H. Eimar from the AIHS. Special thanks are given to Dr. Yazid Hamarneh, who assisted in the statistical analysis. In addition, our special thanks go to Dr. Joanna E MacLean from the Pediatric Sleep Laboratory, Stollery Children's Hospital, University of Alberta. The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

ORCID iD

D. Graf https://orcid.org/0000-0003-1163-8117

References

Alsufyani NA, Noga ML, Witmans M, Major PW. 2017. Upper airway imaging in sleep-disordered breathing: role of cone-beam computed tomography. Oral Radiol. 33(3):161–169.

Apolinario AC, Figueiredo PT, Guimaraes AT, Acevedo AC, Castro LC, Paula AP, Paula LM, Melo NS, Leite AF. 2015. Pamidronate affects the mandibular cortex of children with osteogenesis imperfecta. J Dent Res. 94(3 Suppl):95S–102S.

Boot AM, de Ridder MA, Pols HA, Krenning EP, de Muinck Keizer-Schrama SM. 1997. Bone mineral density in children and adolescents: relation to puberty, calcium intake, and physical activity. J Clin Endocrinol Metab. 82(1):57–62.

Calciolari E, Donos N, Park JC, Petrie A, Mardas N. 2015. Panoramic measures for oral bone mass in detecting osteoporosis: a systematic review and meta-analysis. J Dent Res. 94(3 Suppl):17S–27S.

Chen G, Chen L, Wen J, Yao J, Li L, Lin L, Tang K, Huang H, Liang J, Lin W., et al. 2014. Associations between sleep duration, daytime nap duration, and osteoporosis vary by sex, menopause, and sleep quality. J Clin Endocrinol Metab. 99(8):2869–2877.

Chen X, Liu D, Liu J, Wu Z, Xie Y, Li L, Liu H, Guo T, Chen C, Zhang S. 2015. Three-dimensional evaluation of the upper airway morphological changes in growing patients with skeletal class iii malocclusion treated by protraction headgear and rapid palatal expansion: a comparative research. PLoS One. 10(8):e0135273.

Chen YL, Weng SF, Shen YC, Chou CW, Yang CY, Wang JJ, Tien KJ. 2014. Obstructive sleep apnea and risk of osteoporosis: a population-based cohort study in Taiwan. J Clin Endocrinol Metab. 99(7):2441–2447.

Chervin RD, Hedger K, Dillon JE, Pituch KJ. 2000. Pediatric Sleep Questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Med. 1(1):21–32.

Cunningham TD, Di Pace BS. 2015. Is self-reported sleep duration associated with osteoporosis? Data from a 4-year aggregated analysis from the national health and nutrition examination survey. J Am Geriatr Soc. 63(7):1401–1406.

Eimar H, Saltaji H, Ghorashi S, Isfeld D, MacLean JE, Gozal D, Graf D, Flores-Mir C. 2017. Association between sleep apnea and low bone mass in adults: a systematic review and meta-analysis. Osteoporos Int. 28(6):1835–1852.

Gluer CC, Jergas M, Hans D. 1997. Peripheral measurement techniques for the assessment of osteoporosis. Semin Nucl Med. 27(3):229–247.

Gozal D. 1998. Sleep-disordered breathing and school performance in children. Pediatrics. 102(3 Pt 1):616–620.

Hamada S, Ikezoe K, Hirai T, Oguma T, Tanizawa K, Inouchi M, Handa T, Oga T, Mishima M, Chin K. 2016. Evaluation of bone mineral density by computed tomography in patients with obstructive sleep apnea. J Clin Sleep Med. 1(12):25–34.

Hannon TS, Rofey DL, Ryan CM, Clapper DA, Chakravorty S, Arslanian SA. 2012. Relationships among obstructive sleep apnea, anthropometric measures, and neurocognitive functioning in adolescents with severe obesity. J Pediatr. 160(5):732–735.

Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, Mooser V, Preisig M, Malhotra A, Waeber G, et al. 2015. Prevalence of sleep-disordered breathing in the general population: the hypnolaus study. Lancet Respir Med. 3(4):310–318.

Jennum P, Ibsen R, Kjellberg J. 2013. Morbidity and mortality in children with obstructive sleep apnoea: a controlled national study. Thorax. 68(10):949–954.

Kim TW, Jeong JH, Hong SC. 2015. The impact of sleep and circadian disturbance on hormones and metabolism. Int J Endocrinol. 2015:591729.

Kobayashi D, Takahashi O, Deshpande GA, Shimbo T, Fukui T. 2012. Association between osteoporosis and sleep duration in healthy middle-aged and elderly adults: a large-scale, cross-sectional study in Japan. Sleep Breath. 16(2):579–583.

Kuriyama N, Inaba M, Ozaki E, Yoneda Y, Matsui D, Hashiguchi K, Koyama T, Iwai K, Watanabe I, Tanaka R, et al. 2017. Association between loss of bone mass due to short sleep and leptin-sympathetic nervous system activity. Arch Gerontol Geriatr. 70:201–208.

Liguori C, Mercuri NB, Izzi F, Romigi A, Cordella A, Piccirilli E, Viola S, Costa S, Sbraccia P, Marciani MG, et al. 2016. Obstructive sleep apnoea as a risk factor for osteopenia and osteoporosis in the male population. Eur Respir J. 47(3):987–990.

Liguori C, Romigi A, Izzi F, Mercuri NB, Cordella A, Tarquini E, Giambrone MP, Marciani MG, Placidi F. 2015. Continuous positive airway pressure treatment increases serum vitamin D levels in male patients with obstructive sleep apnea. J Clin Sleep Med. 11(6):603–607.

Luyster FS, Strollo PJ Jr, Zee PC, Walsh JK; Boards of Directors of the American Academy of Sleep Medicine and the Sleep Research Society. 2012. Sleep: a health imperative. Sleep. 35(6):727–734.

Mariani S, Fiore D, Varone L, Basciani S, Persichetti A, Watanabe M, Saponara M, Spera G, Moretti C, Gnessi L. 2012. Obstructive sleep apnea and bone mineral density in obese patients. Diabetes Metab Syndr Obes. 5:395–401.

Narkiewicz K, Somers VK. 1997. The sympathetic nervous system and obstructive sleep apnea: implications for hypertension. J Hypertens. 15(12):1613–1619.

Oishi S, Shimizu Y, Hosomichi J, Kuma Y, Nagai H, Maeda H, Usumi-Fujita R, Kaneko S, Shitano C, Suzuki J, et al. 2016. Intermittent hypoxia induces disturbances in craniofacial growth and defects in craniofacial morphology. Arch Oral Biol. 61:115–124.

Parfitt AM, Travers R, Rauch F, Glorieux FH. 2000. Structural and cellular changes during bone growth in healthy children. Bone. 27(4):487–494.

Paulsson-Bjornsson L, Adams J, Bondemark L, Devlin H, Horner K, Lindh C. 2015. The impact of premature birth on the mandibular cortical bone of children. Osteoporos Int. 26(2):637–644.

Portney L, Watkins M. 2009. Foundations of clinical research: applications to practice. Upper Saddle River (NJ): Pearson/Prentice Hall.

Roberts JA, Drage NA, Davies J, Thomas DW. 2009. Effective dose from cone beam CT examinations in dentistry. Br J Radiol. 82(973):35–40.

Sasaki N, Fujiwara S, Yamashita H, Ozono R, Teramen K, Kihara Y. 2016. Impact of sleep on osteoporosis: sleep quality is associated with bone stiffness index. Sleep Med. 25:73–77.

Seeman E. 2003. The structural and biomechanical basis of the gain and loss of bone strength in women and men. Endocrinol Metab Clin North Am. 32(1):25–38.

Sforza E, Thomas T, Barthelemy JC, Collet P, Roche F. 2013. Obstructive sleep apnea is associated with preserved bone mineral density in healthy elderly subjects. Sleep. 36(10):1509–1515.

Swanson CM, Shea SA, Stone KL, Cauley JA, Rosen CJ, Redline S, Karsenty G, Orwoll ES. 2015. Obstructive sleep apnea and metabolic bone disease: insights into the relationship between bone and sleep. J Bone Miner Res. 30(2):199–211.

Tarasiuk A, Greenberg-Dotan S, Simon-Tuval T, Freidman B, Goldbart AD, Tal A, Reuveni H. 2007. Elevated morbidity and health care use in children with obstructive sleep apnea syndrome. Am J Respir Crit Care Med. 175(1):55–61.

Tauman R, O'Brien LM, Holbrook CR, Gozal D. 2004. Sleep pressure score: a new index of sleep disruption in snoring children. Sleep. 27(2):274–278.

Tian Y, Shen L, Wu J, Xu G, Yang S, Song L, Zhang Y, Mandiwa C, Yang H, Liang Y, et al. 2015. Sleep duration and timing in relation to osteoporosis in an elderly Chinese population: a cross-sectional analysis in the Dongfeng-Tongji cohort study. Osteoporos Int. 26(11):2641–2648.

Tweed CH. 1946. The Frankfort-mandibular plane angle in orthodontic diagnosis, classification, treatment planning, and prognosis. Am J Orthod Oral Surg. 32:175–230.

Yen CM, Kuo CL, Lin MC, Lee CF, Lin KY, Lin CL, Chang SN, Sung FC, Kao CH. 2014. Sleep disorders increase the risk of osteoporosis: a nationwide population-based cohort study. Sleep Med. 15(11):1339–1344.

Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ, Hla KM. 2009. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort Study. WMJ. 108(5):246–249.

Zhang QB, Li YF, Li MX, Kong LY, Jiang LF, Feng HW, Fan XL. 2017. Adenotonsillectomy outcomes regarding bone age and osteocalcin in treatment of obstructive sleep apnea syndrome in children. World J Pediatr. 13(2):158–164.