Bone Mineral Density Attenuation in Obstructive Sleep Apnea by Derived Computed Tomography Screening

Sharon Daniel
Ben-Gurion University of the Negev and Clalit Health Services
Yafit Cohen-Freud
Soroka Medical Center
Ilan Shelef
Soroka University Medical Center
Ariel Tarasiuk (tarasiuk@bgu.ac.il)
Ben-Gurion University of the Negev

Research Article

Keywords: obstructive sleep apnea, bone mineral density, computed tomography

Posted Date: November 16th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1049040/v1

Abstract

The association between obstructive sleep apnea (OSA) and bone mineral density (BMD) is poorly elucidated with contradictory findings. We retrospectively explored the association between OSA and BMD by examining abdominal computed tomography (CT) vertebrae images using clinical information. We included 315 subjects (174 with OSA and 141 without OSA) who performed at least two CT scans (peak voltage of 120 kV). Bone mineral density was attenuated in those with OSA and increased age. BMD attenuation was not associated with the apnea–hypopnea score, nocturnal oxygen saturation, or arousal index. A multivariate linear regression indicated that OSA is associated with BMD attenuation after controlling for age, gender, and cardiovascular diseases. Here, we report that OSA is associated with BMD attenuation. Further studies are required to untangle the complex affect of OSA on BMD loss and possible clinical implication of vertebra depressed fracture or femoral neck fracture.

Introduction

Obstructive sleep apnea (OSA) is a common condition that is associated with recurrent episodes of airway obstruction during sleep.[1,2] It affects more than one in seven adults, many of who are undiagnosed.[1–4] This condition is associated with large body mass index (overweight and obesity), metabolic abnormalities, and cardiovascular diseases.[1] OSA has been associated with impaired motor function, increased risk for accidents, low bone mineral density (BMD), and fractures.[3,5,6–10]

Radiological interpreting of routine spine computed tomography (CT) scans are the first to identify low bone density and osteoporosis, with no additional cost or exposure to unnecessary radiation.[11–14] CT examination allows measurements of BMD independent of large body mass index.[15,16] To our knowledge, only one study investigated the association between OSA and CT-derived BMD attenuation.[17] Hamada[17] et al. found that males with severe OSA had attenuation of lumber vertebra BMD.

Little is information is available on the association between OSA and attenuation of BMD using routine clinical CT scans. Here, we performed a case-control retrospective study to explore attenuation (in Hounsfield units; HU) of longitudinal abdominal CTs for other indications. The study was conducted on enrollees at Soroka University Medical Center from Clalit Health Services (CHS), the largest health maintenance organization in Israel that keeps strict electronic registry of patient records.[3,4,18]

Results

Participant's characteristics

One hundred and seventy-four OSA patients (apnea–hypopnea index ≥ 5 events/hr) (60.9% men) (Fig. 1) and 141 participants without OSA (79, 56% men) were recruited. No significant differences were found in gender distribution (men/women, 79/62 and 106/68) between the no OSA and OSA groups, respectively. The prevalence of hypertension and cardiovascular diseases was significantly higher in the OSA group

(Table 1, $p < 0.001$). Table 2 summarizes patients' characteristics according to OSA severity. Moderate/severe OSA versus mild OSA patents were older ($p = 0.007$), had a higher arousal and awakening index ($p < 0.05$), a higher oxygen desaturation (≥ 4%) index ($p < 0.001$) and a trend of an increased percent sleep time in which oxygen saturation was below 90% (T_{90}) ($p = 0.09$). Women with OSA versus no OSA were about 5 years older than women with no OSA (Table 3, $p < 0.05$). Both groups had a similar duration between their first and second CT scans (Table 3, $p = 0.903$). The 12 thoracic vertebra BMD correlated with the first lumbar vertebra BMD on the first r = 0.863, ($p < 0.001$) and the second CT scan r = 0.868 ($p < 0.001$), respectively (**Supplementary Fig. 1).**

Table 1
Associate morbidity

	No OSA	Mild OSA	Moderate/ Severe OSA	p-value
n	140	77	97	
CVD	28%	39%	51.6%	<0.001
HTN	33.4%	54.6%	54.6%	<0.001
CVD – cardiovascular disease, HTN – hypertension.				
p-value was determined by chi-square test.				

Table 2
Polysomnographic characteristics of obstructive sleep apnea patients

	Mild OSA	Moderate/Severe OSA	p-value
N	77	97	
Men	53.3%	67%	0.11
Age (years)	58.9 ± 12.9	63.8 ±9.9	0.007
BMI (kg/cm^2)	30.1 ± 6.5	35.6 ± 32.2	0.111
ESS (score)	9.3 ± 6.4	8.8 ± 9.7	0.774
Ar index (events/hr)	26.8 ± 27.6	35.0 ± 21.3	0.037
Sleep efficiency (%)	82.8 ± 10.1	81.9 ± 13.8	0.657
Wake O_2	95.7 ± 2.8	95.7 ± 3.0	0.866
T_{90} (%)	8.8 ±14.8	15.1 ± 23.1	0.09
DI (events/hr)	11.9± 5.3	29.4 ± 16.7	0.001
Ar index – Arousal and Awakening Index, BMI – Body Mass Index, ESS – Epworth Sleepiness Scale, T_{90} – percent sleeping time in which oxygen saturation was below 90%, DI – desaturation index ≥ 3%. Values are mean ± SD.			
p-value was determined by an unpaired Student's t-test.			

Table 3
Vertebrae bone mineral density

	All		Women		Men	
	No OSA	OSA	No OSA	OSA	No OSA	OSA
Number of vertebrae	202	238	84	100	118	138
Age (years)	58.8 ± 12.5	61.6 ± 12**	58.3 ± 12.1	63.6 ±11.2**	59.2± 12.7	60.3 ±12.3
TBS (day)	1309	1298				
TBS (rang)	31-3125	37-3207				
F- BMD (HU)	136.3 ± 3.1	134.8 ± 2.9^{+}	138.0 ± 5.5	134.0 ± 4.7^{+}	135.0 ± 3.9	135.3 ± 3.7
S- BMD (HU)	129.0 ± 3.1^{+}	122.0 ± 2.8^{+}	132.4 ± 5.2^{+}	120.7 ± 4.6^{+}	126.7 ± 3.8^{+}	122.9± 3.6^{+}
BMD DIFF (HU)	-7.5 ±1.5	-12.8 ±1.2##	-7.8 ± 2.6	-13.4 ± 1.9	-7.2 ±1.7	-12.4 ± 1.54#

Bone mineral density of combined 12 thoracic (T12) and first lumbar (L1) vertebrae; Data include participants who were not administered a contrast agent; OSA – obstructive sleep apnea (apnea–hypopnea index ≥ 5 events/hr), TBS – Time duration between scans, F – first scan, S – second scan, DIFF – difference in HU between second and first CT scans, negative sign indicates a loss in BMD, HU – Hounsfield unit. Values are mean ± SD for age and SEM for the remaining parameters.

# $p < 0.05$, ## $p < 0.01$ first scan vs. second scan. Statistical differences were determined by a two-tailed t-test.

+ $p < 0.01$, no-OSA vs. OSA, statistical differences were determined by a 2-way repeated measurements ANOVA.

Analysis of BMD including subjects that received contrast agent: The BMD of OSA versus no OSA was significantly attenuated (F = 5.9, $p < 0.05$) and in both groups BMD significantly decreased over time (F = 10.67, $p < 0.001$) (**Supplementary Table S1**). The difference in BMD (i.e., BMD in the second scan minus BMD in the first scan) was significantly attenuated by about 6.6 HU in the OSA versus no-OSA group (**Supplementary Table S1**, $p < 0.01$). Women with OSA compared to those without OSA had a low BMD of about 11–17 HU (F = 6.84, $p < 0.01$), and over time the BMD was attenuated in both groups (F = 4.23, $p < 0.05$). Over time, the BMD in men was significantly attenuated in both groups (F = 6.49, $p < 0.05$). No significant changes were found in the BMD between groups in men (F = 0.59, $p = 0.44$). BMD difference was attenuated significantly more in men with OSA versus non-OSA group by 7 HU (**Supplementary Table S1**, $p < 0.01$).

Analysis of BMD excluding subjects that received contrast agent: For all subjects BMD was significantly attenuated over time in both groups (Table 3, F = 11.03, p < 0.001). BMD was significantly attenuated in

the OSA versus non-OSA group (Fig. 2, F= 5.54, p <0.05), and the BMD difference decreased by 5.3 HU more in the OSA group (p = 0.01). Decreased BMD was found over time in women from both groups (F= 5.21, p <0.05), and it was attenuated in the OSA versus non-OSA group (F= 7.50, p <0.01). Men with OSA had similar BMD as the non-OSA group (F= 0.54, p = 0.46), and over time, BMD was attenuated in both groups (F = 5.83, p <0.05).

Factors associated with BMD attenuation

BMD negatively correlate with age r = -0.49 (p < 0.01) and r = -0.43 (p < 0.01) for OSA and no-OSA, respectively. No correlation was found between BMD (or BMD difference) and polysomnography (PSG) findings such as in the oxygen desaturation, apnea–hypopnea, and arousal and awakening indices. The presence of cardiovascular diseases in the OSA versus non-OSA group was associated with lower BMD 127.4 ± 4.7 (HU) versus 139.8 ± 4.2 (HU) (p = 0.04) and 125.2 ± 3.9 (HU) versus 142.2 ± 7.9 (HU) (p = 0.01), respectively. Hypertension in the OSA versus non-OSA groups was associated with low BMD 126.9 ± 4.3 (HU) versus 142.2 ± 4.6 (HU) (p = 0.01) and 129.7 ± 5.4 (HU) versus 144.4 ± 5.3 (HU) (p = 0.05), respectively. Neither cardiovascular diseases nor hypertension affected the L1 difference (data not shown).

Supplementary Table S2 shows the multivariate linear regression of determinants of BMD and BMD difference attenuation including subjects who were administered an enhancement agent. Age (β = -1.8 HU, p < 0.05) and the presence of OSA (β = -7.7 HU, p < 0.029) were associated with BMD attenuation after controlling for the covariates of gender, enhancement agent and cardiovascular diseases. Age (β = 0.15 HU, p < 0.05), OSA (β = -5.99 HU, p < 0.01) and enhancement agent (β = -9.07 HU, p < 0.01) were associated with attenuation of BMD difference after controlling for the covariates of gender and cardiovascular disease.

Tables 4 exhibit the multivariate linear regression of determinants of BMD and BMD difference attenuation excluding subjects that received enhancement agent. Age (β = -1.55 HU, p < 0.05) and OSA (β = -12.8, p < 0.001) were associated with attenuation of BMD after controlling for gender and cardiovascular diseases. Age (β = 0.21 HU, p < 0.01), OSA (β = -4.62 HU, p < 0.05) and cardiovascular diseases (β = -4.52 HU, p = 0.05) were associated with attenuation of BMD differences after controlling for gender.

Table 4
Multivariate linear regression model on BMD and BMD difference attenuation

	Bone Mineral Density		Bone Mineral Density Difference	
	β	95%-CI	β	95%-CI
Age (years)	-1.55	-1.91 up to -1.17**	0.21	0.032 up to 0.38**
Gender (M/F)	5.0	-13.4 up to 3.21	-1.59	-2.54 up to 5.74
OSA (yes/no)	-12.80	-21.40 up to -4.19 **	-4.62	-8.78 up to -0.47*
CVD (yes/no)	4.96	-4.56 up to - 14.49	-4.52	-9.13 up to -0.01*

β – Unstandardized β, Bone Mineral Density (BMD) of combined 12 thoracic vertebrae and first lumbar vertebra scans. Data include participants who were not administered a contrast agent, OSA – obstructive sleep apnea diagnosis (apnea–hypopnea index ≥ 5 events/hr), CVD – cardiovascular disease, F– females, M – males.

* $p = 0.05$, ** $p < 0.01$

Discussion

A limited number of studies have explored the association between OSA (apnea–hypopnea index ≥ 5 events/hr) and vertebra BMD using clinical CT scans. To the best of our knowledge, this is the first longitudinal case-control study reporting BMD attenuation in OSA using real-life clinical records. OSA is associated with BMD attenuation and differences in this attenuation independent of age, cardiovascular disease, and/or contrast agent. Aspects of the clinical implications of our study need further exploration such as vertebra depressed fracture or femoral neck fracture.

We analyzed BMD following statistical adjustments or exclusion of participants who were administered a contrast agent. BMD decreased more in the OSA relative to the non-OSA group. Administration of a contrast agent to the same patient in a single session may enhance the trabecular space and affect HU in the range of 11–18; however, considerable variability between patients was observed.[19] Recently after analysis of a large retrospective cohort of 20,374 CT scans, Jang[16] et al. concluded that it is debatable whether such differences in HU would be meaningful enough in the setting of optimistic screening.

We found no association between BMD and oxygen saturation or arousals and the awakenings index. Supporting our findings, in a cross-sectional study of 115 obese men and women with OSA, Mariani[20] et al. also found a lack of association between the apnea–hypopnea index and BMD. Hamada[17] et al. found that only an alveolar–arterial oxygen pressure difference in OSA was associated with attenuation of BMD. Cohort studies found that hypoxia, the hallmark of OSA, was associated with an increased risk for falls, incidents of fractures,[21] and osteoporosis.[22] Sleep fragmentation can affect bone resorption via increased sympathetic tone and/or hormonal factors.[7,23–26] In the current study, cardiovascular diseases and/or hypertension, negatively affected BMD and the BMD difference in both groups. It is possible that

the sympathetic overdrive associated with cardiovascular diseases[27,28] contributed to bone loss in our study. Orexin plays a key role in sleep homeostasis and sympathetic activity, and through orexin receptor 1 on bone mass.[29] We recently found that enhanced orexin in chronic upper airway obstruction (a rat model for OSA) can contribute to inadequate sleep and bone mass loss.[30,31]

Measurement of BMD by dual-energy x-ray absorptiometry found an association between OSA and the attenuation of bone metabolism/architecture.[21,32–38] However, dual-energy x-ray absorptiometry is limited in measuring attenuation in a large body mass index.[39–41] Confounding information is available regarding the association between OSA and bone health using dual-energy x-ray absorptiometry scanning.[20,33–35,37–39] Because OSA is associated with overweight and obesity,[1] BMD values determined by dual-energy x-ray absorptiometry may be misleading as large as 5–50% in several studies.[40,41] Further studies are required to reinforce our findings by measuring dual-energy x-ray absorptiometry and bicameral markers at the same time as the CT scans are performed.

Study strengths and limitations

We analyzed routine CT scans of “typical” adults referred for OSA diagnosis.[3] One of the strengths of our study is its "real life" conditions with no research intervention. However, our study does have some limitations due to its retrospective single-center nature, and we do not know the causality or mechanism between OSA and BMD. It is possible that selection bias could be overcome by a prospective study design. However, according to the Israeli National Health Insurance Law (implemented in 1995), all enrollees have free access to medical services.[42] In the current study, we included enrollees of Clalit Health Services, the largest health maintenance organization in Israel (about 53% Israeli population) that keeps strict electronic registry of patient records.[3,4,18] Since physicians are paid per patient by a capitation fee once every 3 months, they do not have economic incentives to prevent or deter patients from medical services.[3,4,18,43] The non-OSA group could not be considered “normal healthy” since they were randomly selected from a database of ambulatory CT scans in a medical arena. We were not permitted to contact the non-OSA group to obtain additional medical information regarding their BMI and snoring because of legislation that protects patient confidentiality.[42] According to our medical registry, the non-OSA participants did not have a history of PSG study; however, due to poor awareness of sleep-disordered breathing, we cannot rule out the possibility that some may have had unrecognized OSA.[44]

Conclusions

To the best of our knowledge, this is the first case-control study reporting the attenuation of BMD in OSA patients. OSA (apnea–hypopnea index ≥ 5 events/hr) was associated with BMD attenuation after controlling for age, gender, and cardiovascular diseases. Further studies are needed regarding clinical implications of BMD attenuation in OSA, such as vertebra depressed fracture or femoral neck fracture.

Methods

Setting

A retrospective case-control study was conducted at the Sleep-Wake Disorders Center and Imaging Institute at Soroka University Medical Center, in which all patients were enrollees of Clalit Health Care Services (CHS). According to the Israeli National Health Insurance Law,[42] all enrollees have free access to medical services, and physicians have no economic incentives to prevent or deter patients from PSG study and/or CT examination.[3,4,18]

This was a retrospective study and a waiver for informed consent was obtained from the Institutional Review Committee of Soroka University Medical Center. All methods were performed in accordance with the Israeli regulations. The Institutional Review Committee of Soroka University Medical Center approved the study protocol (protocol number SOR-20-0250).

Study groups

From June 2010 until September 2020, we retrospectively recruited the entire cohort of adults (n = 259, aged 24 through 85 years), who were referred to overnight PSG diagnosis of OSA and who performed at least two ambulatory abdominal CT examinations (at a constant peak voltage of 120 kV) (**Supplementary Fig. 2**). All subjects had “typical” symptoms of OSA and had been referred by an otolaryngology surgeon, pulmonologist, or neurologist. Subjects who underwent PSG were matched with a comparison group (non-OSA) that was selected randomly from the general population in the Soroka University Medical Center database. According to this database, none of the comparison group had a history of sleep problems or had had a PSG study.

Excluded from both groups were patients with any disease that influenced bone metabolism or who were receiving medicine that could influence bone metabolism (n = 41, Fig. 1) such as: chronic obstructive pulmonary disease, genetic disorders, cancer, autoimmune disorders, chronic liver disease, chronic renal insufficiency, musculoskeletal and connective tissue disorders, lumbar surgery, malabsorption disease, fibromatosis, unspecified anticonvulsants, and endocrine disorders, or who were wheelchair bound. We excluded patients receiving the following medications: oral corticoid, hormone replacement, or osteoporosis therapy; proton pump inhibitors; and anticonvulsant and anticoagulant drugs. Of the remaining 280 patients, two subjects had missing PSG data, and in 15 patients CT data could not be analyzed (the scan was not performed at 120 kV). 201 patients were included in the analysis, and of these, 27 did not have OSA (AHI <5 events/hr). Therefore, the OSA group comprised 174 patients.

CT examination of 124 non-OSA patients were analyzed and, of these, data of 10 CTs could not be analyzed (examination not performed at 120 kV). We grouped 27 PSG patients who tested negative to OSA (AHI < 5 events/h) with the 114 subjects in comparison group; the non-OSA group included 141 subjects.

Medical diagnoses retrieved from the Soroka University Medical Center database are documented only by physicians using the International Classification of Diseases, Ninth Revision (ICD-9) code. This database contains >99% of all patient diagnoses. We reviewed the following diagnosed cardiovascular diseases [codes 410–414, 426–438, 443] and hypertension [code 401–405]. A self-administered questionnaire assessed the Epworth sleepiness scale (ESS), where a higher the score indicates a higher level of sleepiness.[45]

PSG study: Data were acquired using a commercially available sleep monitoring system (Viasys, SomnoStar Pro; Yorba Linda, CA, USA or SomniPro 19 PSG; Deymed Diagnostic, Hronov, Czech Republic), as previously described by our laboratory.[46,47] On the study day, participants were advised to maintain their sleep–wake routine and avoid consumption of caffeine and soft drinks. The overnight PSG included recordings of an EEG (C3/A2, C4/A1, and O2/A1, O1/A2), electrooculogram (right and left outer cantHU), electromyogram, and electrocardiogram. Scoring was done by a trained technologist and reviewed by one of the investigators (A.T.). Arousals and awakenings were scored using the American Sleep Disorders Association (ASDA) assessment.[47] The apnea–hypopnea index was defined as the sum of all obstructive and mixed apneas, plus hypopneas associated with a ≥30% reduction in airflow and either ≥ 4% oxygen desaturation or electroencephalographic arousal, divided by the hours of total sleep time.[46–48] The percent of sleeping time in which oxygen saturation was below 90% (T_{90}) was calculated. OSA severity was defined as AHI 1–4.9 events/h, AHI 5.0–14.9 events/h, or AHI ≥ 15 events/h were considered as no OSA and mild and moderate/severe OSA, respectively.

Measurement of BMD of vertebral bone

We used 1-mm thick abdominal sections from CT examinations obtained during ambulatory or emergency room visits using a Siemens SOMATOM Definition AS+ Scanner (Siemens Healthcare GmbH, Erlangen Germany) or a Philips Brilliance ICT scanner (Haifa, Israel). We retrospectively accessed the CT examinations at a constant peak voltage of 120 kV with a variable mAs tube. We included CT scans with or without a contrast agent and evaluated vertebral BMD on a standard radiology picture archiving and communication (PACS) system workstation, with images viewed in bone windows, i.e., gray-scale assignment of the image display, to emphasize bone without the influence of attenuation/BMD values (**Supplementary Fig. 2**).[16,49] We included examinations either with or without an intravenous enhancement agent. We assessed vertebral BMD by placing a single oval click-and-drag region of interest (ROI) in an axial and sagittal slice over an area of vertebral body trabecular bone and then measured CT attenuation in HU, with a lower HU (lower attenuation) representing less-dense bone, at each of the T12 and L1 levels. On the axial images of the selected slice—the superior part of the vertebra—the elliptical ROI was encompassed manually as the largest possible area at the anterior portion of each vertebral body, and in the sagittal plane, we focused on the upper anterior part of the vertebra in order to avoid the Dense Tracecular zone. The mean CT scan density of the ROI was measured. We avoided placing the ROI near areas that would distort the BMD measurement (focal heterogeneity or lesion, posterior venous plexus, compression fracture, and artifacts). A CHS engineer from the Biomedical Engineering

Department calibrated the CT scanners routinely according to the manufacturer's instructions using an American College of Radiology-accredited phantom. BMD was expressed in milligrams per milliliter of hydroxyapatite.[16]

Statistical Analysis

Statistical analyses were performed using R Statistical Software, version 3.5.2 (Foundation for Statistical Computing, Vienna, Austria). We compared the proportion of cardiovascular diseases and hypertension between patients with and without OSA using a Pearson chi-square test. Age, body mass index, the Epworth sleepiness scale, the arousal and awakening index, sleep efficiency, oxygen desaturation index (> 4%), and the percent of sleeping time in which oxygen saturation was below 90% were compared between patients with mild and moderate/severe OSA using a Student's t-test. The first and second BMD measurements and the difference between the two BMD (i.e., BMD on the second scan minus BMD on the first scan) measurements were compared between the OSA and non-OSA groups using a Student's t-test. We further evaluated the difference within the two measurements between the OSA and non-OSA groups using a two-ways repeated measurements ANOVA. To assess the independent association between OSA and the first measurement BMD and the BMD difference between the two measurements, we used a multivariate linear regression adjusted for patient age, gender, and diagnosis of cardiovascular diseases. The beta values, including the 95% Confidence Interval (CI) and p values for each variable, were calculated. Null hypotheses were rejected at the 5% level.

Declarations

Acknowledgments

This study was supported by the Israel Science Foundation grant no. 164/2018.

Author Contributions

D.S., Y.C.F., I.S., and A.T., conceived and designed the experiments; Y.C.F analyzed the CT scans; S.D. and A.T. analyzed the data; A.T. wrote the final version of the paper and recruited funds.

Conflict of interest

The authors declare that no financial OR non-financial competing interests exist, and that none of the material in this manuscript has previously been published.

References

1. Gottlieb, D.J. & Punjabi, N.M. Diagnosis and management of obstructive sleep apnea: a review. *JAMA* **323**(14), 1389-1400 (2020).
2. Young, T. *et al*. Burden of sleep apnea: rationale design major findings of the Wisconsin Sleep Cohort study. *WMJ* **108**(5), 246-9 (2009).

3. Tarasiuk, A. & Reuveni, H. The economic impact of obstructive sleep apnea. *Curr. Opin Pulm. Med.* **19,** 639-44 (2013).
4. Reuveni, H., Greenberg-Dotan, S., Simon-Tuval, T., Oksenberg, A. & Tarasiuk A. Elevated healthcare utilisation in young adult males with obstructive sleep apnoea. *Eur. Respir. J.* **31**(2), 273-9 (2008).
5. Wright, N.C. *et al.* The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner. Res.* **29**(11), 2520-6 (2014).
6. Sadaf, S., Shameem, M., Siddiqi, S.S., Anwar., S. & Mohd, S. effect of obstructive sleep apnea on bone mineral density. *Turkish Thoracic Journal* **22**(4), 301-31 (2021).
7. Swanson, C.M. *et al.* Obstructive sleep apnea and metabolic bone disease: insights into the relationship between bone and sleep. *J. Bone Miner. Res.* **30**(2), 199-211 (2015).
8. Swanson, C.M. *et al.* The importance of the circadian system & sleep for bone health. *Metabolism* **84**, 28-43 (2018).
9. Sin, D.D., Man, J.P. & Man, S.F. The risk of osteoporosis in Caucasian men and women with obstructive airways disease. *Am. J. Med.* **114,** 10-14 (2003).
10. Huang, T., Tworogerm, S., Redline, S., Curhan, G.C. & Paik, J.M. Obstructive sleep apnea and risk for incident vertebral and hip fracture in women. *J. Bone Miner. Res.* **35**(11), 2143-50 (2020).
11. Johannesdottir, F., Allaire, B. & Bouxsein, M.L. Fracture prediction by computed tomography and finite element analysis: current and future perspectives. *Curr. Osteoporos Rep.* **16**(4), 411-22 (2018).
12. Lee, S.J. & Pickhardt, P.J. Opportunistic screening for osteoporosis using body CT scans obtained for other indications: the UW experience. *Clin. Rev. Bone. Miner. Metab.* **15**(3), 128-137, 2017.
13. Jain R.K., Lee, E., Mathai, C. *et al.* Using opportunistic screening with abdominal CT to identify osteoporosis and osteopenia in patients with diabetes. *Osteoporos Int.* **31**(11), 2189-96 (2020).
14. Romme, E.A. *et al.* Bone attenuation on routine chest CT correlates with bone mineral density on DXA in patients with COPD. *J. Bone Miner. Res.* **27**(11), 2338-43 (2012).
15. Yu, W. *et al.* Spinal bone mineral assessment in postmeno pausal women: a comparison between dual X-ray absorptiometry and quantitative computed tomography. *Osteoporos Int.* **5**(6), 433-9 (1995).
16. Jang, S., Graffy, P.M., Ziemlewicz, *et al.* Opportunistic osteoporosis screening at routine abdominal and thoracic CT: normative L1 trabecular attenuation values in more than 20 000 adults. *Radiology* **291**(2), 360-7 (2019).
17. Hamada, S. Evaluation of bone mineral density by computed tomography in patients with obstructive sleep apnea. *J. Clin. Sleep Med.* **12**(1), 25-34 (2016).
18. Dagan, N. *et al.* BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N. Engl. J. Med.* **384**(15), 1412-23 (2021).
19. Pompe, E. *et al.* Intravenous contrast injection significantly affects bone mineral density measured on CT. *Eur Radiol.* **25**(2), 283-9 (2015).

20. Mariani, S. *et al*. Obstructive sleep apnea and bone mineral density in obese patients. *Diabetes. Metab. Syndr. Obes.* **5,** 395-401 (2012).
21. Cauley, J.A. *et al.* Osteoporotic Fractures in Men Study. Hypoxia during sleep and the risk of falls and fractures in older men: The Osteoporotic Fractures in Men Sleep Study. *J. Am. Geriatr. Soc.* **62**(10), 1853-9 (2014).
22. Upala, S., Sanguankeo, A. & Congrete, S. Association between obstructive sleep apnea and osteoporosis: a systematic review and meta-analysis. *Int. J. Endocrinol Metab.* **2**, 4(3):e36317 (2016l)
23. Almendros, I., Carreras, A., Montserrat, J.M., *et al.* Potential role of adult stem cells in obstructive sleep apnea. *Front Neurol.* **3**, 112 (2012).
24. Oishi, S. Intermittent hypoxia influences alveolar bone proper microstructure via hypoxia-inducible factor and VEGF expression in periodontal ligaments of growing rats. *Front Physiol.* **7**, 416 (2016).
25. Elefteriou, F., Campbell, P. & Ma, Y. Control of bone remodeling by the peripheral sympathetic nervous system. *Calcif. Tissue Int.* **94**(1), 140-51 (2014).
26. Tarasiuk, A. & Segev, Y. Abnormal growth and feeding behavior in upper airway obstruction in rats. *Front Endocrinol*. **9**, 298 (2018).
27. Grassi, G., Seravalle G. & Mancia, G. Sympathetic activation in cardiovascular disease: evidence, clinical impact and therapeutic implications. *Eur. J. Clin. Invest.* **45**(12), 1367-75 (2015).
28. Farhat, G.N. & Cauley, J.A.The link between osteoporosis and cardiovascular disease. *Clin. Cases Miner. Bone Metab*. **5**(1), 19-34 (2008).
29. Wei, W. *et al*. Orexin regulates bone remodeling via a dominant positive central action and a subordinate negative peripheral action. *Cell Metab.* **19**, 927-40 (2014).
30. Assadi, M.H., Segev, Y. & Tarasiuk, A. Upper airway obstruction elicited energy imbalance leads to growth retardation that persists after the obstruction removal. *Sci. Rep.* **10**(1), 3206 (2020).
31. Tarasiuk, A., Levi, A., Assadi, M.H., Troib, A. & Segev, Y. Orexin plays a role in growth impediment induced by obstructive sleep-breathing in rats. *Sleep* **39**, 887-97 (2016).
32. Blake, G.M. & Fogelman, I. The role of DXA bone density scans in the diagnosis and treatment of osteoporosis. *Postgrad. Med. J* **83,** 509-17 (2007).
33. Chen, Y.L. *et al.* Obstructive sleep apnea and risk of osteoporosis: a population-based cohort study in Taiwan. *J. Clin. Endocrinol. Metab.* **99**(7), 2441-7 (2014).
34. Tomiyama, H. Link between obstructive sleep apnea and increased bone resorption in men. *Osteoporos Int.* **19**, 1185-92 (2008).
35. Uzkeser, H. *et al*. Bone mineral density in patients with obstructive sleep apnea syndrome. *Sleep Breath.* **17,** 339-42 (2013).
36. Mariani, S. *et al.* Obstructive sleep apnea and bone mineral density in obese patients. *Diabetes Metab. Syndr. Obes.* **5**, 395-401 (2012).

37. Sforza, E., Thomas, T., Barthélémy, J.C., Collet, P. & Roche, F. Obstructive sleep apnea is associated with preserved bone mineral density in healthy elderly subjects. *Sleep* **36**, 1509-15 (2013).
38. Vilovic, M. *et al.* Bone metabolism parameters and inactive matrix Gla protein in patients with obstructive sleep apnea. *Sleep*. **43**(3), zsz243 (2020).
39. Link, T.M. Osteoporosis imaging: state of the art and advanced imaging. *Radiology* **263**(1), 3-17 (2012).
40. Ho, C.P., Kim, R.W., Schaffler, M.B. & Sartoris, D.J. Accuracy of dual-energy radiographic absorptiometry of the lumbar spine: cadaver study. *Radiology* **176**, 171-3 (1990).
41. Bolotin, H.H. DXA in vivo BMD methodology: an erroneous and misleading research and clinical gauge of bone mineral status, bone fragility, and bone remodelling. *Bone* **41**, 138-54 (2007).
42. National Health Insurance Law. Clause 3(d). Israeli Book of Laws 5754. No. 1469. 1994a.
43. Tarasiuk, A., Reznor, G., Greenberg-Dotan, S. & Reuveni, H. Financial incentive increases CPAP acceptance in patients from low socioeconomic background. *PLoS One* **7**(3), e33178 (2012).
44. Reuveni, H., Tarasiuk, A.,Wainstock, T. *et al.* Awareness level of obstructive sleep apnea syndrome during routine unstructured interviews of a standardized patient by primary care physicians. *Sleep* **27**, 1518-25 (2004).
45. Johns M.W. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep **14**, 540-4 (1991).
46. Goldbart, A.D., Arazi, A., Golan-Tripto, I. *et al.* Altered slow-wave sleep activity in children with rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysregulation syndrome. *J. Clin. Sleep Med*. **16**(10), 1731-5 (2020).
47. Arazi, A. *et al*. Reduced sleep pressure in young children with autism. *Sleep*. **43**(6), zsz309 (2020).
48. Ilber, C., Ancoli-Israel, S., Chesson, A. & Quan, S.F. *The AASM manual for the scoring of sleep and associated events: rules, terminology, ad technical specifications*. Westchester, IL: American Academy of Sleep Medicine (2007).
49. Pickhardt, P.J. *et al.* Simultaneous screening for osteoporosis at CT colonography: bone mineral density assessment using MDCT attenuation techniques compared with the DXA reference standard. *J. Bone Miner. Res.* **26**, 2194-203 (2011).

Figures

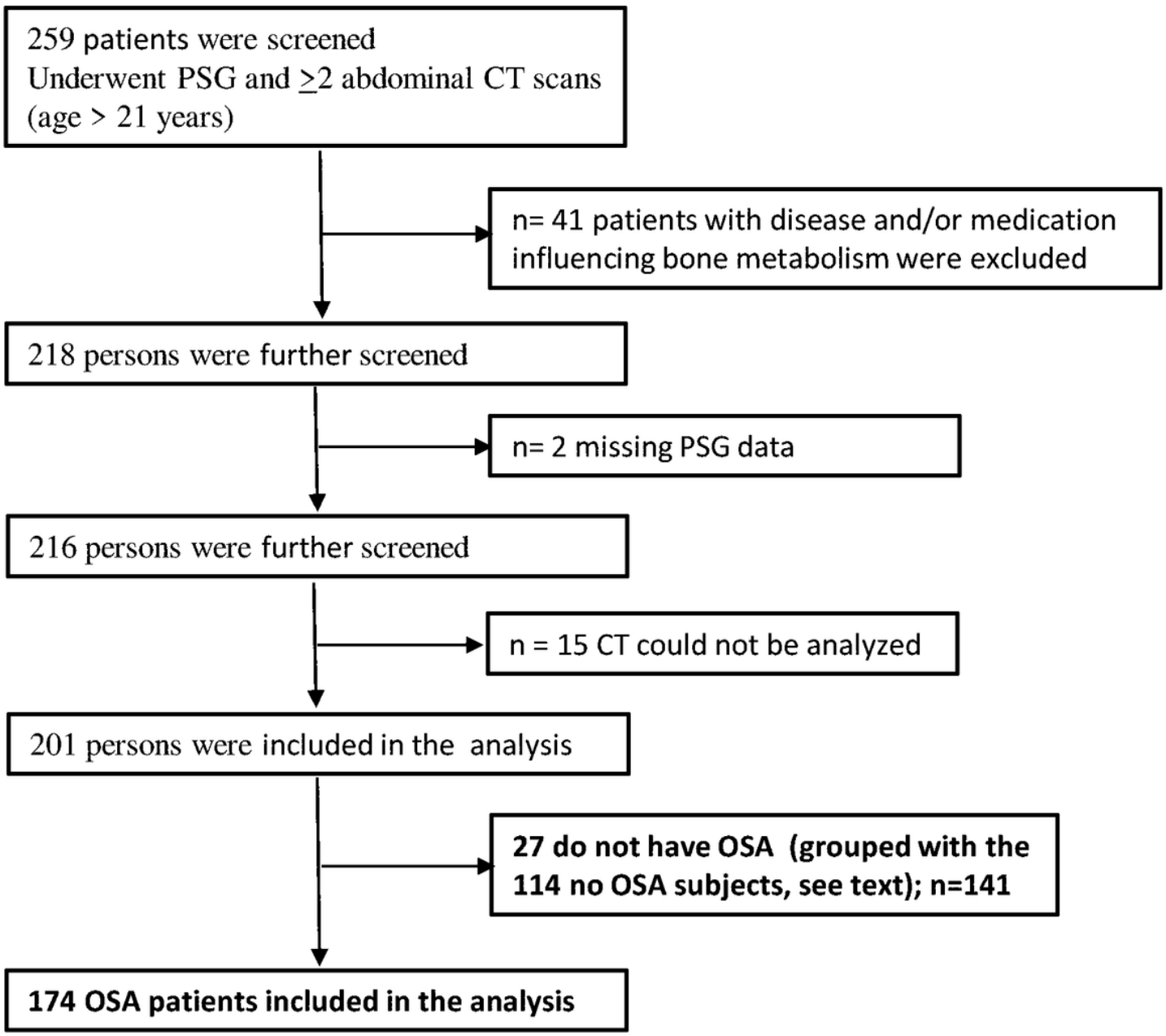

Figure 1

Flow chart of study participants.

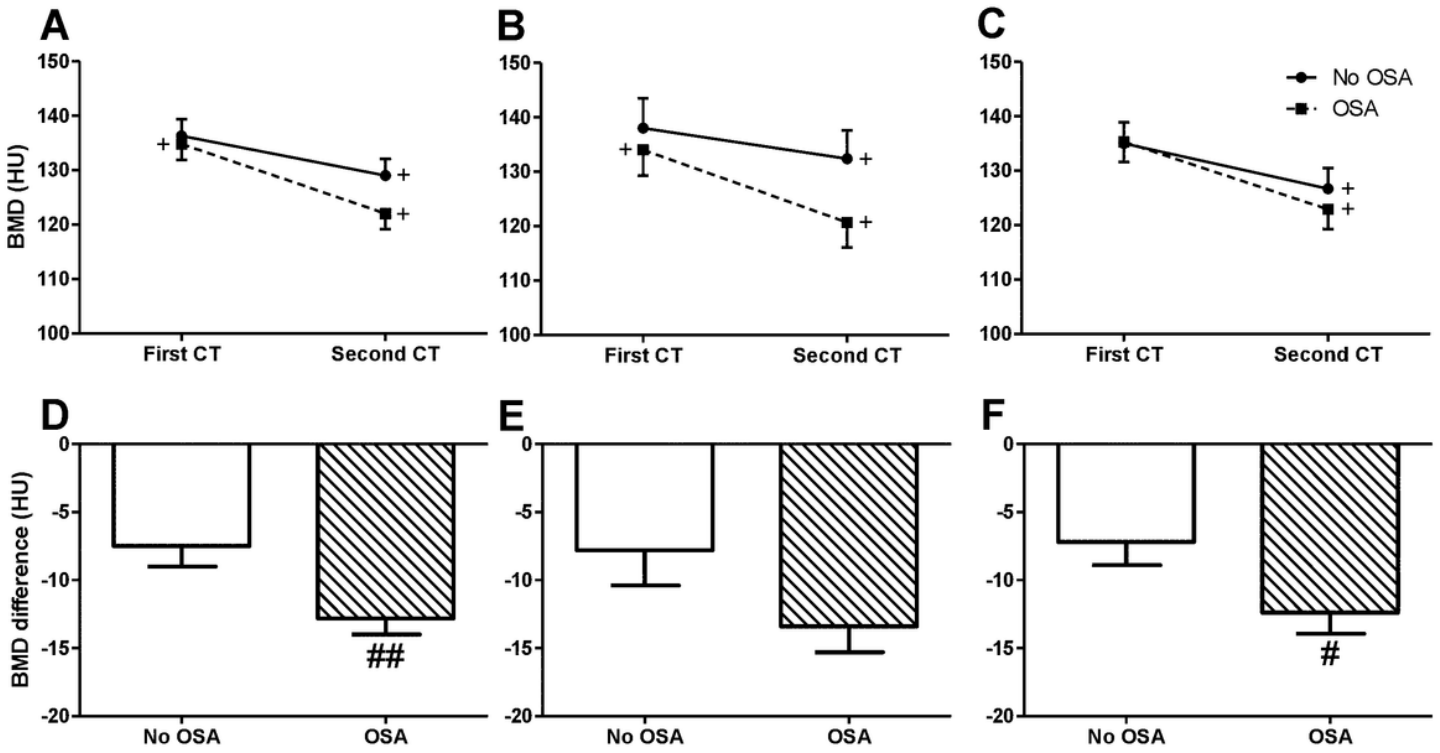

Figure 2

Vertebrae bone mineral density. A) Vertebra BMD for the entire group, B) women's BMD, C) men's BMD, D) DIFF for the entire group, E) DIFF for women, F) DIFF for men. Data showing mean BMD of the 12 thoracic vertebrae and first lumbar vertebra; BMD – bone mineral density, DIFF – difference in HU between the first and second CT scans. HU – Hounsfield unit, OSA – obstructive sleep apnea. # $p < 0.05$, ## $p < 0.01$ first scan vs. second scan BMD. Statistical differences were determined by a two-tailed t test. + $p < 0.01$, no-OSA vs. OSA, statistical differences were determined by a 2-way repeated measures ANOVA.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryInformationfinal.pdf