

Lumbar Spine Abnormalities in Patients With Obstructive Sleep Apnoea

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Abstract

Previous studies suggested cervical spondylosis as a risk factor for development of obstructive sleep apnoea (OSA). We aimed to assess lumbar disc degeneration in patients with OSA and correlate the findings with symptoms and disease severity.

Twenty-seven patients with OSA and 29 non-OSA controls underwent sleep studies and lumbar magnetic resonance imaging (MRI), and completed the Epworth Sleepiness Scale and the 24-item Roland-Morris Disability Questionnaire questionnaires. Plasma klotho was determined with enzyme-linked immunosorbent assay.

Patients with OSA had higher number of disc bulges (4.6 ± 3.7 vs. 1.7 ± 2.5 , $p < 0.01$) and anterior spondylophytes (2.7 ± 4.2 vs. 0.8 ± 2.1 , $p < 0.01$), increased Pfirrmann score (16.7 ± 4.7 vs. 13.2 ± 4.1 , $p < 0.01$) and vertebral fatty degeneration (7.8 ± 4.7 vs. 3.8 ± 3.7 , $p < 0.01$). Markers of OSA severity, including the apnoea-hypopnoea index, oxygen desaturation index and percentage of total sleep time spent with saturation $< 90\%$ as well as plasma levels of klotho were correlated with the number of disc bulges and anterior spondylophytes following adjustment on age, gender and body mass index (all $p < 0.05$). Markers of disc degeneration were related to chronic pain.

OSA is associated with lumbar spondylosis likely through chronic intermittent hypoxaemia inducing inflammation in the lumbar discs. Our study highlights the importance of lumbar imaging in patients with OSA reporting lower back pain.

Introduction

Obstructive sleep apnoea (OSA) is a common disease which is characterised by recurrent episodes of partial or total collapse of the upper airways during sleep [8]. Chronic pain is a common symptom in patients with sleep disorders and people with chronic pain often have difficulties with their sleep [29]. If chronic pain, sleep disturbances, and mood disorders are present at the same time, an umbrella term of fibromyalgia is often used [37]. The link between sleep disorders and chronic pain is related to genetic and neuroendocrine factors, altered sensitivity of pain and systemic inflammation [10, 29]. Interestingly, because of the strong association between disturbed sleep and chronic pain, imaging studies to reveal possible structural musculoskeletal abnormalities are often not performed [12].

The prevalence rate of OSA in patients with chronic pain is 32% [19], and the prevalence of excessively sleepy patients with OSA among those with chronic pain is 14% [25]. This is compatible with the estimated prevalence of OSA and excessively sleepy OSA in the general adult population [1]. In line with this, no association has been found with OSA and musculoskeletal pain [15]. However, it has been demonstrated that chronic pain may impair normal sleep architecture [19] and has significant consequences on the quality of life in patients with OSA [15].

Previous studies focusing on cervical spine reported that OSA was associated with increased number of cervical fusions and osteophytes [13]. More recently, cervical spondylosis was reported as a risk factor for OSA [38]. Yang et al. hypothesised that spondylosis leads to increased collapse potential of the upper airways [38]. Interestingly, no studies assessed the lumbar spine region in OSA, despite the fact that around one third of patients with chronic back pain had abnormalities in their lumbar region [18]. The study of Yang suggested a unilateral causal relationship between cervical spondylosis and OSA. However, there is some evidence that OSA could also lead to spinal deformities directly through chronic intermittent hypoxia [31] and indirectly through vitamin D deficiency [17]. Most importantly, intermittent hypoxia may lead to oxidative stress and inflammation in the lumbar discs which could contribute to spinal disc degeneration [9]. A potential molecule which could be a link between OSA and discopathy is the anti-inflammatory klotho protein, which levels were found decreased both in plasma samples of patients with OSA [24] and in the nucleus pulposus specimens in disc degeneration [3].

We hypothesised that OSA may lead to disc degeneration which could eventually contribute to chronic pain. To check on this, we performed a sleep study, a lumbar MRI and measured plasma klotho levels in patients with OSA and non-OSA controls.

Methods

Study subjects and design

Fifty-six volunteers from the Hungarian Twin Registry [34] who attended a sleep study [33] and had a lumbar magnetic resonance imaging (MRI) took part in this study. Only one member of the twin pair was randomly selected for this analysis. None of the subjects had previously been diagnosed with obstructive sleep apnoea or lumbar spinal disease, hence none received any treatment for these.

The subjects first attended the Sleep Laboratory, Department of Pulmonology, Semmelweis University. In the evening after taking their medical history, they filled out the Epworth Sleepiness Scale (ESS), the 24-item Roland-Morris Disability Questionnaire (RMDQ) and a custom made back-pain questionnaire (Supplement 1). This was followed by an inpatient polysomnography (n = 39) or cardiorespiratory polygraphy (n = 17). The following day fasting blood was taken for klotho which was measured with commercially available enzyme-linked immunosorbent assay as described previously [24].

Patients then attended a lumbar spine MRI on a Siemens Magnetom Verio 3T scanner in the Borsod-Abaúj-Zemplén County Hospital (Miskolc, Hungary) or on a Philips Ingenia 1.5T in the Medical Imaging Centre of Semmelweis University (Budapest, Hungary).

Comorbidities were derived from subject reports and their medications. Exclusion criteria included acute heart failure, pregnancy, breastfeeding, those with a positive pregnancy test, immunosuppressive/immunomodulatory therapy in the last 30 days, including systemic steroid-containing medicines, chemotherapy in the last year, major surgery in the last 2 months, transfusion,

receiving other blood products in the last 2 months, pacemaker, ICD, other implanted device, magnetisable metal object in the body, claustrophobia and aphasia.

This study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committees (Semmelweis University TUKEB 30/2014 and Borsod-Abaúj-Zemplén County Hospital in Miskolc, Hungary). All volunteers gave their written informed consent before participating in the study. The study was not preregistered.

Sleep studies

Sleep studies were performed with the Somnoscreen Plus Tele PSG and the Somnoscreen RC devices (Somnomedics GmbH) between 22:00 and 06:00 as described previously [20]. Apnoea was defined by a 90% decrease of the nasal airflow, which lasted for more than 10 s, and hypopnea was defined as at least 30% airflow decrease lasting for at least 10 s, which related to a $\geq 3\%$ oxygen desaturation or an arousal. We recorded the total sleep time (TST) and sleep period time (SPT). Apnoea-hypopnoea index (AHI), oxygen desaturation index (ODI) and percentage of time spent with oxygen saturation below 90% (TST90%) were calculated as markers of OSA severity. Sleep efficiency was calculated as TST/SPT. OSA was defined by an AHI ≥ 5 /hours.

Lumbar magnetic resonance imaging

Sagittal T1-weighted, T2-weighted, short tau inversion recovery (STIR) and axial T2-weighted images were performed. Grading was performed on T2-weighted and STIR images retrospectively by two experienced radiologists. Axial sections were obtained at selected levels to assess structural changes in individuals who had features suggesting prolapse.

The presence or absence of disc dehydration, disc height narrowing, disc bulging and disc herniation was noted based on the standardized criteria [5, 6, 35]. Disc dehydration was established based on sagittal T2-weighted images when signal intensity of the disc was lower compared to the cerebrospinal fluid. We did not distinguish between the varying levels of dehydration. Disc height narrowing was registered when the height of the disc proved to be equal or lower than the one directly cranial to it on sagittal T1-weighted images. Disc height narrowing of the L5 disc was registered only if its height was lower than that of the L4 disc. In case of an intervertebral disc material extending beyond the space between the vertebral bodies, bulging or herniation was noted when the overextension was broad (more than 25% of disc circumference) or narrow (less than 25% of disc circumference) respectively on axial T2-weighted images. All disc bulging and hernia was counted and summarized as a total value between Th12 and S1 segments. Total endplate score (TEPS) was used to assess the level of endplate degeneration [28]. Endplate defect was evaluated on T1-weighted scans and classified into six types according to severity of damage (type 1 to type 6) assessed on T1-weighted sequences. TEPS was derived from each disc by adding up the endplate defect scores of both rostral and caudal endplates of the disc. Disc degeneration was assessed by the Pfirrmann's grading (Pfirrmann score) on T2-weighted images and discs were considered to be healthy if they were Grade I, II or III and degenerated if they were Grade IV or V [27] and the total score for the entire lumbar spine was calculated. Due to the degeneration of the disc and small

joints, the vertebrae may move. In order to characterize this feature of degeneration, the presence and severity (length compared to the lower vertebral body) of anterolisthesis, which refers to anterior displacement (forward slip) of a vertebral body relative to the one below, and retrolisthesis was also recorded [2]. To evaluate superior and inferior endplate disease, each endplate was evaluated on T1-weighted scans and classified into 4 types as no abnormality (0), mild (1 to 5 mm), moderate (5 to 10 mm) and severe (over 10 mm) defect and the average score was calculated for the entire lumbar spine. Presence (1) or absence (0) of superior and inferior Schmorl nodes, defined as endplate breaks with depression of subchondral bone of incremental severity, were recorded on T1- or T2- weighted scans. Vertebral fatty degeneration was analysed on T1-weighted scans and characterized as none (0), mild (1, up to 25% fatty infiltration), moderate (2, 25–50% fatty infiltration) and severe (3, 50–100% fatty infiltration) and total score for the lumbar spine was calculated. The presence of anterior and posterior spondylophytes was recorded. The presence of annular high intensity zone (HIZ), a high-intensity focal signal on T2-weighted sequences in the posterior annulus fibrosus with a considerably brighter signal intensity than nucleus pulposus that is distinctly dissociated, was marked [36].

Statistical analysis

The Statistica 12 (StatSoft, Inc., Tulsa, OK, US) software was used for analysis. The normality of the data was assessed with the Kolmogorov-Smirnov test. The OSA and control groups were compared with t-test, Mann-Whitney, Fisher and Chi-square tests. Comparisons of back pain and MRI results were adjusted for age, gender, and body mass index (BMI). Sleep parameters were correlated with outcomes of pain questionnaires and MRI parameters using Spearman's correlation (continuous variables), negative binomial model (count variables) and logistic regression (dichotomous variables). The latter two analyses were adjusted for gender, age, and BMI. The relationship between discopathy and chronic pain was assessed with logistic regression analysis or negative binomial model following adjustment for age, gender, BMI and ODI. The relationship between klotho levels lumbar spine pathology was assessed with logistic regression or negative binomial model adjusted for gender, age, BMI and ODI. A p value < 0.05 was considered significant.

Sensitivity analyses of the post-hoc power calculation showed that we were able to detect an effect size greater than 0.67 with a power of 0.80 and an alpha error of 0.05.

Results

Comparison of the OSA and control groups

OSA was diagnosed in 27 participants, 21 had mild (AHI < 15/h) disease. Patients with OSA were older, had higher prevalence of smoking history, hypertension, cardiovascular or cerebrovascular disease and osteoporosis (all p < 0.05) and tended to have higher BMI (p = 0.05). As expected, AHI, ODI and TST90% was higher in patients with OSA (p < 0.05, Table 1).

Table 1
Comparison of demographics and clinical characteristics of patients with OSA and controls

	OSA (n = 27)	Controls (n = 29)	p
Age (years)	60 /53–68/	41 /28–54/	< 0.01
Gender (male %)	33	28	0.64
BMI (kg/m ²)	26.6 /23.3–29.6/	24.4 /21.0-27.7/	0.05
Smoker (ever %)	26	3	0.01
Hypertension (%)	67	28	< 0.01
Cardiovascular or cerebrovascular disease (%)	26	3	0.01
Diabetes (%)	22	10	0.22
Dyslipidaemia (%)	48	38	0.44
Asthma (%)	11	7	0.58
COPD (%)	7	3	0.51
Osteoporosis (%)	19	0	0.01
ESS	6 /4.5–10.5/	6	0.76
TST (min)	394 /378–430/	416 /362–424/	0.67
SPT (min)	435 /406–462/	425 /407–437/	0.41
Sleep %	95 /89–98/	96 /92–99/	0.32
AHI (1/h)	9.4 /6.5–14.2/	2.3 /1.0-2.8/	< 0.01
ODI (1/h)	8.4 /4.9–11.2/	0.9 /0.2–1.7/	< 0.01
TST90% (%)	1.3 /0.2–2.9/	0.0 /0.0–0.0/	< 0.01

AHI – apnoea-hypopnoea index, BMI – body mass index, COPD – chronic obstructive pulmonary disease, ESS – Epworth Sleepiness Scale, ODI – oxygen desaturation index, OSA – obstructive sleep apnoea, Sleep% - sleep efficiency, SPT – sleep period time, TST – total sleep time, TST90% – percentage of total sleep time spent with oxygen saturation below 90%.

Chronic pain in patients with OSA and controls

There was no difference in the life-time prevalence of lower back pain between the OSA (85%) and control groups (72%, unadjusted, $p = 0.29$, adjusted $p = 0.47$). Thirty-eight percent of the patients and 34% of controls reported lower back pain in the last 4 weeks (unadjusted $p = 0.87$, adjusted $p = 0.40$). In contrast, 55% of patients compared to 28% controls reported that lower back pain limits their daily activities (unadjusted $p = 0.04$, adjusted $p = 0.06$). However, there was no difference in the RMDQ score between the two groups (0 /0-3.5/ vs. 0 /0–1/; OSA vs. controls, respectively, unadjusted $p = 0.32$, adjusted $p = 0.48$).

Similarly, no significant difference was found regarding responses to other questions between the two groups (all $p > 0.05$).

None of the sleep parameters related to the life prevalence of lower back pain or lower back pain in the last 4 weeks ($p > 0.05$). Interestingly, those participants who reported limitations in their daily life due to back pain had higher ESS ($\beta = 0.29$, $p = 0.04$), but no other sleep parameter related to this outcome. In line with this, there was a tendency for a direct relationship between RMDQ and ESS ($\rho = 0.27$, $p = 0.07$). There was no relationship between chronic pain and BMI (all $p > 0.05$).

Lumbar spine spondylosis in patients with OSA and controls

Patients with OSA had an increased number of disc bulges and anterior spondylophytes, a higher Pfirrmann score and increased magnitude of vertebral fatty degeneration (all $p < 0.01$). There was no difference in any other degenerative parameter (Table 2).

Table 2

Characteristics of lumbar spine spondylosis and discopathy in patients with OSA and controls

	OSA (n = 27)	Controls (n = 29)	p
Disc hernia (all types %)	28	26	0.92
Number of all disc hernias (n)	0.6 ± 1.0	0.3 ± 0.5	0.93
Total endplate score (n)	20.9 ± 7.8	20.8 ± 9.7	0.37
Disc bulging (any %)	85	52	< 0.01
Number of all disc bulgings (n)	4.6 ± 3.7	1.7 ± 2.5	< 0.01
Pfarrmann score (total n)	16.7 ± 4.7	13.2 ± 4.1	< 0.01
Anterolisthesis (any %)	15	3	0.12
Anterolisthesis (mm)	0.7 ± 1.8	0.1 ± 0.7	0.13
Retrolisthesis (any %)	12	3	0.11
Retrolisthesis (mm)	0.3 ± 1.0	0.2 ± 1.1	0.28
Superior endplate disease (n)	0.8 ± 1.6	0.7 ± 2.1	0.24
Inferior endplate disease (n)	0.8 ± 1.3	0.7 ± 2.0	0.16
Superior Schmorl nodes (n)	0.8 ± 1.2	0.9 ± 1.4	0.89
Inferior Schmorl nodes (n)	0.4 ± 0.8	0.7 ± 1.1	0.56
Vertebral fatty degeneration (score between 0 and 18)	7.8 ± 4.7	3.8 ± 3.7	< 0.01
Anterior spondylophytes (n)	2.7 ± 4.2	0.8 ± 2.1	0.01
Posterior spondylophytes (n)	1.1 ± 2.4	0.4 ± 0.9	0.47
Disc height narrowing (mm)	3.3 ± 2.1	3.0 ± 3.2	0.15
Annular high intensity zone (n)	0.6 ± 1.2	0.3 ± 0.6	0.40
*analyses were adjusted for age, gender and BMI.			

Correlation analysis showed significant differences between the number of disc bulges and markers of OSA severity, such as AHI, ODI, TST90% (all $p < 0.05$, Fig. 1) as well as the number of anterior spondylophytes and AHI, ODI and TST90% (all $p < 0.05$, Fig. 2). Of note, a direct relationship was noted between the number of disc bulges and the number of anterior spondylophytes ($\rho = 0.54$, $p < 0.01$). The number of posterior spondylophytes correlated only with ODI ($p < 0.05$). The Pfarrmann score significantly related to AHI ($\rho = 0.40$, $p < 0.01$), ODI ($\rho = 0.56$, $p < 0.01$) and TST90% ($\rho = 0.61$, $p < 0.01$). There was a significant relationship between the disc height narrowing and ODI ($\rho = 0.28$, $p < 0.05$) as well as TST90%

($\rho = 0.29$, $p < 0.05$). None of the other sleep parameters or ESS correlated with any characteristics of lumbar spondylosis (all $p > 0.05$).

The relationship between lumbar spine spondylosis, discopathy and chronic pain

Participants who had any disc bulging had higher RMDQ score ($\beta = 0.92$, $p = 0.04$, Fig. 3), however there was no relationship between disc bulging and life prevalence or 4-week prevalence of lower back pain, or if the pain limited their daily activities (all $p > 0.05$). Interestingly, there was no relationship between the number of disc bulges and RMDQ ($p = 0.20$) or the other pain outcomes ($p > 0.05$).

There was a significant relationship between the Pfirrmann and the RMDQ score ($\rho = 0.32$, $p = 0.02$). There was also a significant relationship between the RMDQ score and number of superior endplate disease, inferior endplate disease as well as the number of anterior spondylophytes (all $p < 0.05$). None of the other characteristics of spondylosis or discopathy were related to measures of chronic pain.

The role of klotho in lumbar spine spondylosis and discopathy associated with OSA

Plasma klotho levels were inversely related to the number of disc bulges ($p < 0.05$, Fig. 4), and there was a tendency for an inverse correlation with total endplate score ($\rho = -0.26$, $p = 0.07$) as well as annular high intensity zones ($\rho = -0.27$, $p = 0.06$). However, there was no further relationship with any other characteristics of spondylosis or discopathy (all $p > 0.05$).

Discussion

According to our knowledge, this is the first study investigating the relationship between obstructive sleep apnoea and lumbar spine abnormalities. We found that OSA was significantly associated with the presence of certain abnormalities, most strongly with disc bulges and anterior spondylophytes which could be the reason for back pain experienced by some patients.

Previous studies focusing on the cervical spinal region reported increased number of spondylophytes in OSA [4, 38] and suggested they may contribute to the development of sleep apnoea [38]. Spondylophytes are bony projections that form along joint margins. Usually, they are associated with the degeneration of the lumbar disc which starts losing water content and leads to a decrease in the intervertebral disc height. To compensate the loss of the flexibility of the annulus fibrosus, apophyseal joints start to grow a new bone [4, 13]. In line with this, we found a significant direct relationship between the number of spondylophytes and disc bulges. Our study extends the previous observations on the cervical spine region to the lumbar region, as the number of disc bulges and spondylophytes were higher in OSA and related to disease severity.

The relationship between OSA and disc degeneration can be explained by multiple mechanisms. Several genes of collagen biosynthesis and inflammation were found to be associated with OSA [26] and disc degeneration [23] as well suggesting for a common genetic origin. Age, male gender and obesity, risk factors for OSA [8], are associated with an increased likelihood for the development of disc degeneration [23, 30]. Of note, the relationship between OSA and discopathy in the present study was present after adjustment for these factors. OSA is also associated with abnormal bone formation likely due to the accelerated remodelling induced by intermittent hypoxia [31] and vitamin D deficiency in sleep apnoea [17]. Chronic intermittent hypoxia in OSA leads to oxidative stress and inflammation [8], both of which are associated with disc degeneration [23]. More particularly, reactive oxygen species can induce the expression of extracellular matrix proteases and proinflammatory markers in disc cells [7]. In line with this, a direct relationship was seen between markers of overnight hypoxaemia and markers of disc degeneration in the current study. In addition, systemic inflammation generated in OSA may also contribute to inflammation in lumbar disc [21].

A potential molecule which is involved in the pathomechanism of both diseases is the klotho protein [3, 24]. This protein is synthesised predominantly in the kidneys, but other organs, such as parathyroid gland, ovary, testis and placenta also express the klotho gene [16]. Klotho is involved in the phosphate homeostasis, it regulates the aldosterone synthesis, has an anti-aging, anti-oxidative stress and anti-inflammatory role [14]. We have reported low levels of klotho in OSA which were associated with markers of overnight hypoxaemia [24]. In line with this, hypoxaemia [11] and oxidative stress [3] lead to decreased klotho expression in nucleus pulposus cells. Klotho attenuates inflammation at the same site [3] and it is hypothesised that lower klotho levels contribute to disc degeneration [3]. In line with this, klotho gene polymorphisms were associated with lumbar spondylosis [22].

In line with previous reports [15], we did not find a significant difference in the reported back pain between patients with OSA and controls. In contrast, back pain was associated with increased daytime sleepiness. Chronic pain can disturb the normal sleep architecture [19] with subsequent daytime effects. Although excessive daytime sleepiness is a common symptom of OSA [8], our study highlights that other factors than OSA can lead to this symptom and these should be explored in clinical practice. Most particularly, clinicians may not accept chronic pain as a natural component of the fibromyalgia syndrome but should investigate anatomic causes for pain and sleepiness. In contrast to OSA, chronic pain was associated with lumbar spondylosis and discopathy. This may highlight an indirect mechanism between spondylosis and OSA development, as chronic pain may limit mobility eventually leading to weight gain. Obesity is a leading cause for OSA and limited exercise could subsequently cause OSA development [8]. A previous meta-analysis concluded that obesity is significantly associated with low back pain [32]. However, our study did not find any relationship between BMI and pain outcomes.

Our study has limitations. First, the number of subjects was relatively low, and increasing the numbers more complex relationships could be detected. Second, two different MR machines were used, however, both members of the twin pair were scanned on the same machine. Third, most of the patients with OSA had mild disease. Enrolling patients with more severe disease could reveal more precisely the relationship

between OSA and lumbar spine degeneration. More importantly, the lack of relationship between OSA and chronic pain could be due to the milder disease severity. Of note, the relationship between OSA and disc bulges as well as spondylophytes was evident even at this severity. None of the patients were treated with continuous positive airway therapy (CPAP). Follow up trials are warranted to see if CPAP could be beneficial in preventing or slowing down spondylosis in patients with OSA. Despite these limitations, we believe that our pioneering study may serve a potential basis for designing large scale studies.

In summary, we report that markers of OSA severity is associated with lumbar spondylosis likely through chronic intermittent hypoxaemia inducing inflammation in lumbar discs. Our study highlights the importance of lumbar imaging in patients with OSA reporting lower back pain.

Declarations

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Author contributions

ADT, DLT, CO, MP, PF, LK, JP, LK, AB made substantial contributions to the conception and design of the work; ADT, DLT, CO, MS, DTK, AD, BF, MM, JP, LK, AB performed the acquisition, MP, JP, AB performed the statistical analysis, ADT, DLT, CO, MP, BF, MP, PF, MM, JP, LK, AB contributed to the interpretation of data; ADT, DLT and AB have drafted the work; all authors substantively revised the work, have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Competing Interests Statement

The authors have no conflict of interest to declare and no competing interests.

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

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Figures

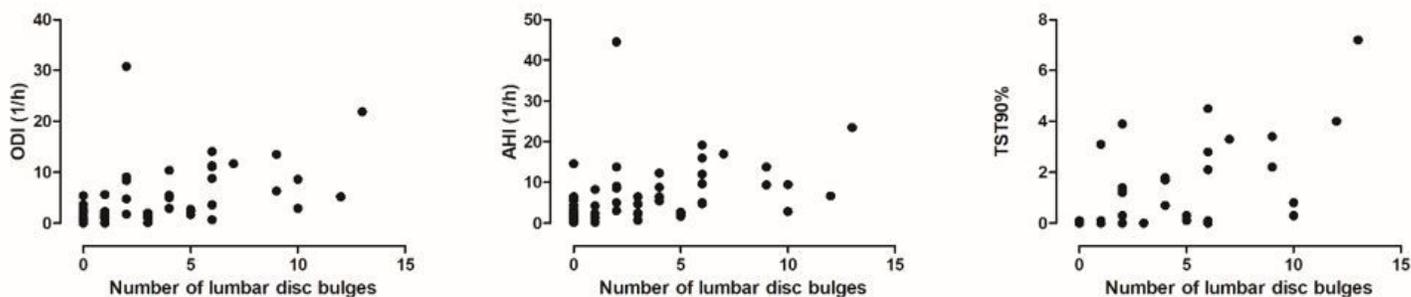


Figure 1

The relationship between the number of lumbar disc bulges and markers of OSA severity

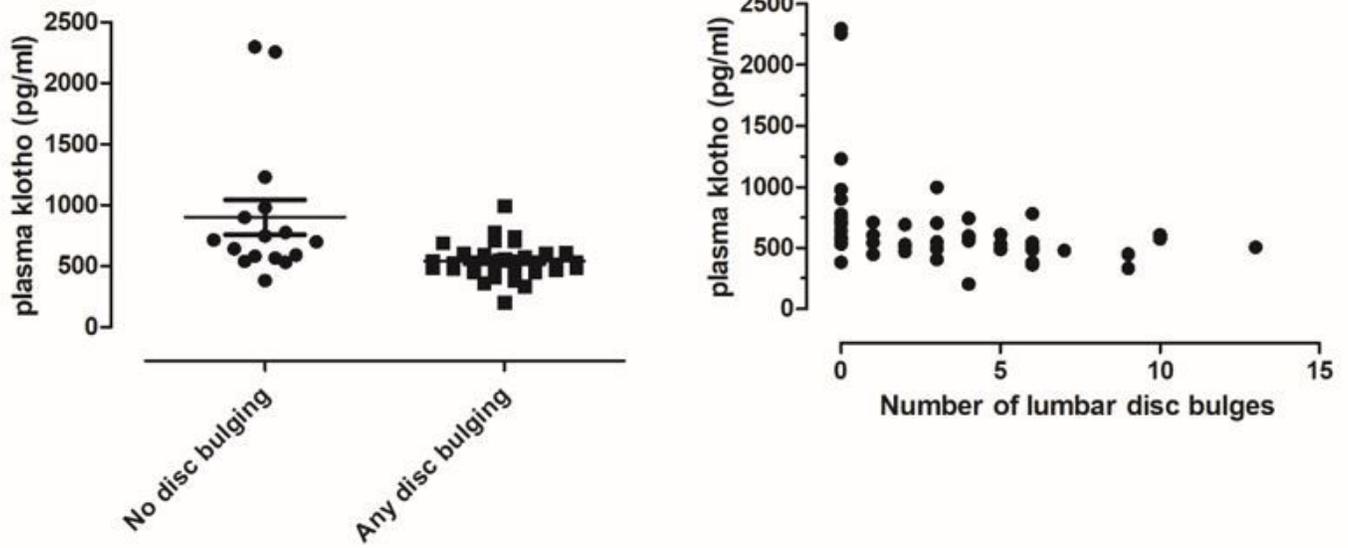


Figure 4

The relationship between plasma klotho levels and lumbar disc bulges.