Could vagus nerve stimulation influence bone remodeling?

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Abstract

Objectives: To investigate the effect of vagus nerve stimulation (VNS) on the bone mineral density (BMD) in epileptic patients. Methods: A prospective cohort study was conducted on individuals with refractory seizures who underwent VNS surgery between January 2012 and December 2018. BMD was measured preoperatively and between 6 months and one year after surgery. Results: Twenty-one patients (mean age (±SD)=23.6±12.3 years) were recruited for the implantation of a VNS device. The mean absolute increase in lumbar BMD in the 21 patients was 0.04±0.04 g/cm² resulting in an overall percent increase from baseline of 4.7±6.1%. BMD increased by an amount ≥ the least significant change (LSC) for the lumbar spine in 13 patients (61.9%). The lumbar Z score also increased in these patients from -1.22±1.15 to -0.88±1.22, P=0.006). Pre and Post VNA femoral BMD was measured in only 11 patients and, of those 3 showed a significant increase in BMD, 1 a significant decrease and 7 no change. Conclusion: The implantation of a VNS was associated with an increase in lumbar BMD. This study could lead to a new application for VNS in the treatment of osteoporosis.

Keywords: Bone Mineral Density, Epilepsy, Osteoporosis, Stimulation, Vagus Nerve

Introduction

The vagus nerve is a mixed autonomic nerve originating from the medulla oblongata. It provides an extensive afferent and efferent network of innervation for viscera and plays an important role in the communication between higher central nervous system (CNS) circuits and the autonomic control circuitry of the brain stem¹. The afferent branches of the vagus nerve are integrated in the brain stem at the level of the nucleus tractus solitarii (NTS), before projecting to the rest of CNS. The role of the brain stem in the integration of the different afferent signals, and the transmission of the efferent signals to the peripheral organs is still not well understood.

Vagus nerve stimulation (VNS) therapy has been used in the treatment of refractory seizures in adults and children since the mid-nineties². The precise mechanisms by which VNS therapy achieves seizure reduction are not well established. Several potential mechanisms have been postulated which are partially supported by animal and human studies. These mechanisms include afferent vagal projections to seizure generating regions in the basal forebrain, the stimulation of locus cerealis, desynchronization of hypersynchronized cortical activity, cortical inhibition secondary to the release of glycine and gamma-aminobutyric acid (GABA) and increased blood flow and neural activity in the thalamus, limbic system and multiple cortical regions².

Epilepsy has been associated with decreased bone
mineral density (BMD) and increased fracture risk. The increased fracture risk in epileptic patients has been attributed to seizure-related-falls and low BMD. Previous reports have highlighted the role of the autonomic system in bone remodeling. Moreover, recent studies have shown that cholinergic stimulation using acetylcholinesterase inhibitors could decrease fracture risk in patients with dementia and improve bone quality in animal models. In this pilot study, we aimed to investigate the effect VNS on BMD in epileptic patients.

Material and method

Regulatory Approval

This study was approved by the Institutional Review Board (IRB) of Jordan University Hospital.

Patient recruitment

This was a pilot prospective cohort study on individuals with refractory seizures who underwent VNS surgery between January 2012 and December 2018. Only patients with multifocal and central cephalic seizures were included with exclusion of patients with lesional epilepsy, vascular anomalies and congenital focal dysplasia.

The following parameters were extracted from patients’ records: age at the time of surgery, gender, seizure type and frequency, use of anti-epileptic drugs (AEDS) (i.e., phenytoin, valpromic acid, barbiturates, bezodiacepines, topiramate, leviteracepam and tegretol), neurophysiological data (video-electroencephalography (video–EEG), electrocorticography (ECG) in specific cases), brain MRI reports, ictal and/or inter-ictal brain perfusion single-photon emission computed tomography (SPECT) and date of surgery (Table 1).

Surgical procedure

An intraoperative dose of cloxacinilline was administered in all cases. The procedure was performed under general anesthesia. Patients were positioned in supine position on a headrest, with the head extended and turned slightly to the right. The head was maintained in a higher position than the heart to facilitate venous flow. A 3–4 cm transverse skin incision was made halfway between the mastoid and the clavicle and extended from the midline to medial border of the sternocleidomastoid muscle. The platysma was then divided, and progressive dissection was made until the carotid sheath and jugular vein. At this point, a surgical microscope was used to dissect the vagus nerve between the common carotid artery and the internal jugular vein for a length of 4 cms.

The tethering (inferior) anchor was then inserted around the vagus nerve, followed by the positive (middle helical contact), and the negative (upper helical contact) electrodes. After the implantation of the electrodes, the VNS therapy® device (models 102 and 103, Livanova, PLC London, United Kingdom) was checked by temporarily connecting the battery to the lead electrode (model 303 and 304, Livanova, PLC London, United Kingdom) to test the lead impedance by a single stimulation impulse lasting 1 min with specific parameters (1 mA, 550 μs, 20 Hz). Then, a subcutaneous pocket was bluntly generated 5 cm in length and height, and 5 cm below the clavicle, at the union between the middle third to the outer third of the clavicle. The stimulator was then inserted by passing the tunnelizer from the subcutaneous thoracic pocket to the cervical incision. The leads were secured with non-absorbable sutures to silicon head holders at the deep cervical fascia, and near to the sternocleidomastoid muscle. The battery was fixed to the lead electrode and anchored by non-absorbable sutures to the fascia of the pectoralis mayor muscle. The functionality of the device was checked again before wound closure. The duration of the procedure ranged between 40–60 minutes.

A postoperative chest x-ray was performed in all cases and patients were normally discharged 48 hours after surgery. The VNS was usually started between 72 hours and one week after surgery with the following stimulation settings: 0.25 mA; 500 μs pulse width; 20–30 Hz; 30 s ON, 5 min

Table 1. Demographic features of the study group.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study group (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of epilepsy</strong></td>
<td></td>
</tr>
<tr>
<td>GTC + PSZ</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>GTC + PSZ</td>
<td>11 (52.4)</td>
</tr>
<tr>
<td>GTC + PSZ + PCS</td>
<td>1 (4.7)</td>
</tr>
<tr>
<td><strong>Antiepileptic drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Valpromic acid</td>
<td>12 (57.1)</td>
</tr>
<tr>
<td>Tegretol</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>1 (4.7)</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>4 (19.1)</td>
</tr>
<tr>
<td>Benzodiacepines</td>
<td>7 (33.3)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>6 (28.6)</td>
</tr>
<tr>
<td>Leviteracepam</td>
<td>1 (4.7)</td>
</tr>
</tbody>
</table>

Data are presented as No. (%) or mean ± standard deviation. Abbreviations: generalized tonic clonic seizure, GTC; partial simple seizure, PSZ; partial complex seizure, PCS. *Under 18 years of age.

*Measured as weight in kilograms divided by the square of height in meters.
OFF. These settings were gradually reached with 3.0 mA increases according to the clinical response of the patients. Patients were instructed to stop stimulation with a magnet in case of discomfort, and to reactivate the system if a seizure aura was noticed.

### BMD analysis

Baseline BMD was measured using a dual-energy X-ray absorptiometer (DEXA) (lunar iDEXA-GE, Madison, WI, USA), which included lumbar spine (i.e., L1 to L4) and femoral neck.

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Table 2. Lumbar mineral density: baseline vs. postoperative results.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Preoperative DEXA scan (n=21)</th>
<th>Postoperative DEXA scan (n=21)</th>
<th>Mean difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Lumbar BMD, g/cm²</td>
<td>1.00 ± 0.23</td>
<td>1.04 ± 0.21</td>
<td>0.04</td>
<td>0.001*</td>
</tr>
<tr>
<td>Males</td>
<td>1.00 ± 0.23</td>
<td>1.03 ± 0.21</td>
<td>0.03</td>
<td>0.027*</td>
</tr>
<tr>
<td>Pediatric</td>
<td>0.80 ± 0.25</td>
<td>0.86 ± 0.23</td>
<td>0.06</td>
<td>0.091</td>
</tr>
<tr>
<td>Adult</td>
<td>1.13 ± 0.1</td>
<td>1.15 ± 0.11</td>
<td>0.02</td>
<td>0.165</td>
</tr>
<tr>
<td>Females</td>
<td>1.01 ± 0.25</td>
<td>1.05 ± 0.23</td>
<td>0.04</td>
<td>0.014*</td>
</tr>
<tr>
<td>Pediatric</td>
<td>0.88 ± 0.49</td>
<td>0.93 ± 0.48</td>
<td>0.05</td>
<td>0.101</td>
</tr>
<tr>
<td>Adult</td>
<td>1.06 ± 0.16</td>
<td>1.09 ± 0.14</td>
<td>0.03</td>
<td>0.082</td>
</tr>
<tr>
<td>Overall Lumbar Z-score</td>
<td>-0.97 ± 1.17</td>
<td>-0.77 ± 1.14</td>
<td>0.20</td>
<td>0.026*</td>
</tr>
<tr>
<td>Males</td>
<td>-1.05 ± 0.89</td>
<td>-0.90 ± 0.82</td>
<td>0.15</td>
<td>0.102</td>
</tr>
<tr>
<td>Pediatric</td>
<td>-1.58 ± 1.08</td>
<td>-1.47 ± 0.79</td>
<td>0.11</td>
<td>0.395</td>
</tr>
<tr>
<td>Adult</td>
<td>-0.72 ± 0.62</td>
<td>-0.54 ± 0.64</td>
<td>0.18</td>
<td>0.143</td>
</tr>
<tr>
<td>Females</td>
<td>-0.84 ± 1.57</td>
<td>-0.58 ± 1.57</td>
<td>0.26</td>
<td>0.157</td>
</tr>
<tr>
<td>Pediatric</td>
<td>-0.43 ± 1.97</td>
<td>-0.02 ± 2.4</td>
<td>0.41</td>
<td>0.395</td>
</tr>
<tr>
<td>Adult</td>
<td>-0.98 ± 1.61</td>
<td>-0.77 ± 1.15</td>
<td>0.21</td>
<td>0.355</td>
</tr>
</tbody>
</table>

*Statistically significant results.

Data are presented as No. (%) or mean ±. Abbreviations: BMD, bone mineral density; DEXA, Dual-energy X-ray absorptiometry.
Z-scores (i.e., compares one's BMD to the average BMD of people of the same age and gender). A second scan was performed between 6 months and one year after surgery. The DEXA machine was calibrated daily using a standard phantom provided by the manufacturer. Measurements were maintained within precision standards of 1.0%. The least significant change (LSC) for lumbar spine (L1-L4) BMD at our institution is 0.028 g/cm$^2$ while the LSC for the left femur BMD is 0.033 g/cm$^2$.

All scans were performed by trained technicians and analyzed by an experienced radiologist (MJ or AA). Quality control procedures were followed in accordance with the manufacturer’s recommendations. Height was measured without shoes to the nearest 0.1 cm using a fixed stadiometer. Body weight (kilograms) was measured to the nearest 0.1 kg with the participant in light clothing without shoes. Body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters.

Statistical analysis

Data were analyzed with SPSS 22.0 software (SPSS Inc, Chicago, IL, USA), Origin Pro 8.0 (OriginLab Corporation, Northampton, USA), and G*power 3.0.10 (Universität Kiel, Germany). Mean values were expressed with their corresponding standard deviation (SD). Normal distribution was confirmed in each group using the Shapiro–Wilk test. Differences between continuous variables were analyzed using student’s-t test for paired samples or a Wilcoxon test. Differences were considered significant when the two-tailed P values were <0.05. Power analyses were performed using post-hoc t-test for two independent means with an α-error probability of 0.05.

Results

A total of 152 patients with refractory seizures were identified during the study period of whom 21 were recruited into this study. The mean (±SD) age of the participants was 23.62±12.3 years [range 5-50 years]. There were 7 (33.3%) children and 14 (66.7%) adults with a male: female ratio of 1.63. The mean BMI of the participants was 23.62 ± 0.54 kg/m$^2$. Valproic acid was used in 12 (57.1%), 5 (23.8%) tegretol, 1 (4.7%) phenytoin, 4 (19.1%) barbiturates, 6 (28.6%) topiramate, 1 (4.7%) levetiracetam, and 7 (33.3%) used benzodiazepines (Table 1). During the postoperative period, anti-epileptic treatment was modified in 7 patients (i.e., one patient was started on levetiracetam, one changed from clonazepam to levetiracetam, one was started on lamotrigine and clonazepam, one on benzodiazepin, one was switched from topiramate to levetiracetam, one was started on levetiracetam and phenobarbital, and one was started on topiramate). The distribution of the preoperative antiepileptic drugs within the study group is presented in Table 1. Lumbar BMD was measured pre and post VNA in all the 21 patients whereas femoral neck BMD was measured in only 11 of the 21 patients. Seven patients in whom femoral BMD was not determined were children, where normal values for this age group were not available in our center to enable calculation of the z-scores.

Following VNS, Lumbar BMD increased from 1.00±0.23 g/cm$^2$ to 1.04±0.21 g/cm$^2$ (P=0.001, power 97.2%). The mean absolute increase in lumbar BMD in the 21 patients was 0.04±0.04 g/cm$^2$ resulting in an overall percent increase from baseline of 4.7±6.1%. The increase in lumbar BMD was significant in both males (1.00±0.23 g/cm$^2$ to 1.03±0.21; P=0.027, power=85.4%) and females (1.01±0.25 g/cm$^2$ to 1.05±0.23 g/cm$^2$; P=0.014, power=99.9%). The overall lumbar Z-score increased from -0.97±1.17 to -0.77±1.14 (P=0.026, power=61.0%) (Table 2 and Figure 1). No significant statistical differences were found between the preoperative and postoperative femoral neck BMD and Z-scores in male or female patients (Table 3 and Figure 1). No significant differences were observed in the BMD change from baseline between the patients who remained on the same medication and the 7 patients who modified their treatment after surgery (0.038±0.016 g/cm$^2$ vs. 0.037±0.013 g/cm$^2$, respectively, p=0.950).

Lumbar BMD increased in 18 out of 21 patients (85.7%); however, it increased by an amount ≥ the LSC of 0.028 g/cm$^2$ using our DEXA machine in 13 of the 21 patients (61.9%), significantly decreased in one and remained stable in the other 7 patients. The mean absolute increase in lumbar BMD in the 13 patients in whom the increase was ≥ the LSC, was 0.062±0.036 g/cm$^2$ resulting in a percent increase from baseline of 7.8±5.9% (range: 2.4-21.5%) and there was a highly significant difference (P<0.0001, power 99.9%) between the pre and post VNS lumbar BMD in these patients. In the one patient with decreased BMD, there was a 0.038 g/cm$^2$ decrease or 3.3% decrease from baseline while in the other 7 patients an insignificant change of 0.002±0.019 g/cm$^2$ or 0.24±1.8% change from baseline was observed.

Significant increases in lumbar BMD ≥ the LSC were seen in 5 of the 8 females and 8 of the 13 males who had pre and post VNS lumbar DEXA with a similar magnitude of increases in both sexes (7.3±3.3% in females vs. 8.0±7.1% in males).

As expected, the lumbar Z score increased in the 13 patients with BMD increases ≥ the LSC (Z score of -1.22±1.15 pre VNS vs. -0.88±1.22 post VNS, P=0.006, power 86.5%). Post VNS the lumbar BMD changed from being below to being within the expected range for age- and sex-matched population in 2 patients.

Femoral BMD increased by an amount ≥ the LSC of 0.033 g/cm$^2$ using our DEXA machine in 3 of the 11 patients (27.3%) in whom the femoral BMD was measured prior to and post VNS. In these three patients the absolute increases in BMD were 0.034, 0.037 and 0.043 g/cm$^2$ with percent increases from baseline of 3.2%, 6.2% and 4.2%, respectively. In one patient the femoral BMD decreased by 0.056 g/cm$^2$, a 6.3% decrease from baseline while in the remaining 7 patients an insignificant change in femoral BMD of 0.009±0.012 g/cm$^2$ or 0.105±1.1% change from baseline was observed.
Discussion

Our pilot study in a relatively small number of epileptic patients found that the implantation of a VNS device is associated with a significant increase in lumbar BMD. Following 6-12 months of VNS implantation, a mean of 4.7% increase in lumbar BMD was observed in the 21 patients who underwent lumbar DEXA. The magnitude of this increase is similar to the approximately 5% increase observed in postmenopausal women after 1 year of 10 mg of oral alendronate daily, the bisphosphonate regularly used in the treatment of osteoporosis\textsuperscript{8}. Moreover, in this study, lumbar BMD increased in 85.7% patients 6-12 months after the implantation of the VNS device. These results are comparable to previous research that has shown that over 96% of the women treated with alendronate for a period of 3 year experienced a measurable increase in the lumbar BMD\textsuperscript{8}. Even more remarkable is the change in the 13 patients in whom the lumbar BMD increased by an amount ≥ the least significant change (LSC) using our DEXA machine with a mean absolute increase of 0.062 g/cm\textsuperscript{2} or more than twice the LSC. In these patients, the mean percent increase in lumbar BMD of 7.8% is similar to that observed in postmenopausal women after 3 years of 10 mg of alendronate daily (about 8% increase)\textsuperscript{8}.

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\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|}
\hline
Characteristics & Preoperative DEXA scan (n=11) & Postoperative DEXA scan (n=11) & Mean difference & P value \\
\hline
Femoral BMD, g/cm\textsuperscript{2} & 0.91 ± 0.16 & 0.92 ± 0.16 & 0.01 & 0.511 \\
Males & 1.01 ± 0.11 & 1.01 ± 0.12 & 0.00 & 0.992 \\
Females & 0.80 ± 0.15 & 0.82 ± 0.14 & 0.02 & 0.133 \\
Femoral Z-score & -0.95 ± 1.01 & -0.79 ± 0.79 & 0.16 & 0.337 \\
Males & -0.53 ± 0.65 & -0.53 ± 0.78 & 0.00 & 1.000 \\
Females & -1.58 ± 1.23 & -1.18 ± 0.74 & 0.40 & 0.317 \\
\hline
\end{tabular}
\caption{Femoral neck mineral density: baseline vs. postoperative results.}
\end{table}
Our findings of an effect of vagus nerve stimulation on bone metabolism are concordant with previous clinical and animal studies suggesting a possible association between the cholinergic system and bone. However, this is the first study showing that a direct electrical stimulation of the vagus nerve could enhance bone formation.

Previous research has shown that the cholinergic fibers from the parasympathetic and sympathetic systems innervate bone tissue. Neural signals are transmitted through cholinergic fibers from the parasympathetic system nuclei within the central nervous system to cholinergic receptors located in bone. The vagus nerve carries cholinergic fibers from the parasympathetic system with the efferent projections emerging from the brain stem through the carotid artery and esophagus before branching diffusely to innervate the viscera. These fibers are responsible for driving cardiorespiratory and gastrointestinal autonomic tone as well as other autonomic functions. The afferent projections of the four vagal nuclei (i.e., dorsal nucleus, nucleus ambiguous, solitary nucleus, spinal trigeminal nucleus) provide critical control of the autonomic brain stem before projecting to other regions of the CNS. However, the complete innervation extent of the vagus nerve remains unknown. The vagus nerve is composed of unmyelinated C-fibers from the visceral organs, and myelinated A- and B-fibers which play an important role in somatic sensory, motor, and parasympathetic innervation. Vagus nerve fibers are primarily cholinergic but other noncholinergic non-adrenergic neurotransmitters are also involved. Previous studies have shown that the periosteum in bone tissue, which contains progenitor cells that differentiate into osteoblasts, is innervated by cholinergic fibers from the autonomic nervous system. This indicates that cholinergic fibers could play a role in the regulation of bone remodeling. Moreover, the denervation of the periosteum is associated with delayed bone healing in animal models, suggesting that the periosteal nerves may also play a significant role in fracture healing.

Vagus nerve stimulation therapy has been traditionally used in the treatment of epilepsy and depression. However, it is being currently explored as a potential treatment for a wide range of diseases, such as infections, lung injury, rheumatoid arthritis, traumatic brain injury, and diabetes. The results of this study are in concordance with previous reports which suggests that the stimulation of the cholinergic signal could be associated with an increase in bone formation. Evidence suggests that bone remodeling is regulated by the autonomic nervous system through the activity of its two arms: the adrenergic system and the cholinergic system. The activity of the adrenergic system has a negative effect on bone formation. Drugs that inhibit the adrenergic signal (e.g., β-blockers) increase bone accrual in vivo, bone mineral density in humans, reduce the risk of fractures in humans, and decrease the risk of aseptic loosening in joint replacement surgery. On the other hand, the stimulation of the cholinergic system has an anabolic effect on bone. Moreover, in vitro studies have demonstrated that cholinergic agonists such as nicotine and muscarine, could enhance osteoblastic proliferation. The anabolic effect of cholinergic stimulation on bone has also been confirmed by several clinical studies. A recent nested case-control study has observed that indirect cholinergic stimulation using acetylcholinesterase inhibitors in patients with Alzheimer’s disease was associated with a significant decrease in fracture risk. Moreover, patients taking these medications had a lower risk of suffering a second hip fracture following a primary hip fracture.

On the other hand, research has shown that the inhibition of the cholinergic signal could favor bone loss in animal models. In vivo studies on muscarinic-3-receptor-knockout-mice have observed that the absence of this receptor is associated with bone loss, caused by osteoclastic proliferation and a decrease in the number of osteoblasts. In another study, nicotinic subtype-a2 receptor knockout mice were found to be osteoporotic because of osteoclastic proliferation. Moreover, mice subjected to subdiaphragmatic sectioning of the vagus nerve, were found to have a lower bone mass in their lumbar spine.

Interestingly, in this study, an overall significant increase in the BMD was observed in the lumbar spine and not in the femur, perhaps this could be explained by differences in the diffusion of the vagal cholinergic fibers between the lumbar spine and hip joint. Nevertheless, the innervation of the vagus nerve is not known to reach the either the femoral head nor lumbar vertebrae. However, the complete innervation extent of the vagus nerve is still unknown. In addition, trabecular bone usually has a higher turnover rate compared with cortical bone. Therefore, it would be expected to identify changes secondary to VNS in the predominantly trabecular vertebral bone with shorter exposures. Another possible explanation of the vagus-nerve regulated bone remodeling could be an indirect diffusion of acetylcholine in the blood stream eventually reaching the muscarinic receptors in bone cells. Nevertheless, the lack of effect on the femoral BMD could, in part be attributed to the small sample of patients who underwent a femoral DEXA scan in this study, especially since significant increases in femoral BMD were observed in 3 of the 11 patients studied.

The vagus nerve also innervates the thyroid gland and kidneys and could potentially contribute to bone remodeling through the regulation of these organs. A previous animal study has shown that a vagal nerve section could produce an increase in norepinephrine release in renal nerves. Accordingly, vagal afferents participate in the inhibition of renal sympathetic activity, which is known to be involved in bone remodeling. However, no changes in renal norepinephrine excretion were observed during vagal stimulation. Other reports have shown that VNS increased thyroid hormone secretions in animal models. Human studies demonstrate that T3 appears to increase bone resorption. Adult mice with deletion of the gene for TR alpha with normal circulating T3 increased trabecular bone mass and reduced osteoclast numbers. In another study, pigeons subjected to bilateral cervical vagotomy, resulted in significant activation of the thyroid follicular cells and a significant decrease in T4, and an increase in
T3. Moreover, research has shown that exposure to TSH does not alter the differentiation or function of osteoblasts or osteoclasts in vitro, and that the hypothalamic-pituitary-thyroid axis regulation of skeletal development relies on the actions of T3.

On the other hand, a previous study has shown that rats subjected to bilateral section of the thyroid or inferior laryngeal nerves resulted in a significant decrease in total serum calcium, and increased serum parathyroid hormone (PTH) levels. Another animal study has shown that the electrical stimulation of the vagus nerve results in a suppression of chief cell activity within the parathyroid gland; therefore, suggesting a possible inhibition of PTH production. Previously discussed evidence suggests that the vagus nerve could stimulate bone accrual through osteoclastic inhibition, mediated either by the down regulation of T3 and PTH production, or by the stimulation of acetylcholine secretion. The vagus nerve could also enhance bone formation through acetylcholine-mediated osteoblastic activity (Figure 2).

**Strengths and weaknesses**

Our study is the first to provide clinical evidence suggesting that VNS could increase BMD in humans. This pilot study could lead to a new application for VNS in the treatment of conditions associated with low BMD and bone fractures. However, VNS implant is a surgical procedure and, as such, it may be associated with various complications such as infection, vocal cord paralysis, difficulty swallowing, pain, scars, voice changes, and hoarseness. Therefore, it would not be recommended as a first line treatment of osteoporosis, and further investigations would be necessary before the implantation of VNS for this purpose. Nevertheless, VNS stimulation could be a potentially useful therapeutic option in cases where bisphosphonates are contraindicated such as in hypocalcemia, hypersensitivity to the bisphosphonates, chronic kidney disease with a glomerular filtration rate of less than 30 to 35 mL/min, in patients with achalasia, esophageal stricture, esophageal varices, Barrett’s esophagus, history of bariatric surgery, patients with atypical femoral fractures, and osteonecrosis of the jaw secondary to bisphosphonates, if further studies with a larger sample size confirm these observations.

The sample size was small and 11 of our patients were not subjected to femoral DEXA scan. In addition, we did not analyze the correlation between the power of stimulation and the BMD and, due to technical difficulties, we did not record the cumulative time of VNS during the study period. Despite these limitations we found a statistically significant increase in lumbar BMD that appears to be related to VNS therapy. In this study, 7 patients were subjected to changes in their respective antiepileptic treatment during the postoperative period. This could lead to a potential bias. However, no significant differences were observed in the BMD change from baseline between the patients who remained on the same medication and the 7 patients who modified their treatment after surgery. In five of those 7 patients, new anti-epileptic drugs were added to existing medications and since most antiepileptic drugs are known to decrease BMD, it is unlikely that the added anti-epileptic drugs increased the BMD in those patients. In the other two patients, there was a switch in anti-epileptic drugs to leviteracetam. Data on this and other new antiepileptic drugs is limited and inconclusive.

Nevertheless, we cannot exclude the possibility that the change in anti-epileptic drugs in those patients may have, at least in part been affected by the postoperative change in anti-epileptic medications.

**Conclusions**

The implantation of a VNS device in epileptic patients was associated with a statistically significant increase in lumbar BMD. This novel observation requires further confirmation by larger prospective studies and, when confirmed could lead to a new application for VNS in the treatment of conditions associated with treatment-resistant low BMD.

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**References**

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