Nutrient insufficiencies and deficiencies involved in the pathogenesis of bruxism (Review)

IOANNIS A. PAVLOU[1], DEMETRIOS A. SPANDIDOS[2], VASSILIS ZOUMPOURLIS[3] and MARIA ADAMAKI[3]

[1]Private Practice, Iasis Dental, 12241 Athens; [2]Laboratory of Clinical Virology, Medical School, University of Crete, 71003 Heraklion; [3]Biomedical Applications Unit, Institute of Chemical Biology, National Hellenic Research Foundation, 11635 Athens, Greece

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Abstract. Stress has been well-documented to have a significant role in the etiopathogenesis of bruxism. Activation of the hypothalamic-pituitary-adrenal axis (HPA) and subsequent release of corticosteroids lead to increased muscle activity. Neurological studies have demonstrated that chronic stress exposure induces neurodegeneration of important neuronal structures and destabilization of the mesocortical dopaminergic pathway. These disruptions impair the abilities to counteract the overactivity of the HPA axis and disinhibit involuntary muscle activity, while at the same time, there is activation of the amygdala. Recent evidence shows that overactivation of the amygdala under stressful stimuli causes rhythmic jaw muscle activity by over activating the mesencephalic and motor trigeminal nuclei. The present review aimed to discuss the negative effects of certain vitamin and mineral deficiencies, such as vitamin D, magnesium, and omega-3 fatty acids, on the central nervous system. It provides evidence on how such insufficiencies may increase stress sensitivity and neuromuscular excitability and thereby reduce the ability to effectively respond to the overactivation of the sympathetic nervous system, and also how stress can in turn lead to these insufficiencies. Finally, the positive effects of individualized supplementation are discussed in the context of diminishing anxiety and oxidative stress, neuroprotection and in the reversal of neurodegeneration, and also in alleviating/reducing neuromuscular symptoms.

Correspondence to: Dr Ioannis A. Pavlou, Private Practice, Iasis Dental, 7 Stefanou Sarafi Street, 12241 Athens, Greece
E-mail: iasisdental@gmail.com

Abbreviations: AChe, acetylcholinesterase; ACTH, adrenocorticotropic hormone; BLA, basolateral amygdala; BMS, burning mouth syndrome; CeA, central nucleus of the amygdala; CK, creatinine kinase; CNS, central nervous system; CRS, chronic restrained stress; GABA, gamma-aminobutyric acid; GDNF, glial cell-derived neurotrophic factor; GR, glucocorticoid; HPA, hypothalamic-pituitary-adrenal (axis); HT, hydroxytryptamine; HT2RA, serotonin-2A receptor; LC, locus coeruleus; Me5, mesencephalic trigeminal nucleus; N.Acc, nucleus accumbens; RDC, research diagnostic criteria; SAM, sympathetic-adreno-medullar; SB, sleep bruxism/bruxists; SSRIs, selective serotonin reuptake inhibitors; TMD, temporomandibular disorder; VP, ventral pallidum; vSub, ventral subiculum; VTA, ventral tegmental area

Key words: bruxism, neurodegeneration, vitamin D, magnesium, iron, omega-3 fatty acids

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1. Introduction

Bruxism is a parafunctional condition affecting more than two-thirds of the population at some point in their life; however, only 25% of affected individuals are aware of this condition and seek medical attention (1). According to an international consensus, Bruxism is defined as repetitive jaw muscle activity characterized by clenching or grinding of the teeth and/or bracing or thrusting of the mandible; however, it is not regarded a movement disorder or a sleep disorder in otherwise healthy individuals (2). Bruxism can be distinguished into awake and sleep bruxism based on the time of occurrence (circadian manifestation). In a systematic review by Manfredini *et al* (3), it was shown that the prevalence of awake bruxism ranges from 22 to 31%, whereas sleep bruxism has a prevalence of 12.8%. Finally, women are more prone to bruxism compared to men with a ratio of 5:1 (4).

Although numerous factors have been implied to contribute to the etiopathogenesis of bruxism, stress and emotional disturbances are the most commonly accepted (5,6). Emotional stress is associated with an increase in head and muscle tonicity, as well as an increase in non-functional muscle activity (7,8). In addition, the activation of the sympathetic system in response to stressful stimuli leads to increased

muscle tone and reduced pain thresholds (8,9). In a systematic review and meta-analysis published in 2021, Fritzen *et al* (10) verified increased levels of salivary cortisol in bruxists. These increased levels correlate with strong circadian rhythms with peak levels during the activation periods (11). Under experimental stress, there is increased masseter activity, which returns to baseline levels upon relaxation (12). In animal studies, stress-induced muscle hyperactivity was associated with muscle dysfunction and pain (13), whereas humans who experience panic attacks more frequently exhibit tooth clenching, bruxism and nail-biting (14). Overactivation of the sympathetic system and hypothalamic-pituitary-adrenal axis (HPA) axis can make an individual more vulnerable to new stress, as evidenced by animal and human studies (15,16). Patients with temporomandibular disorders (TMD) exhibit higher levels of anxiety (17), while TMD symptoms worsen whenever a person is under stress (18,19).

Based on findings in neurological diseases (20-23) and pharmacological interactions (24-27), it appears that a malfunction of 5-hydroxytryptamine (HT)2 receptors may have a major role in the pathogenesis of bruxism. The role of 5-HT2 receptors in the mediation of orofacial musculature is well documented (28,29). Stress can affect 5-HT receptors, but this effect varies from area to area. For instance, it may induce a decrease in 5-HT1 receptors in the hippocampus and an increase in cortical 5-HT1 (30,31), while leaving the 5-HT2 receptors in the trigeminal nuclei unaffected (30,32). This is also supported by the work of Inan *et al* (33), who concluded that bruxism occurs as a result of abnormally reduced inhibition of trigeminal motor neurons. In another study by Lauria *et al* (34), it was shown that a neuropathy in the nigrostriatal system leads to loss of inhibition of the trigeminal nerve. The neuroanatomy of masticatory modulation is a 2-neuron chain where serotonergic neurons from the Raphe nucleus synapse with dopaminergic neurons in the ventral tegmental area (VTA) (35).

Two important neuronal areas are implicated in the genesis of bruxism and are highly affected by stress: The mesencephalic trigeminal nucleus (Me5) and the mesocortical dopaminergic pathway. Me5 controls the masseter inhibitory reflex, which, when activated, suppresses the trigeminal motor nucleus and inhibits masseter and temporalis contraction. The mesocortical dopaminergic tract connects the VTA with the nucleus accumbens (N.Acc) via either the ventral subiculum (vSub) or amygdala (36). N.Acc receives glutamatergic projections from the hippocampus and basolateral amygdala (BLA) and sends projections to mesencephalic motor effector sites, and is therefore considered to be a motor-limbic interface (37). The mesocortical tract is equally important because it inhibits undesired muscular movements (38). In acute mild stressors, the tract follows the vSub-ventral pallidum (VP)-N.Acc route (39,40). The hippocampus is essential in counteracting overactivation of the HPA axis (41). However, in chronic stressors, the hippocampus presents with neurodegenerative alterations that attenuate this pathway, while at the same time, they activate the BLA-VP-N.Acc pathway (42). Studies in mice have revealed that a direct projection from CeA to trigeminal motor nucleus is highly activated during hunting of prey and that it promotes strong biting attacks (43). Of note, the same pathway has recently been identified in humans, and in higher distribution than BLA-Mo5 (Trigeminal Motor Nucleus) (44), further highlighting that the same association may also apply to humans and warranting further research in this field. Fig. 1 diagrammatically represents the effect of certain nutrients on the mesocortical dopaminergic pathway.

Chronic stress exposure and increased circulating levels of corticosterone impair progenitor cell proliferation, inhibit neuronal differentiation and suppress cell survival in the hippocampal dentate gyrus (45-49), events that affect hippocampal neurogenesis (50-52). This is happening as a result of oxidative stress due to auto-oxidation of catecholamines (53). Oxidative stress due to increased cellular activity induces nitrogen oxide (NO) production, which activates microglia. The latter further releases NO and reactive oxygen species (ROS) that induce neuroinflammation and neurodegeneration (54,55). This in turn negatively modulates the ability of the hippocampus to control hyperactivity of the HPA axis. Neurodegeneration of the hippocampus and attenuation of the vSub-VP-N.Acc pathway invoke alterations in the mesocortical dopaminergic neurons that are implicated in neuropathic and chronic pain (56-58). The dysregulation of dopamine D2 receptor expressing indirect pathway output neurons promotes hypersensitivity to pain and increased impulsivity due to reduced levels of dopamine in N.Acc (59,60). The attenuation of the vSub-VP-N.Acc pathway and the activation of the BLA-VP-N.Acc cause further reduction of dopamine neurons in the VTA (42). All these aforementioned events have a strong effect on Me5. Animal electrophysiological studies have shown that chronic restrained stress induces an increase in the excitability of Me5 and glutamatergic neurotransmission from Me5 to Mo5 (61). This was evidenced by increased levels of acetylcholinesterase (Ache) and creatine kinase (CK-MM) in the masseter muscles (61). In another study by Ueno *et al* (62), it was demonstrated that activation of the ventral part of amygdala in guinea pigs may cause rhythmic jaw movement.

Recent evidence has revealed similar degenerative findings in bruxists. Keskinruzgar *et al* (63), by studying the retinas of bruxists, found that retinal nerve fiber layer (axon) thickness, inferior parietal lobe (dendrites) and granule cell layer (soma) volume are significantly reduced. The retina is considered to be a continuation of the brain; therefore, any neurodegenerative changes in the retina are representative of those induced in the mesocortical dopaminergic tract. In the same study, an increase in choroidal thickness was also demonstrated. The choroid is an important site of vascularization and is responsible for transport of nutrients and oxygen (63). This study, however, does not specify the cause of neurodegeneration or an association between bruxism and neurodegeneration. The fact that bruxism is a common comorbid condition or symptom in other neurodegenerative disorders such as Parkinson's disease or Parkisonism (64), as well as in rapid eye movement sleep behavior disorder (65), constitutes enough evidence so as to not exclude neurodegeneration from this equation. Ozcan-Kucuk *et al* (66) concluded that there is a significant increase in oxidative stress and prolidase activity in bruxists. Increased levels of prolidase, an enzyme found in the plasma and several organs, including the brain, are associated with higher levels of proline, a brain neurotransmitter, which can induce oxidative stress and subsequently neurodegeneration (67). These effects have been examined in anxiety (68),

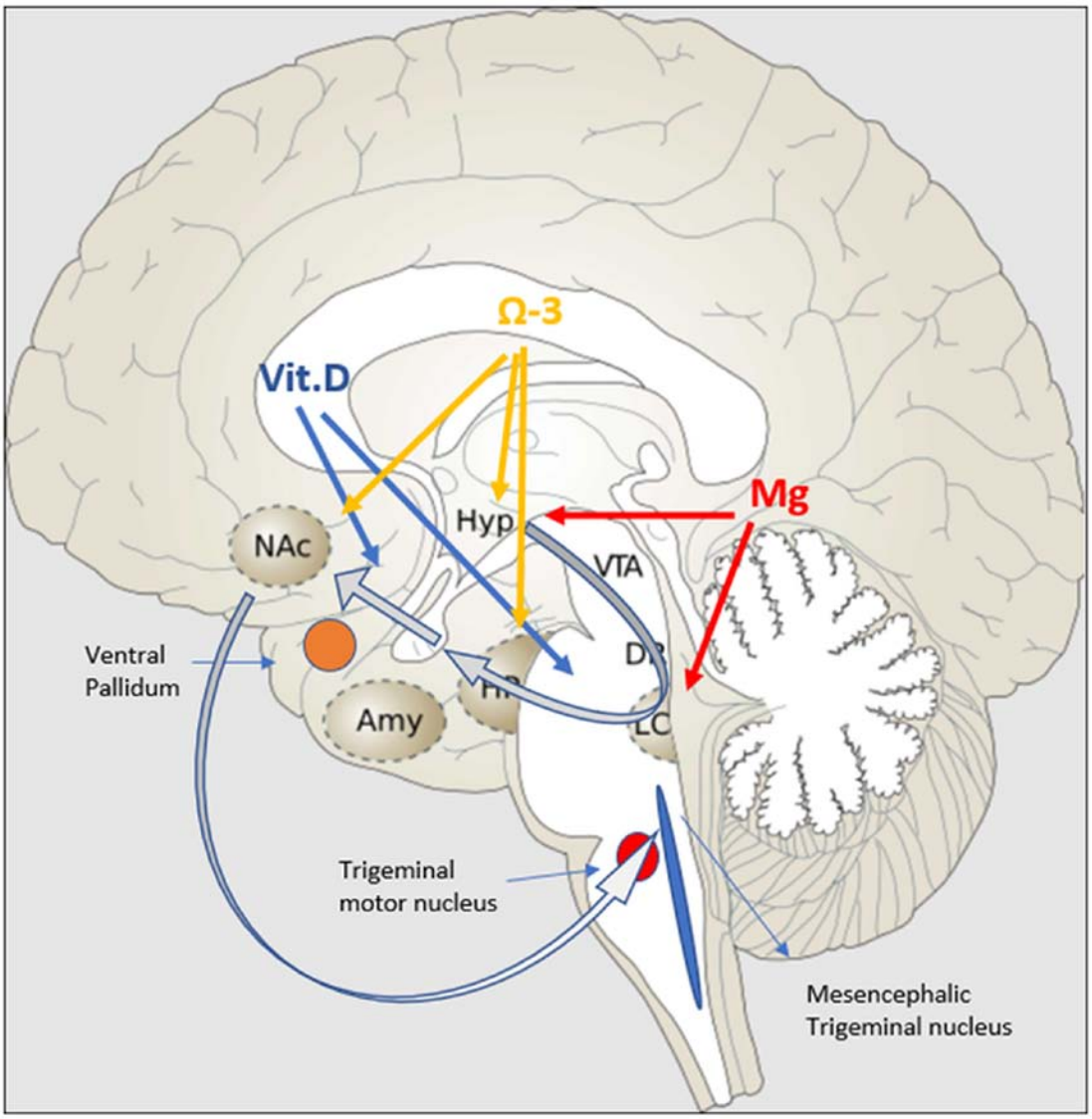

Figure 1. Effects of vitamin D, omega-3 fatty acids and magnesium on the mesocortical dopaminergic pathway (grey arrows). Vitamin D acts on the mesocortical dopaminergic pathway by protecting dopaminergic neurons (blue arrows). Omega-3 fatty acids suppress overactivity of the HPA axis and increase neurogenesis and synaptic activity in the hippocampus and N.Acc (orange arrows). Magnesium suppresses HPA and SAM axis overactivation by acting on the hypothalamus and LC, respectively (red arrows). Amy, amygdala; HPA, hypothalamic-pituitary-adrenal; HP, hippocampus; Hyp, hypothalamus; LC, locus coereleus; Mg, magnesium; N.Acc, nucleus accubens; SAM, sympathetic adrenal medullary; Vit.D. vitamin D; VTA, ventral tegmental area.

several musculoskeletal disorders (e.g. ankylosis, osteoarthritis) (69,70) and neuropsychiatric diseases (Alzheimer's, bipolar disorder) (67,71). Fig. 2 illustrates the sequence of events that connect stress with jaw muscle activity.

Based on these findings, particularly on the neurodegeneration of the hippocampus, the attenuation of the vSub-VP-N.Acc pathway and the fact that a malfunction may occur at any given point in the mesocortical dopaminergic tract, it is difficult to identify a therapeutic target. According to a systematic review from 2022 by Minakuchi *et al* (72), none of the already used treatment modalities is able to achieve universal positive results. As far as pharmacologic agents are concerned, the evidence of efficacy has low to moderate confidence, with numerous adverse effects; at the same time, the efficacy of cognitive behavioral therapy is still low and does not appear to improve the symptoms in <6 months (72). Overwhelming evidence points towards insufficiencies and deficiencies of necessary elements for the homeostasis and normal function of the central nervous system (CNS), with vitamin D (vit.D), magnesium and omega-3 fatty acids being the most studied ones.

2. Vit.D and the pathogenesis of bruxism

Effect on physiological function. Vit.D) is a very important nutrient, not only for maintaining a healthy musculoskeletal system but also for the positive effect on the nervous system. It has long been known that vit.D has a vital role in calcium and phosphorous metabolism, in three main ways: i) By enhancing intestinal absorption, ii) by controlling the synthesis of parathyroid hormone and iii) by promoting the maturation of pre-osteoclasts into osteoclasts (73-75). However, current evidence suggests that vit.D also has a major role in neuroimmune modulation, neuroplasticity and neurological oxidative stress reduction (76). This property is supported by the abundance of vit.D receptors throughout the CNS (77), as well as by its ability to cross the blood brain barrier (78). Vit.D is

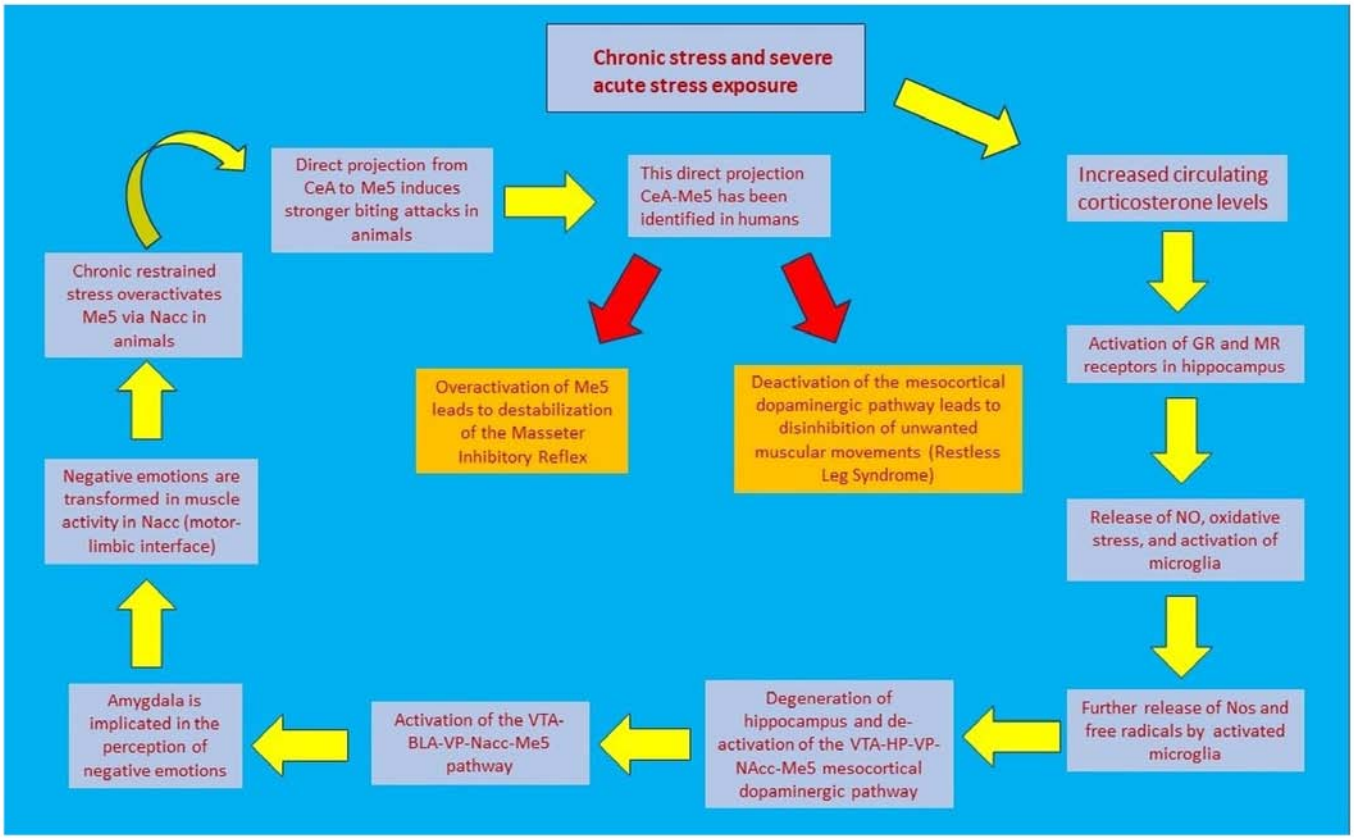

Figure 2. Schematic representation of events that lead from stress to jaw muscle activity. BLA, basolateral amygdala; CeA, central amygdala; GR, glucocorticoids; HP, hippocampus; Me5, mesencephalic trigeminal nucleus; MR, mineralocorticoid; N.Acc, nucleus accubens; NO, nitric oxide; VP, ventral pallidum; VTA, ventral tegmental area.

also known to control ~3% of the human genome via the vit.D receptor (VDR), which forms a heterodimer with the retinoid X receptor (79,80). This heterodimer complex binds to specific DNA sequences and alters the expression of genes that are involved in glutamatergic and GABAergic neurotransmission, calcium regulation and also the expression of neurotrophic factors and genes involved in neuroprotection (81,82).

The strong antioxidant capacity of vit.D helps to improve brain enzyme activity and to reduce lipid peroxidation. Oxidative stress has a major role in neurodegenerative diseases, mainly through auto-oxidation of catecholamines (53,54). Mitochondrial dysfunction leads to a rise in ROS and activated microglia, resulting in nitric oxide (NO) and ROS production during neuroinflammation (55). Vit.D also protects the brain by suppressing inflammatory cytokines such as IL-6 (83). However, the most important function of vit.D is the protection of dopaminergic neurons. Although the mechanism has remained to be fully elucidated, there is sufficient evidence to suggest that it can affect calcium metabolism, apoptosis, inflammation, immunomodulation, detoxification and neurotrophin upregulation (84-86). Cholecalciferol (VD3) may directly modulate tyrosine hydroxylase, a rate-limiting enzyme in dopamine synthesis, as evidenced by immunohistochemical staining. The glial cell-derived neurotrophic factor (GDNF) protein also appears to be increased by these effects, thereby supporting the neuroprotective effects of VD3 on dopaminergic neurons (87). Orme *et al* (87) demonstrated that adding VD3 to mesencephalic cultures of dopaminergic neurons increased their number and upregulated GDNF. Furthermore, VD3 has also been shown to regulate factors involved in dopaminergic system ontogeny (88), as evidenced through studies in animals with altered dopaminergic metabolism due to VD3 deficiency, where VD3 supplementation resulted in a reduction of the degree of dopaminergic denervation (87,89).

Association of vit.D deficiency with anxiety. Vit.D deficiency and insufficiency have been strongly implicated in anxiety and depression. Huang *et al* (90) showed that a decrease of 1 ng/ml in 25(OH)D (Calcidiol, a hydroxylated form of vit.D) was associated with greater anxiety and depression. Similar results were obtained by Altinbas (91) on intensive care unit personnel. In another study by Al-Atram *et al* (92), vit.D deficiency was positively correlated with anxiety but not with depression. However, none of these studies clarified the insufficiency and deficiency cut-off points, with the majority accepting <30 ng/ml as insufficiency and <20 ng/ml as deficiency (93). When compared to subjects with normal (adequate) vit.D levels, vit.D deficiency seemed to be associated with a reduction in brain volume, particularly in the hippocampus (94). According to certain researchers, vit.D deficiency has a direct effect on sleep because of the association between sleep-wake regulation brain regions and vit.D target neurons in the diencephalon (95). The main causes of vit.D deficiency or insufficiency are inadequate UVB exposure or decreased bioavailability, as well as through certain types of medication, such as glucocorticoids (GR), antiretrovirals and anticonvulsants (96).

Association of vit.D with bruxism. Recent evidence has unveiled a strong association between bruxism, particularly sleep bruxism (central), and vit.D deficiency. Alkhatatbeh *et al* (97) showed that there is a significant link between vit.D deficiency and sleep bruxism, with 60% of bruxism patients exhibiting low levels of vit.D compared to 34% of the controls. In the same study, the authors also assessed the daily dietary intake of calcium and reported that only 26% of bruxists had a daily dietary calcium intake of >600 mg/day, compared to 42% of the controls (97). This association can be explained by the neuroprotective role of vit.D. Low vit.D levels may disrupt calcium homeostasis, affecting neuron excitability (98). Furthermore, because vit.D is responsible for calcium homeostasis, low vit.D levels will result in low serum calcium levels, i.e. hypocalcemia, which has an immediate effect on neuromuscular function, and the potential to cause muscle spasms and cramps (95). In another study by Allaf and Abdul-Hak (99), insufficiency or deficiency of vit.D were shown to increase with the severity of bruxism, while in non-bruxists, insufficiency and deficiency was present in 41 and 16% of individuals, respectively. In subjects with mild bruxism, these numbers appeared to rise to 50 and 30%, respectively, and in moderate and severe bruxism to 58%, whereas in extremely severe bruxism, insufficiency and deficiency can reach 72% in total.

Association of vit.D with TMD. An association has been highlighted between low levels of vit.D and TMD. In individuals suffering from osteoarthritis, vit.D is linked to cartilage regeneration (100): vit.D deficiency is observed in individuals suffering from headaches attributed to TMD, as well as from tension-type headaches (101,102), while low levels of vit.D in combination with the *Bsml* variant of the *VDR* gene are highly associated with the etiology and pathogenesis of disc displacement with reduction (103). Similarly, Wu *et al* (104) found an association between low serum levels of vit.D and arthritis, muscle pain and chronic widespread pain. Finally, Demir and Ersoz (105) concluded that the levels of parathyroid hormone in response to vit.D deficiency were significantly higher in TMD subjects as compared to controls. On the other hand, the observation that supplementation of vit.D reduces or alleviates neurological and muscular pain (106-109), is rather encouraging. This effect is thought to occur due to a reduction in oxidative protein damage and in the neuronal levels of Ca.

Vit.D insufficiency and stress. Another well-documented observation during exposure to stress are the low levels of 1,25(OH)2D, the active form of vit.D. This can be the result of increased acute hemodilution and interstitial extravasation, or due to a decrease in the synthesis of binding proteins that augment renal wasting of 25(OH)D (110), or a result of hypocalcemia, a common finding during stress. Specifically, under high stress, particularly conditions that present hyperventilation, the body may respond with respiratory alkalosis, which can lead to hypocalcemia. This may, in turn, cause a compensatory increase in parathyroid hormone (PTH), which could further increase the conversion of 25(OH)D to 1,25(OH)2D in order to maintain calcium homeostasis. In the presence of secondary hyperparathyroidism, 25(OH)D consumption would exacerbate vit.D deficiency (111). Therefore, in acute stress situations, vit.D deficiency may represent a discrepancy between tissue requirement and substrate supply, where the local tissue is unable to generate adequate 1,25(OH)2D, despite maximal stimulation of 1-a-hydroxylase by PTH (112). PTH resistance, which occurs in hypomagnesaemia, renal failure and hypoparathyroidism, can further impair the formation of 1,25(OH)2D (112).

3. Magnesium

Role of magnesium in physiological function. Magnesium (Mg) is the body's fourth most abundant cation and the second most abundant intracellularly; aerobic and anaerobic metabolism, bioenergetic reactions, metabolic pathway regulation, signal transduction, ion channel activity, cell proliferation, differentiation, apoptosis, angiogenesis and membrane stabilization are all biological processes that involve magnesium (113-115). More than 325 enzymes, many of which are specific to the nervous system, are Mg-dependent, highlighting the importance of this particular mineral in CNS physiological function (116).

Stress is known to promote oxidative stress through catecholamine auto-oxidation: it aggravates lipid peroxidation, increases DNA oxidative damage marker production and decreases plasma anti-oxidative activity (117,118). During a stressful event, there is activation of the HPA axis and release of corticotropin-releasing factor (CRF) from parvocellular neurons. Mg antagonizes the glutamate-stimulated CRF release, stabilizes CRF receptor binding and stimulates the Na/K ATPase, which decreases CRF-receptor activity (119-121). Mg also reduces adrenocorticotropic hormone release by suppressing HPA-axis activity via angiotensin II antagonism (122).

Mg has been shown to have a direct suppressive effect on locus coeruleus (LC) activity and low Mg levels seem to increase sensitivity to stress (123). The release of substance P, a neuropeptide that preferentially activates tachykinin NK1 receptors, can explain many of the effects of Mg deficiency in stress situations: Low Mg concentrations reduce Mg-gated blockade of N-methyl-D-aspartate (NMDA) receptor channels, resulting in the release of substance P and calcitonin gene-related peptide (CGRP) from sensory C fibers, i.e. neuropeptides that are involved in the production of reactive oxygen and nitrogen species and in the induction of neurogenic inflammation that is characterized by an increase in inflammatory cells and cytokines (124,125).

Magnesium is also essential for the synthesis of kynureninase. Therefore, in cases of hypomagnesemia, increased levels of kynurenines are observed in the circulation, which in turn promotes anxiety, an increase in the release of noradrenaline, reduced levels of serotonin, GABA receptor blockade and locomotor hyperactivity (126). The increased neural excitability observed in hypomagnesemia is believed to occur from the increased activity of NMDA receptors, which in turn induces anxiety, increased dopamine release and modulation of serotonin receptors (127).

Magnesium deficiency reduces the activity of B6 by inhibiting alkaline phosphatase, an enzyme necessary for the transformation of the active form of B6, pyridoxal phosphate. This causes increased levels of kynurenines, increased sympathetic activation and increased sensitivity to

glucorticoids (128). As B6 is known to participate in decarboxylation of glutamic acid to GABA, of DOPA to dopamine and of 5-hydroxytryptophan to serotonin, it is regarded as a neuroprotective and antitoxic agent (129).

Implication of magnesium in bruxism. The possible involvement of magnesium in the pathogenesis of bruxism can be further supported by the fact that hypomagnesemia is observed in burning mouth syndrome (BMS), particularly in cases where the tongue is involved (130). BMS is caused by hyperactivity of somatosensory fibers of the trigeminal nerve and loss of central inhibition. This hyperactivity may be caused by parafunctional habits. Another important function of Mg is that it exhibits a direct enhancing effect on 5-HT1A serotonin receptor transmission by acting as a cofactor of tryptophan hydroxylase, which has a major role in the dopaminergic system (131). Mg levels are inversely correlated with estrogen levels, showing a sex-related difference (132).

Mg deficiency symptoms include neuromuscular irritability and weakness, headaches, hyperemotionality, generalized anxiety, insomnia, and asthenia (116,133,134). In Mg-deficient animals, there are increased plasma corticosterone levels, increased irritability and aggressive behavior (123,135). Experimentally-induced Mg deficiency in animal studies has been associated with disrupted sleep patterns, while an increase in the amplitude of daily variation of sleep and slow-wave sleep delta power has also been observed (135). Chronic sleep deprivation in humans is associated with progressively decreasing intracellular Mg levels, reduced duration of cardiopulmonary exercise and increased hypersensitivity to sympathetic nervous stimulation (136). In a study by Sarchielli *et al* (137), patients who suffered from migraine and tension-type headaches, very common symptoms in patients with bruxism and TMD, presented with significantly lower levels of serum and salivary Mg. This is because hypomagnesaemia makes cerebral arteries more sensitive to CO_2, which promotes cerebral vasospasm and headache (138,139). Hypomagnesaemia is also linked to exacerbated neural excitability, migraine, orofacial tardive dyskinesia and increased anxiety, symptoms that may be improved by combined supplementation of Mg and B6 (140).

Potential implication of magnesium deficiency in stress. Cernak *et al* (141) showed that stress, chronic and subchronic, causes significant reductions in magnesium concentrations in two ways: First, by stimulating neuroendocrine factors that increase urinary magnesium and second, by inducing complex hormonal alterations that subsequently impair magnesium homeostasis. At the same time, a 9- to 11-fold increase in plasma superoxide anion generation was observed, as well as a reduction in antioxidant enzyme concentrations, such as those of superoxide dismutase (141).

Overall, Mg has a strong neuroprotective role. As mentioned earlier, stress has a deleterious effect on neurons because of the increased levels of IL-6 that initiate microglial activation. Increased inducible NO synthase levels that are expressed during stressful periods impair hippocampal neurogenesis (142,143). Mg deficiency increases neuronal calcium influx and, as a result, NO production, which has been linked to cytotoxic effects (116). Mg counteracts the effects of calcium and reduces ROS production via the phospholipase lipoxygenase and cyclooxygenase pathways (144).

4. Iron

Iron, although not having been linked to bruxism, has recently been associated with restless leg syndrome (RLS), a common neurologic disorder characterized by involuntary muscle movement, which is associated with malfunction of the mesocortical dopaminergic pathway (145). This pathway, as discussed earlier, may be implicated in the pathogenesis of sleep (central) bruxism. Some consider bruxism as a manifestation of RLS, based on the fact that ~40% of patients with RLS report a history of bruxism (146), while others assume that bruxism and RLS are comorbid conditions (147). Both entities share some common features as they are both observed in non-REM sleep and are linked to basal ganglia dysfunction (148).

Brain iron deficiency has a critical role in the pathogenesis of RLS. Anemia and pregnancy are two conditions characterized by systemic iron deficiency, which are highly associated with RLS symptoms (149-151). Similar to bruxists, females are more susceptible to RLS. In a study by Umbreit (152), it was found that RLS without anemia exhibits a sex-dependent preference. Patients with RLS with and without anemia present with more profound tiredness, poorer sleep quality and less energy during the day (151). Depleted iron stores are associated with decreased activity of iron-dependent enzymes, reduced cellular oxidative capacity, as well as decreased energy efficiency (153,154). Previous clinical studies have shown that peripheral iron deficiency increases the risk of RLS prevalence (151). Reduced serum iron concentrations reduce brain iron levels, and iron therapy benefits patients with RLS with low peripheral iron levels (155). In a systematic review and meta-analysis, it was shown that iron therapy, in a way similar to that of a dopamine agonist, reduces restlessness and RLS severity (156).

Both human and animal studies have demonstrated that stress exposure causes a reduction in serum iron ranging from 27 to 44%, a reduction in ferritin by 24% and and a reduction in hemoglobin by 12.5% (157,158).

5. Omega-3 fatty acids

Omega-3 fatty acids-physiological function. Although omega-3 fatty acids have not been directly linked with bruxism, they have been highly implicated in anxiety and emotional mood disorders (159), as well as in neuroinflammation and neurodegeneration (159-162). They are esterified into phospholipids in the sn-2 position of the cell membrane (160), playing a key role in the structure and function of the brain cell membrane. Overwhelming evidence signifies their involvement in hippocampal development and synaptic function (162).

Omega-3 fatty acids may be found in numerous brain regions, but more abundantly in the prefrontal cortex, hippocampus and hypothalamus (163). They have been classified into n-6 polyunsaturated fatty acids (PUFA) and n-3 PUFA, with their main metabolites being arachidonic acid and docosahexaenoic acid (DHA), respectively. The free forms of PUFA are transformed into specific derivatives, such as eicosanoids, specialized proresolving mediators (SPM) and endocannabinoids (eCBs), which strongly regulate inflammation (160). The eCBs are lipids produced by the membrane's fatty acids after neuronal stimulation and bind to cytochrome

P450 carbonyl reductase 1 (164). Activation of this receptor causes an inhibition in glutamate and GABA release from presynaptic neurons (165). Regulation of eCBs in the brain by PUFA has a strong impact on hippocampal synaptic plasticity and in eCB-dependent plasticity (166), while CB1-associated signaling pathways in the prefrontal cortex (PFC) and N.Acc are also affected. Another signaling pathway, GPR120, which functions as an omega-3 fatty acid receptor, signals DHA activity that is highly prominent in the hypothalamus and N.Acc (167), areas that are closely linked to the pathogenesis of anxiety and bruxism, as discussed earlier.

Consequences of omega-3 fatty acid insufficiency. As these substances cannot be synthesized, they can only be obtained through diet (168). However, in Western civilizations, there is a shift in the consumption of fatty acids towards n-6 and less towards n-3 (169), resulting in an imbalance between the two types that is associated with serious consequences, as described below. A decrease in plasma DHA for 49 consecutive days has been shown to cause a 5% DHA reduction in the brain, with the prefrontal cortex and hippocampus being more sensitive (160). DHA, in particular, has been shown to influence neurite growth, synaptogenesis, synapsin and glutamate receptor subunit levels, as well as synaptic activity in hippocampal neurons. This has been supported by *in vitro* studies demonstrating impaired long-term potentiation, shorter neurites, fewer branches, and fewer synapsin-positive puncta in DHA-deficient cultures, while DHA supplementation appears to restore neurite growth and synaptogenesis (162).

Implication of omega-3 fatty acid deficiency in stress. Animal studies have also shown that n-3 PUFA deficiencies induce emotional and neuronal disturbances through adrenal activation that resemble those observed after social defeat stress (161,170,171). Similar to chronic stress, HPA hyperactivity, due to a reduction in CB1 receptor function, invokes a marked increase in corticosterone levels. This action, in combination with a disturbance in the GR-mediated signaling pathway, leads to neuronal atrophy of the PFC by means of pyramidal neuron arborization atrophy. The GR signaling pathway and its downstream target bone-derived neurotrophic factor have a crucial role in neuroplasticity (161,172). As discussed earlier, chronic stress exposure, as well as stress induced by DHA deficiency, eventually cause hippocampal degeneration and attenuation of the mesocortical dopaminergic tract (namely the vSub-VP-N.Acc pathway), whilst at the same time activating the BLA-VP-N.Acc pathway that induces rhythmic jaw activity and possibly bruxism.

Oxidative stress causes NO production, which activates microglia. The latter are glial cells of myeloid origin, important in maintaining brain homeostasis and in protecting nerve cells (173). Activation of microglia causes further production of NO and ROS, leading to neuroinflammation (174). DHA deficiency induces abnormal microglial activation through changes in their membrane fluidity and the modulation of several proinflammatory transcription factors (175). These changes are gender- and area-dependent. Adult females have more microglia than males in the paraventricular nucleus of the hypothalamus, amygdala and hippocampus, particularly in the dentate gyrus (175), which has a crucial role in controlling the HPA axis. This is probably the reason why females appear to be more vulnerable to stress and more prone to bruxism.

Effects of omega-3 supplementation. *In vitro* evidence has highlighted that application of eicosapentaenoic acid (EPA) on microglial cultures inhibits the production and expression of inflammatory enzymes, such as NO synthase and COX-2, as well as the production of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) (174). Levine *et al* (176) demonstrated that application of EPA plus DHA increases microglial autophagy, an important process for the homeostasis of immune cells that are able to diminish inflammatory processes. Another SPM form of DHA, Neuroprotectin D1, seems to protect the brain from leukocyte infiltration, reducing cyclooxygenase-2 expression, cytokine production and microglia activation (177). An *in vivo* study by Lynch *et al* (178) reported that omega-3 supplementation, and particularly EPA, significantly reduced marker expression of microglial activation and production of IL-1β by microglia, while at the same time, there was an increase in anti-inflammatory IL-4 expression. In neuropathic pain and retina degeneration models, N-3 PUFA supplementation was shown to cause a reduction in microglial density/activation, which can be linked to reduced neuroinflammation (179,180).

In a study by Ferraz *et al* (159), it was concluded that supplementation of PUFAs to animals under restrained stress was able to counteract the anxiolytic effects by suppressing the HPA axis and reducing the plasma corticosterone levels. It was also shown that there is an increase in serotonin and dopamine levels particularly in the hippocampus, both of which constitute actions that further promote an increase in the brain-derived neurotrophic factor and synaptophysin expression, as well as hippocampal neurogenesis. Similar results were obtained in humans, as shown by Kiecolt-Glaser *et al* (181), where supplementation of EPA and DHA in medical students for 12 weeks appeared to successfully reduce the release of IL-6 and anxiety symptoms compared to controls.

Finally, noteworthy findings have also been obtained in individuals with morning headaches, a common symptom in bruxists. Morning headaches usually exhibit the characteristics of migraine (182). Numerous hypotheses have been made regarding the mechanism of their genesis, with oxidative stress and activation of the trigeminovascular pathway being the two most prevalent (183). In this context, the role of CGRP has been highlighted both as a mediator and a potential therapeutic target (184). First of all, the release of CGRP has also been shown to be regulated by oxylipin receptors in the trigeminal nerve endings and central pain processing pathways (185,186). Furthermore, a recent study by Marchetti *et al* (184) showed that supplementation of PUFAs at a ratio of 1.5 omega-6/1 omega-3 induced a marked reduction in migraine symptoms, frequency and pain intensity; the explanation given by the authors was that EPA, DHA and their SPM activate innate and adaptive immune systems, remove ROS, and inhibit COX-2 and NF-κB intracellular signaling pathways. Table I summarizes the main characteristics of the nutrients discussed in this section and evidence that highlights their potential implication in the etiopathogenesis of bruxism.

6. Concluding remarks

This review has discussed the effects of chronic stress exposure in the pathogenesis of bruxism. In particular, oxidative stress, through the release of NO and the activation of

Table I. Normal functions of vitamin D, magnesium, iron and omega-3 fatty acids and their implications in the pathogenesis bruxism.

Nutrient	Normal function	Implication in the pathogenesis of bruxism
Vitamin D	Neuroimmune modulation, neuroplasticity (76) Oxidative stress reduction (76) IL-6 suppression (83) Regulation of dopamine synthesis and dopaminergic system ontogeny (88,89) Protection of dopaminergic neurons (87)	Deficiency: Increases anxiety and neuromuscular excitability (90,98), worsens with the severity of bruxism (99); associated with osteoarthritis and headaches (100-102,104) Supplementation: Reduces or alleviates neurological and muscular pain symptoms (106-109)
Magnesium	Suppresses HPA axis and reduces ACTH release (119-122) Suppresses LC activity (123) Controls the release of Substance P and CGRP (124,125) Essential for the synthesis of kynureninase and B6 (126) Enhances 5-HT1A activity (131)	Deficiency: Neuromuscular irritability, headaches, hyperemotionality, general anxiety, hypersensitivity to sympathetic stimulation, disrupted sleep patterns (116,133-135) Supplementation: Counteracts the effect of neuronal calcium influx and reduces ROS production (144)
Iron	Increases cellular oxidative capacity through iron-dependent enzymes (153,154)	Deficiency: Tiredness, poor sleep quality, headaches (151), involuntary muscular movements (restless leg syndrome) (145). Linked to stress exposure and basal ganglia dysfunction (148) Supplementation: Acts similarly to dopamine agonist, reduces restlessness (156)
Omega-3 fatty acids	Improvement of neurite growth, synaptogenesis and synaptic activity in hippocampal neurons (162,166) Suppression of HPA axis (159) Increase of serotonin and dopamine levels in the hippocampus (159) Inhibition of NO, COX-2, IL-6, IL-1b, TNF-a production by activated microglia (176,178) Neuroprotectin D1 protects brain from neurogenic inflammation (177)	Deficiency: Induces stress and increased corticosterone levels. Causes morphological and functional disturbances in PFC and hippocampus (161,170,171) Supplementation: Reduces anxiety and corticosterone levels (159,181). Reduces neuropathic pain (179). Reduces morning headaches frequency and pain severity (184)

ACTH, adrenocorticotropic hormone; CGRP, calcitonin gene-related peptide; COX-2, cyclooxygenase-2; HPA, hypothalamic-pituitary-adrenal; LC, locus coeruleus; NO, nitric oxide; PFC, prefrontal cortex; ROS, reactive oxygen species.

microglia, has been shown to lead to neurodegeneration of the hippocampus and destabilization of the mesocortical dopaminergic pathway. It has also been highlighted that the former impairs the ability to counteract HPA axis overactivity, while the latter results in loss of inhibition of unwanted (involuntary) muscle movements. Based on recent evidence, it appears that attenuation of the vSub-VP-N.Acc route leads to activation of the BLA-VP-N.Acc pathway. The prevailing route has a strong yet opposing effect on the Me5, a nucleus that inhibits the involuntary contraction of masseter muscles by controlling the masseter inhibitory reflex. Indeed, activation of the amygdala appears to induce rhythmic jaw activity, while overactivation of Me5 under chronic stress exposure causes overactivation of Mo5, as evidenced by increased levels of CK-MM and pain in masseter muscles (61).

This report, instead of focusing on pharmacological agents, has shifted the attention towards homeostatic disturbances and deficiencies in important elements, such as vit.D, magnesium, omega-3 fatty acids, and, to a lesser degree, iron. Their neuroprotective properties, their capacity to reduce oxidative stress to suppress the HPA and LC axes, and their positive action on the neuroplasticity and neuronal growth of the hippocampus, particularly in the case of omega-3, further support this notion. Conversely, a decrease in the levels of these elements in the brain is associated with neurodegeneration, increased anxiety, increased neuromuscular excitability, bruxism, muscle spasms and pain. Of note, appropriate and individualized supplementation of these nutrients appears to reduce or alleviate the neurological and musculoskeletal symptoms (108,109). Future studies should focus on whether these concentration alterations have a causal effect or whether they constitute the aftermath of chronic stress exposure, and if re-establishment of the nutrient balance has a significant impact on the pathogenesis and chronicity of bruxism.

The present review has certain limitations. Regarding the pathogenesis of bruxism, the articles included constitute a small number of cases, with self-reporting subjective symptoms, which makes it difficult to provide a definite diagnosis. On the other hand, the actual levels of Mg and omega-3 fatty acids in the patients' circulation (plasma) and brain may not be easily assessed. In addition, patient variability is probably the reason behind the inconsistency in achieving the desired outcome in affected individuals, while there is also a lack of data regarding the optimum duration of nutrient supplementation to achieve the desired outcome. However, despite the small number of studies addressing these issues and their associated limitations, the existing evidence supports the rationale that subsequent research should be conducted in this field, with the aim to further enhance the current understanding of this complex, multifactorial condition and hopefully to provide the affected individuals with alternative and more effective therapeutic modalities.

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