Can melatonin ameliorate smoking-related cadmium-included decreases in bone mineral density?

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Abstract Cadmium, an environmental toxin, is associated with a range of adverse health effects including decreased bone mineral density and osteoporosis, due to its induction of oxidative stress, leading to DNA damage, mitochondrial dysfunction, and endoplasmic reticulum stress. Notably, cadmium is found at concentrations 4-5x higher in the blood of smokers versus non-smokers. Experiments performed in human cancer cells indicate that melatonin may directly protect against cadmium-induced tissue damage via regulation of mitochondrial activity. Further, recent evidence has demonstrated that melatonin can improve bone health for individuals with osteoporosis and partially protect against cadmium-associated inhibition of bone repair. Here we review these data and argue that the effects and therapeutic potential of melatonin treatment against the negative impacts of cadmium toxicity on bone mineral density should be investigated.

INTRODUCTION

A 2019 study estimated that there were 1.14 billion cigarette smokers globally, indicating that smoking remains a widespread risk factor to human health (GBD 2019 Tobacco Collaborators, 2021). Amongst the many negative health consequences associated with smoking, it is a known risk factor for osteoporosis and poor bone health, with one meta-analysis estimating the risk of osteoporotic fracture being 32% higher in smoking men and women compared to non-smokers (Kanis et al., 2005). Multiple mechanisms have been proposed that can potentially mediate this association, including the alteration of sex hormones and increased oxidative stress (Al-Bashaireh et al., 2018). Cadmium, an environmental toxin known to promote increased production of Reactive Oxygen Species (ROS) and mitochondrial dysfunction, is present in tobacco at concentrations ranging from 0.5-1.0 g of cadmium per cigarette, and is found at concentrations 4-5x higher in smokers versus non-smokers (Ganguly et al., 2018).

Longitudinal cohort and cross-sectional studies have established that exposure to cadmium is a risk factor for decreased bone mineral density (BMD) and osteoporosis. Experimental support for these epidemiological findings has shown that bone health, as measured by BMD, is highly sensitive to cadmium exposure even at levels as low as 0.3-10 mg/kg body weight (Buha et al., 2019), through both inhibition of the activity of osteoblasts, thus decreasing bone deposition, and stimulation of osteoclast differentiation, resulting in increased resorption and pit formation within bone (X. Chen et al., 2009, 2013; W. Liu et al., 2020; Ou et al., 2021). Ultimately, this results in the characteristic imbalance between bone deposition and resorption typically associated with the onset of osteoporosis in later life (X. Chen et al., 2009, 2013; W. Liu et al., 2020; Ou et al., 2021).

A study by Li and colleagues (2020) investigated how much the smoking-associated risk of osteoporosis was mediated by cadmium. Analysis of retrospective cohort data revealed that each 10-pack year (packs of cigarettes smoked per day, multiplied by the smoking duration, in years) could lead to 1.06 additional hip fractures per 1000 person-years, with 0.67 of this risk due to cadmium from tobacco smoke (Li et al., 2020). These results were supported by Elbeialy & Eldosouky (2018), who found an inverse relationship between serum and urinary cadmium and bone health. Thus, smoking is a known risk factor for poor bone health, with cadmium exposure being a relatively well characterized mediator of this risk. Despite this, no treatment or preventative measure has been identified that specifically mitigates the effects of cigarette smoking-associated cadmium-induced decreases in bone health.

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LITERATURE REVIEW

Intracellular cadmium toxicity

Much of the data regarding the mechanisms of cadmium toxicity has centered around its impacts on ROS production and mitochondrial function, where it is able to inhibit the coupling of the electron transport chain (ETC) and phosphorylation reactions, resulting in the inhibition of ATP synthesis within the mitochondria (Bradley et al., 1956), in addition to impeding succinate- and malate/pyruvate-stimulated respiration (Müller & Ohnesorge, 1984). Cadmium's direct role in Complex-I derived ROS production has been relatively well characterized. It has been demonstrated that cadmium binds to the Q-site of Complex I in the ETC or other NADPH dependent enzymes resulting in uncoupling (Cameron et al., 1986), and a significant increase in . ROS production (Hirst et al., 2008). Furthermore, the reduced Complex I activity results in electrons accumulating at the Q site and their transfer to molecular oxygen, forming $O_2\bullet-$ (Doughan et al., 2008). Cadmium has also been implicated in Complex III dysfunction; by inhibition of electron flow (Miccadei & Floridi, 1993) and binding to the Q-site of complex III preventing electron delivery from semi-ubiquinone to heme b_{566} causing semi-ubiquinone to accumulate and go on to donate the electron to O_2 forming $O_2\bullet-$ (Y. Wang et al., 2004). Similarly, Complex II is also thought to be a target for cadmium resulting in increased ROS formation, and playing a key role in cadmium induced cytotoxicity (Belyaeva, 2018).

In terms of ROS-independent mechanisms of cellular toxicity, cadmium also causes oxidative stress through intracellular depletion of glutathione (GSH), which acts as a key redox buffer within the cell, due to the fact that GSH contains thiol groups present in cysteine residues which cadmium has a strong affinity for (Nemmiche, 2017). Cadmium, like other heavy metals, can displace the zinc in thiols thereby disrupting the protein function (Bertin & Averbeck, 2006). Cadmium related depletion of GSH has been implicated in cell death of hepatocytes and primary oligodendrocytes (Almazan et al., 2000; Nemmiche, 2017).

Cadmium exposure has also been observed to up-regulate genes associated with cell cycle regulation, and proteins such as Growth Factor Receptor Bound Protein 2 (GRB2) and Shc adaptor protein, which are involved in cell proliferation and differentiation through the RAS pathway (Misra et al., 2003). Furthermore, it has also been shown that cadmium is able to compromise DNA integrity by inhibiting mismatch repair even at low concentrations such as 5 M through inhibition of ATP hydrolysis of mutS homolog 6 (MSH6) (Clark & Kunkel, 2004; Dally & Hartwig, 1997). Nucleotide excision repair is similarly inhibited by cadmium by reducing the DNA binding capacity of the xeroderma pigmentosum A protein thereby decreasing DNA damage recognition (Hartmann & Hartwig, 1998; Hartwig, 1998). Finally, base excision repair is impacted as cadmium exposure depletes human 8-oxoguanine-DNA glycosylase-1 protein (OGG1) by reducing the DNA binding activity of the transcription factor specificity protein-1 (Sp1) to the OGG1 promoter (Youn et al., 2005). Sp1 contains a zinc-finger motif whose cysteines may be targets for cysteine modification by cadmium, resulting in disruption of the protein. Additionally, high cadmium concentrations inhibit the nuclease activity of apurinic/apyrimidic (AP) endonuclease I which initiates repair of damaged bases (McNeill et al., 2004).

Cadmium toxicity in bone

As described above, cadmium exposure is associated with decreased BMD and osteoporosis, and many studies have examined the cellular and molecular mechanisms by which cadmium negatively affects bone health. Bone marrow mesenchymal stem cells (BMMSC) are multipotent stem cells capable of differentiation into osteoblasts (the cells responsible for producing new bone matrix), adipocytes, and chondrocytes (L. Hu et al., 2018). Rodriguez and Mandalunis (2016) demonstrated that cadmium decreased BMMSC viability, increased BMMSC differentiation into adipocytes, and relatedly decreased differentiation of BMMSCs into osteoblasts. Abnosi and Golami (2017) also reported that cadmium reduced BMMSC viability and proliferation and significantly reduced the concentration of intracellular calcium and alanine aminotransferase (ALT) and aspartate aminotransferase activities. Lv et al. (2019) demonstrated that cadmium interacts with BMMSCs through the receptor activator of the nuclear factor kappa B ligand (RANKL)/RANK/osteoprotegerin (OPG) signalling pathway resulting in suppression of osteogenic differentiation in vivo. This finding was supported by Knani and colleagues (2019) who also demonstrated that cadmium-induced bone damage mainly occurred as a result of suppression of osteogenic differentiation and relatedly caused an increase in adipocyte differentiation indicating the importance of osteoblast and adipocyte presence on bone health and homeostasis.

More recently, Hu and colleagues (2023) investigated the mechanisms behind cadmium induced inhibition of osteogenic differentiation in rat primary BMMSCs. Cadmium was observed to induce nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome pathways and resulted in autophagosome accumulation in BMMSCs, resulting in primary BMMSC cell death caused by impeded lysosome and autophagolysosome formation. Further, cadmium stimulated ROS/NLRP3/caspase-1/p20/IL- 1β inflammatory signalling pathways, causing BMMSC cell senescence and apoptosis. In addition, cadmium exposure resulted in the differentiation of primary osteoclasts and bone resorption activity. Finally, the authors also determined that Keap1/Nrf2/Are signalling is hindered which worsens oxidative stress within BMMSCs. They concluded that the toxicity of Cd in BMMSCs is induced through autophagy dysfunction and NLRP3 pathways (Hu et al., 2023). These results provide key insights into how cadmium impacts bone health at the biochemical level.

Differentiated osteoblasts are also a target for cadmium, which has been observed to induce osteoblast apoptosis. Zhao and colleagues (2015) determined that cadmium-induced apoptosis is mediated by the activation of caspase-3 and adenosine 5′monophosphate (AMP)-activated protein kinase (AMPK). Further, Liu and colleagues (2014) described that calcium-calmodulin-mediated mitochondrial dysfunction as well as cytochrome-C release hastened cadmium-induced apoptosis. As summarized by Ma and colleagues (2021), osteoblast apoptosis caused by mitochondrial dysfunction, endoplasmic reticulum stress, and oxidative stress, is a major component of bone health dysfunction because abnormal apoptosis can contribute to bone loss.

Cadmium is also known to affect the differentiation and activity of osteoclasts, the cells which are responsible for bone resorption. For example cadmium is observed to increase prostaglandin E2 (PGE2) synthesis and in turn stimulate increased bone resorption by osteoclasts (Collins & Chambers, 1991; Suzuki et al., 1989). A key mechanism that underlies greater osteoclast differentiation following cadmium exposure, as described by Chen and colleagues (2013) is that, following cadmium exposure, expression of RANKL increases while the expression of OPG, a decoy receptor for RANKL, decreases resulting in greater RANKL signalling and osteoclast differentiation.

Finally, a further study by Knani et al (2020) described how cadmium induced toxicity in rat bone was associated with reduced activity of glycogen synthase kinase 3- (GSK3), resulting in decreased levels of the proteins Wnt3a and -catenin. The Wnt/-catenin pathway is involved in the regulation of bone metabolism, where it induces the expression of osteoblast genes (Aida et al., 2018; Piters et al., 2008), mediating osteoblastogenesis as well as bone proliferation, differentiation, and mineralization (Baron et al., 2006; Glass et al., 2005; Mbalaviele et al., 2005). Rats exposed to cadmium showed a downregulation of osteogenic-related genes including Runx2, Ocn, and Alp (Knani et al., 2020). This downregulation of osteogenic genes caused by decreased Wnt3a and -catenin proteins, therefore results in the disruption of the careful balance between osteoblast bone deposition and osteoclast bone resorption, favouring a decrease in bone mineral density.

Preventing loss of bone mineral density

Widely used treatments for decreased BMD include anti-resorptive drugs and hormone replacement therapies (HRT). However, both these treatments have significant limitations. For example, anti-resorptive drugs can have significant side effects for the patient including osteonecrosis of the jaw and harsh repression of bone turnover (Brown, 2017; Kennel & Drake, 2009). Furthermore, HRT is used to balance estrogen levels within peri- and post-menopausal women to prevent the rapid bone loss common in post-menopause (Gambacciani & Levancini, 2014). HRT is not commonly used for women pre-menopause as estrogen levels in pre-menopausal women typically maintain serum estrogen above the threshold level required for maintenance of bone health (Stevenson, 2023). In addition, as reviewed by Gosset al (2021), there are associated risks with taking exogenous estrogen. Thus, HRT treatment is prescribed following an important risk-benefit analysis based on the type, dose and length of treatment as well as the woman's individual risk profile (Gosset et al., 2021). Adverse effects can include cardiovascular events, thromboembolism, stroke, and breast cancer (Rozenberg et al., 2020). Importantly, estrogens also mediate an important role in the bone health of men among other functions pertaining to fertility, fat formation, regulating insulin signaling, and regulating pancreas β cell function among others (Vandenput & Ohlsson, 2009). It has been described that men who are deficient in estrogen, for example those with aromatase deficiency due to a mutation in CYP19AI, or mutations in estrogen receptors that result in estrogen resistance, have delayed bone growth and unfused epiphyses (Morishima et al., 1995; Smith et al., 1994). However, men do not typically experience the same decrease in estrogen that women do with age meaning the addition of exogenous estrogen is unnecessary in most cases (Vandenput & Ohlsson, 2009). Furthermore, estrogen treatment in males is known to cause impaired development and function of the testes, prostate and seminal vesicles (Hammes & Levin, 2019; Masson & Selye, 1943). An additional important consideration is the cost-effectiveness of HRT. As reviewed by Rozenberg and colleagues (2020), menopausal hormone therapy (MRT) amongst females with a uterus was cost effective "only in those with a prior vertebral fracture" indicating that MRT use is not favorable in cases where fracture risk is low. This indicates that the use of hormone therapy as a preventative measure against bone loss caused by cadmium would be cost-ineffective, especially for those with financial restrictions. Thus, HRT is not a practical bone health prevention option for men or women pre-menopause. Cigarette smokers are present across the lifespan, found within both sexes, and are often chronic users/consumers. Thus, the existing treatments to improve BMD are insufficient to address the needs of this large and varied population of individuals.

Importantly, recent data has indicated that melatonin can protect against cadmium-induced oxidative stress (Hyun et al., 2023) and may attenuate the negative effects of cadmium exposure on bone repair (Luo et al., 2021). However, the efficacy of melatonin use in cigarette smokers and those regularly exposed to cadmium to preserve bone mineral density has not yet been characterized. Given this information, we propose that supplementation with melatonin could be an appropriate strategy for the prevention of bone density loss in individuals who are regularly exposed to cadmium by limiting oxidative stress and mitochondrial impairment.

Melatonin & bone health

Melatonin is a hormone synthesized and produced by the pineal gland (Cipolla-Neto & Amaral, 2018). The primary function of melatonin is in regulating the sleep-wake cycle and the modulation of circadian rhythms, and hence is a widely accessible pharmaceutical used to treat sleep-wake disturbances (Geoffroy et al., 2015; Tordjman et al., 2017; Xie et al., 2017).

Recent studies have found that melatonin also positively affects bone homeostasis and has been proposed as a potential treatment for osteoporosis/osteopenia (Amstrup et al., 2015; X. Wang et al., 2019). Melatonin is known to have strong antioxidant properties, which may in part explain its protective effects on bone (X. Liu et al., 2013; X. Lu et al., 2021; Tordjman et al., 2017). Melatonin's antioxidant capacities are exerted directly through its ability to scavenge free radicals and indirectly through activating antioxidative enzymes, inhibiting pro-oxidative enzymes, and tempering DNA repair pathways (Galano et al., 2018; Majidinia et al., 2017; Reiter et al., 2010). These mechanisms allow for melatonin to protect against free-radical-associated DNA damage (Galano et al., 2018). Furthermore, melatonin is thought to preserve the antioxidant capacity and bone-formation potential of bone-marrow-derived mesenchymal stem cells (BMMSCs) (W. Chen et al., 2020). In addition, melatonin has broader effects on bone, including promotion of osteoblast cell differentiation and type I collagen synthesis, thereby stimulating bone proliferation, and inhibition of bone resorption through the downregulation of RANKL-mediated osteoclast formation and activation (Koyama et al., 2002; X. Lu et al., 2021; Nakade et al., 1999; Xu et al., 2018). Within human populations, randomized control trials have found that melatonin supplementation is both well-tolerated and effective at improving physical symptoms in perimenopausal women with osteoporosis (Kotlarczyk et al., 2012); and was able to

increase bone mineral density at the femoral neck in a well-tolerated dose-dependent manner (Amstrup et al., 2015). Melatonin is also thought to be effectively non-toxic and is capable of improving circadian rhythm sleep disorders and poor sleep quality (Amstrup et al., 2015; Zisapel, 2018). Thus, melatonin is a safe, potential therapeutic for osteoporosis that is advantageous over other drugs, such as hormone replacement therapy and anti-resorptive drugs that often have significant side effects.

Melatonin & cadmium

Interestingly, previous observational and experimental studies have noted that cigarette smoking and third-hand smoke is associated with lower serum melatonin levels (Jiang et al., 2021; Ursing et al., 2005). Third-hand smoke is defined as the environmental hazard created via accumulation of second-hand smoke toxins on indoor objects (Jiang et al., 2021). Evidence indicates that polycyclic aromatic hydrocarbons (PAHs) in cigarette smoke can increase the activity of cytochrome P450(CYP)1A2 (Ursing et al., 2005). CYP1A2 is associated with the breakdown of melatonin by the liver, which may explain the observed association between smoking and abnormally decreased serum melatonin (Ursing et al., 2005). However, other studies have found higher circulating daytime levels of melatonin in smokers (Tarquini et al., 1994). Thus, the association between smoking and melatonin levels remains to be clarified.

Recently, a study by Hyun and colleagues (2023) has revealed that melatonin directly counteracts the effect of cadmium on ROS levels within human prostate stromal cells and mouse embryonic fibroblasts. This is because melatonin enhanced the expression of mitochondrially-localized signal transducer and activator of transcription 3 (mitoSTAT3) that is reduced by cadmium exposure. MitoSTAT3 is thought to play an important role in the modulation of the electron transport chain (ETC), ROS homeostasis, transcription of mitochondrial DNA, ATP production, and apoptosis (Hyun et al., 2023). STAT3's role in ATP production has not been fully elucidated, however, mitoSTAT3 absence was shown to greatly decrease the activity of complex V in the ETC. Whether mitoSTAT3 affects the activity of Complex V or instead has some upstream effects on elements of the ETC is not yet fully understood (Gough et al., 2009; Meier & Larner, 2014). In addition, mitoSTAT3 maintains Complex I of the ETC's activity under ischemic conditions thereby restricting cytochrome c release (Szczepanek et al., 2011). This then preserves cell viability under cellular stress. Despite that STAT3's role in mitochondrial reperfusion injury is similarly not fully understood, STAT3 may modulate the mitochondrial permeability transition pore (MPTP) (Boengler et al., 2010). The MPTP is an important component in ischemia and reperfusion injury which remains opens under certain stimuli such as ROS and excess calcium, causing swelling of the mitochondria, mitochondrial dysfunction and culminating in apoptosis or necrosis (Halestrap et al., 2000). Tammineni et al (2013) determined using in-vitro studies that the gene associated with retinoid interferon induced cell mortality 19 (GRIM-19), a component of Complex I in the electron transport chain, acts as a chaperone to facilitate the recruitment of STAT3 into the mitochondria. GRIM-19 is also thought to increase the incorporation of STAT3 into Complex I (Tammineni et al., 2013). Notably, mitochondrial levels of GRIM-19 are altered by both melatonin and cadmium. Long-term exposure to CdCl2 decreased GRIM-19 levels in the mitochondria of WPMY-1 human prostate stromal cells (Hyun et al., 2023). Further, melatonin increases mitoSTAT3 levels following cadmium treatment, contributing to protection against ROS damage, mitochondrial dysfunction, and cell death (Hyun et al., 2023).

When specifically applied to osteogenic cells, Luo et al (2021) determined that pre-treatment with melatonin helped to maintain the integrity of the mitochondrial structure of BMMSCs and decrease DNA damage caused by cadmium within these cells, thereby protecting them against apoptosis. The authors conclude that melatonin may help to prevent cadmium-associated premature aging and apoptosis of BMMSCs (Luo et al., 2021). BMMSCs can differentiate into osteoblasts. Therefore, preventing cadmium-associated apoptosis of these cells, could increase osteoblast numbers (L. Hu et al., 2018). In addition, Knani et al (2019) determined that melatonin also protected against cadmium-induced accumulation of adipocytes within the bone marrow and concurrent metabolic disruption, most likely by maintaining the GSK2 kinase activity and promoting Wnt3a and -catenin signalling (Knani et al., 2020). As discussed above, cadmium encourages differentiation of BMMSCs into adipocytes while inhibiting differentiation into osteoblasts, resulting in dysregulated bone homeostasis. These findings suggest that increasing or maintaining the number of functional osteoblasts through preventative melatonin supplementation may help to rebalance bone deposition and resorption, thereby suppressing cadmium-associated loss of bone mineral density.

Thus, the use of melatonin in the prevention of cadmium-associated damage may be a mechanism to improve bone mineral density and osteoporosis outcomes within populations regularly exposed to cadmium, including smokers. However, the clinical relevance of melatonin supplementation in this population has yet to be explored. Given melatonin supplementation's well-tolerated nature and its potential to protect against cadmium-related exposure, examining this link may provide a new avenue for treating and preventing bone-mineral loss disorders such as osteoporosis within individuals who are exposed to cadmium.

Suggested Experimental Approach

We propose testing this intervention initially within human cell culture and animal models to better understand the effects of melatonin on cadmium induced decreases in bone mineral density in vitro. Previously, Luo et al (2021) used bone marrow-derived mesenchymal stem cells to determine that pre-treatment with melatonin was able to prevent cadmium-induced mitochondrial dysfunction and DNA damage, which are key impairments associated with cellular senescence. However, no studies have been done examining the effectiveness of melatonin treatment on osteocytes. To approach this, we suggest the use of monolayer osteocyte cell culture as described by Shah et al (2016) and osteocyte 3D organoid cultures, described by Knowles et al (2023) and Bernhardt et al (2020). Cultures could be pretreated with melatonin, then exposed to cadmium, in addition to separate cultures treated with melatonin following cadmium exposure to differentiate between these conditions. Analysis of key markers related to cadmium toxicity would include levels of ROS, mitochondrial function, endoplasmic reticulum function, autophagy, apoptosis (Ma et al., 2021) as well as ROS/NLRP3/caspase-1/p20/IL- 1β inflammatory signalling pathways and GRIM-19, Wnt3a and beta-catenin signalling as these have all been

implicated in cadmium-induced stress on osteoclasts and/or BMMSCs (R. Hu et al., 2023; Hyun et al., 2023; Knani et al., 2020).

Following these cell-based experiments, animal models should be used to test the effectiveness of melatonin treatment in preventing cadmium-related bone damage in vivo. The protocol for exposure of mice to cadmium as described in Hu and colleagues (Hu et al., 2023) would be an appropriate model, with bone health quantified in accordance with Lu et al.'s (2021) procedure for using microCT and pQCT to determine bone mineral density. In addition, femoral and tibial extraction could be utilized to assess the bone mineral matrix, and oxidative stress markers including tiobarbituric acid reactive substances (Junqueira et al., 2021); as well as bone cytokines such as the RANK RANKL/RANK/OPG system for measuring osteoclast activity (Xu et al., 2018). Finally, osteogenic-related proteins Wnt3a/β-catenin and their associated genes including Runx2, Ocn, and Alp should also be analyzed (Knani et al., 2020).

If the cellular and animal model studies prove successful, this would pave the way for testing the efficacy of melatonin within randomized control trials that compare the effect of melatonin supplementation on bone mineral density, and fracture rate, across cigarette smokers of all ages. Additional consideration may be given to matched case-control trials that consider inclusion criteria such as age, number of cigarettes smoked per week, serum cadmium levels, or basal melatonin levels, given that endogenous melatonin levels can differ widely between individuals (Burgess & Fogg, 2008). Importantly, melatonin supplementation in smokers with unusually high melatonin at baseline may not provide any important benefit. As suggested by Tarquini and colleagues (1994), smokers may have supra-physiologically high levels of melatonin compared to their non-smoking counterparts. As a result, the signalling pathways that melatonin effects such as increasing the expression of mitoSTAT3 may become saturated (Hyun et al., 2023). As melatonin has been shown to help prevent age-related osteoporosis, these results could also be compared to the effectiveness of melatonin in preventing bone mineral density loss in age-matched non-smoking individuals.

Based on our proposed experiments we would expect to find that the loss of BMD over time within cigarette smokers supplemented with melatonin should be less pronounced than that of smokers who did not supplement for melatonin. We predict that this difference will result from increased expression of mitoSTAT3, which will in turn protect against the production of reactive oxygen species through modulating the electron transport chain (Gough et al., 2009; Meier & Larner, 2014) and the MPTP pore (Boengler et al., 2010), thereby facilitating the survival and function of osteocytes and osteogenic cells (Hyun et al., 2023). Furthermore, we would also expect the Wnt/-catenin pathway may play a key role in melatonin's reversal of cadmium toxicity as described by Knani at al (2020).

CONCLUSIONS

Cadmium, an environmental toxin known to cause decreased bone mineral density, is introduced into the body through cigarette smoking among other methods. To improve health outcomes for cigarette smokers, the authors propose the use of melatonin as a supplement. Melatonin is a widely used and well-tolerated over-the-counter pharmaceutical commonly utilized in the modulation of sleep-wake disorders. Importantly, new research has revealed that melatonin may be capable of attenuating ROS damage and mitochondrial dysfunction associated with cadmium exposure, as well as preventing apoptosis of BMMSC's. Importantly, melatonin supplementation would be a cost-effective and widely accessible treatment to prevent bone loss in smokers. Evidence supporting this strategy would present an option to improve health outcomes for millions of cigarette smokers globally and may overall reduce the burden of fractures related to loss of bone-mineral density. Thus, the proposal that supplementation with melatonin will prevent bone density loss in individuals who are regularly exposed to cadmium is one that should be considered for further clinical research.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

REFERENCES

[1] Abnosi, M. H., & Golami, S. (2017). Cadmium chloride treatment of rats significantly impairs membrane integrity of mesenchymal stem cells via electrolyte imbalance and lipid peroxidation, a possible explanation of Cd related osteoporosis. Iranian Journal of Basic Medical Sciences, 20(3), 280–287. https://doi.org/10.22038/IJBMS.2017.8356

[2] Aida, Y., Kurihara, H., & Kato, K. (2018). Wnt3a promotes differentiation of human bone marrow-derived mesenchymal stem cells into cementoblast-like cells. In Vitro Cellular & Developmental Biology. Animal, 54(6), 468–476. https://doi.org/10.1007/s11626-018-0265-3

[3] Al-Bashaireh, A. M., Haddad, L. G., Weaver, M., Chengguo, X., Kelly, D. L., & Yoon, S. (2018). The Effect of Tobacco Smoking on Bone Mass: An Overview of Pathophysiologic Mechanisms. Journal of Osteoporosis, 2018, 1206235. https://doi.org/10.1155/2018/1206235

[4] Almazan, G., Liu, H. N., Khorchid, A., Sundararajan, S., Martinez-Bermudez, A. K., & Chemtob, S. (2000). Exposure of developing oligodendrocytes to cadmium causes HSP72 induction, free radical generation, reduction in glutathione levels, and cell death. Free Radical Biology & Medicine, 29(9), 858–869. https://doi.org/10.1016/s0891-5849(00)00384-1

[5] Amstrup, A. K., Sikjaer, T., Heickendorff, L., Mosekilde, L., & Rejnmark, L. (2015). Melatonin improves bone mineral density at the femoral neck in postmenopausal women with osteopenia: A randomized controlled trial. Journal of Pineal Research, 59(2), 221–229. https://doi.org/10.1111/jpi.12252

[6] Baron, R., Rawadi, G., & Roman-Roman, S. (2006). Wnt signaling: A key regulator of bone mass. Current Topics in Developmental Biology, 76, 103–127. https://doi.org/10.1016/S0070-2153(06)76004-5

[7] Belyaeva, E. A. (2018). Respiratory complex II in mitochondrial dysfunction-mediated cytotoxicity: Insight from cadmium. Journal of Trace Elements in Medicine and Biology: Organ of the Society for Minerals and Trace Elements (GMS), 50, 80–92. https://doi.org/10.1016/j.jtemb.2018.06.009

[8] Bertin, G., & Averbeck, D. (2006). Cadmium: Cellular effects, modifications of biomolecules, modulation of DNA repair and genotoxic consequences (a review). Biochimie, 88(11), 1549–1559. https://doi.org/10.1016/j.biochi.2006.10.001

[9] Boengler, K., Hilfiker-Kleiner, D., Heusch, G., & Schulz, R. (2010). Inhibition of permeability transition pore opening by mitochondrial STAT3 and its role in myocardial ischemia/reperfusion. Basic Research in Cardiology, 105(6), 771–785. https://doi.org/10.1007/s00395-010-0124-1

[10] Bradley, L. B., Jacob, M., Jacobs, E. E., & Sanadi, D. R. (1956). Uncoupling of oxidative phosphorylation by cadmium ion. The Journal of Biological Chemistry, 223(1), 147–156.

[11] Brown, J. P. (2017). Antiresorptives: Safety Concerns—Clinical Perspective. Toxicologic Pathology, 45(7), 859–863. https://doi.org/10.1177/0192623317737066

[12] Buha, A., Jugdaohsingh, R., Matovic, V., Bulat, Z., Antonijevic, B., Kerns, J. G., Goodship, A., Hart, A., & Powell, J. J. (2019). Bone mineral health is sensitively related to environmental cadmium exposure- experimental and human data. Environmental Research, 176, 108539. https://doi.org/10.1016/j.envres.2019.108539

[13] Burgess, H. J., & Fogg, L. F. (2008). Individual Differences in the Amount and

Timing of Salivary Melatonin Secretion. PLoS ONE, 3(8), e3055. https://doi.org/10.1371/journal.pone.0003055
[14] Cameron, I., McNamee, P. M., Markham, A., Morgan, R. M., & Wood, M. (1986). The effects of cadmium on succinate and NADH-linked substrate oxidations in rat hepatic mitochondria. Journal of Applied Toxicology: JAT, 6(5), 325–330. https://doi.org/10.1002/jat.2550060505
[15] Chen, W., Chen, X., Chen, A. C., Shi, Q., Pan, G., Pei, M., Yang, H., Liu, T., & He, F. (2020). Melatonin restores the osteoporosis-impaired osteogenic potential of bone marrow mesenchymal stem cells by preserving SIRT1-mediated intracellular antioxidant properties. Free Radical Biology and Medicine, 146, 92–106. https://doi.org/10.1016/j.freeradbiomed.2019.10.412
[16] Chen, X., Wang, G., Li, X., Gan, C., Zhu, G., Jin, T., & Wang, Z. (2013). Environmental level of cadmium exposure stimulates osteoclasts formation in male rats. Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association, 60, 530–535. https://doi.org/10.1016/j.fct.2013.08.017
[17] Chen, X., Zhu, G., Gu, S., Jin, T., & Shao, C. (2009). Effects of cadmium on osteoblasts and osteoclasts in vitro. Environmental Toxicology and Pharmacology, 28(2), 232–236. https://doi.org/10.1016/j.etap.2009.04.010
[18] Cipolla-Neto, J., & Amaral, F. G. do. (2018). Melatonin as a Hormone: New Physiological and Clinical Insights. Endocrine Reviews, 39(6), 990–1028. https://doi.org/10.1210/er.2018-00084
[19] Clark, A. B., & Kunkel, T. A. (2004). Cadmium Inhibits the Functions of Eukaryotic MutS Complexes*. Journal of Biological Chemistry, 279(52), 53903–53906. https://doi.org/10.1074/jbc.C400495200
[20] Collins, D. A., & Chambers, T. J. (1991). Effect of prostaglandins E1, E2, and F2α on osteoclast formation in mouse bone marrow cultures. Journal of Bone and Mineral Research, 6(2), 157–164. https://doi.org/10.1002/jbmr.5650060209
[21] Dally, H., & Hartwig, A. (1997). Induction and repair inhibition of oxidative DNA damage by nickel(II) and cadmium(II) in mammalian cells. Carcinogenesis, 18(5), 1021–1026. https://doi.org/10.1093/carcin/18.5.1021
[22] Doughan, A. K., Harrison, D. G., & Dikalov, S. I. (2008). Molecular mechanisms of angiotensin II-mediated mitochondrial dysfunction: Linking mitochondrial oxidative damage and vascular endothelial dysfunction. Circulation Research, 102(4), 488–496. https://doi.org/10.1161/CIRCRESAHA.107.162800
[23] Elbeialy, A. A., & Eldosouky, H. A. (2018). AB0984 Cadmium toxicity as a probable cause of smoking induced bone loss. Annals of the Rheumatic Diseases, 77(Suppl 2), 1614–1614. https://doi.org/10.1136/annrheumdis-2018-eular.3369
[24] Galano, A., Tan, D.-X., & Reiter, R. J. (2018). Melatonin: A Versatile Protector against Oxidative DNA Damage. Molecules: A Journal of Synthetic Chemistry and Natural Product Chemistry, 23(3), 530. https://doi.org/10.3390/molecules23030530
[25] Gambacciani, M., & Levancini, M. (2014). Hormone replacement therapy and the prevention of postmenopausal osteoporosis. Przegląd Menopauzalny = Menopause Review, 13(4), 213–220. https://doi.org/10.5114/pm.2014.44996
[26] Ganguly, K., Levänen, B., Palmberg, L., Åkesson, A., & Lindén, A. (2018). Cadmium in tobacco smokers: A neglected link to lung disease? European Respiratory Review: An Official Journal of the European Respiratory Society, 27(147), 170122. https://doi.org/10.1183/16000617.0122-2017
[27] GBD 2019 Tobacco Collaborators. (2021). Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019: A systematic analysis from the Global Burden of Disease Study 2019. Lancet (London, England), 397(10292), 2337–2360. https://doi.org/10.1016/S0140-6736(21)01169-7
[28] Geoffroy, P. A., Etain, B., Franchi, J.-A. M., Bellivier, F., & Ritter, P. (2015). Melatonin and Melatonin Agonists as Adjunctive Treatments in Bipolar Disorders. Current Pharmaceutical Design, 21(23), 3352–3358. https://doi.org/10.2174/1381612821666150619093448
[29] Glass, D. A., Bialek, P., Ahn, J. D., Starbuck, M., Patel, M. S., Clevers, H., Taketo, M. M., Long, F., McMahon, A. P., Lang, R. A., & Karsenty, G. (2005). Canonical Wnt signaling in differentiated osteoblasts controls osteoclast differentiation. Developmental Cell, 8(5), 751–764. https://doi.org/10.1016/j.devcel.2005.02.017
[30] Gosset, A., Pouillès, J.-M., & Trémollieres, F. (2021). Menopausal hormone therapy for the management of osteoporosis. Best Practice & Research Clinical Endocrinology & Metabolism, 35(6), 101551. https://doi.org/10.1016/j.beem.2021.101551
[31] Gough, D. J., Corlett, A., Schlessinger, K., Wegrzyn, J., Larner, A. C., & Levy, D. E. (2009). Mitochondrial STAT3 Supports Ras-Dependent Oncogenic Transformation. Science, 324(5935), 1713–1716. https://doi.org/10.1126/science.1171721
[32] Halestrap, A. P., Doran, E., Gillespie, J. P., & O'Toole, A. (2000). Mitochondria and cell death. Biochemical Society Transactions, 28(2), 170–177. https://doi.org/10.1042/bst0280170
[33] Hammes, S. R., & Levin, E. R. (n.d.). Impact of estrogens in males and androgens in females. The Journal of Clinical Investigation, 129(5), 1818–1826. https://doi.org/10.1172/JCI125755
[34] Hartmann, M., & Hartwig, A. (1998). Disturbance of DNA damage recognition after UV-irradiation by nickel(II) and cadmium(II) in mammalian cells. Carcinogenesis, 19(4), 617–621. https://doi.org/10.1093/carcin/19.4.617
[35] Hartwig, A. (1998). Carcinogenicity of metal compounds: Possible role of DNA repair inhibition. Toxicology Letters, 102–103, 235–239. https://doi.org/10.1016/s0378-4274(98)00312-9
[36] Hirst, J., King, M. S., & Pryde, K. R. (2008). The production of reactive oxygen species by complex I. Biochemical Society Transactions, 36(Pt 5), 976–980. https://doi.org/10.1042/BST0360976
[37] Hu, L., Yin, C., Zhao, F., Ali, A., Ma, J., & Qian, A. (2018). Mesenchymal Stem Cells: Cell Fate Decision to Osteoblast or Adipocyte and Application in Osteoporosis Treatment. International Journal of Molecular Sciences, 19(2), 360. https://doi.org/10.3390/ijms19020360
[38] Hu, R., Luo, H., Ji, Y., Wang, Z., Zheng, P., Ouyang, H., Wang, X., Wang, Y., Bao, B., Liao, G., & Xu, B. (2023). Activation of NLRP3 signaling contributes to cadmium-induced bone defects, associated with autophagic flux obstruction. Science of The Total Environment, 893, 164787. https://doi.org/10.1016/j.scitotenv.2023.164787
[39] Hyun, M., Kim, H., Kim, J., Lee, J., Lee, H. J., Rathor, L., Meier, J., Larner, A., Lee, S. M., Moon, Y., Choi, J., Han, S. M., & Heo, J.-D. (2023). Melatonin protects against cadmium-induced oxidative stress via mitochondrial STAT3 signaling in human prostate stromal cells. Communications Biology, 6(1), Article 1. https://doi.org/10.1038/s42003-023-04533-7
[40] Jiang, W., Wu, H., Yu, X., Wang, Y., Gu, W., Wei, W., Li, B., Jiang, X., Wang, Y., Hou, W., Dong, Q., Yan, X., Li, Y., Sun, C., & Han, T. (2021). Third-hand smoke exposure is associated with abnormal serum melatonin level via hypomethylation of CYP1A2 promoter: Evidence from human and animal studies. Environmental Pollution, 277, 116669. https://doi.org/10.1016/j.envpol.2021.116669
[41] Kanis, J. A., Borgstrom, F., De Laet, C., Johansson, H., Johnell, O., Jonsson, B., Oden, A., Zethraeus, N., Pfleger, B., & Khaltaev, N. (2005). Assessment of fracture risk. Osteoporosis International: A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 16(6), 581–589. https://doi.org/10.1007/s00198-004-1780-5
[42] Kennel, K. A., & Drake, M. T. (2009). Adverse Effects of Bisphosphonates: Implications for Osteoporosis Management. Mayo Clinic Proceedings, 84(7), 632–638.
[43] Knani, L., Bartolini, D., Kechiche, S., Tortoioli, C., Murdolo, G., Moretti, M., Messaoudi, I., Reiter, R. J., & Galli, F. (2019). Melatonin prevents cadmium-induced bone damage: First evidence on an improved osteogenic/adipogenic differentiation balance of mesenchymal stem cells as underlying mechanism. Journal of Pineal Research, 67(3), e12597. https://doi.org/10.1111/jpi.12597
[44] Knani, L., Venditti, M., Kechiche, S., Banni, M., Messaoudi, I., & Minucci, S. (2020). Melatonin protects bone against cadmium-induced toxicity via activation of Wnt/β-catenin signaling pathway. Toxicology Mechanisms and Methods, 30(4), 237–245. https://doi.org/10.1080/15376516.2019.1701595
[45] Kotlarczyk, M. P., Lassila, H. C., O'Neil, C. K., D'Amico, F., Enderby, L. T., Witt-Enderby, P. A., & Balk, J. L. (2012). Melatonin osteoporosis prevention study (MOPS): A randomized, double-blind, placebo-controlled study examining the effects of melatonin on bone health and quality of life in perimenopausal women. Journal of Pineal Research, 52(4), 414–426. https://doi.org/10.1111/j.1600-079X.2011.00956.x
[46] Koyama, H., Nakade, O., Takada, Y., Kaku, T., & Lau, K. H. W. (2002). Melatonin at pharmacologic doses increases bone mass by suppressing resorption through down-regulation of the RANKL-mediated osteoclast formation and activation. Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research, 17(7), 1219–1229. https://doi.org/10.1359/jbmr.2002.17.7.1219
[47] Li, H., Wallin, M., Barregard, L., Sallsten, G., Lundh, T., Ohlsson, C., Mellström, D., & Andersson, E. M. (2020). Smoking-Induced Risk of Osteoporosis Is Partly Mediated by Cadmium From Tobacco Smoke: The MrOS Sweden Study. Journal of Bone and Mineral Research, 35(8), 1424–1429. https://doi.org/10.1002/jbmr.4014
[48] Liu, W., Le, C. C., Wang, D., Ran, D., Wang, Y., Zhao, H., Gu, J., Zou, H., Yuan, Y., Bian, J., & Liu, Z. (2020). Ca2+/CaM/CaMK signaling is involved in cadmium-induced osteoclast differentiation. Toxicology, 441, 152520. https://doi.org/10.1016/j.tox.2020.152520
[49] Liu, W., Zhao, H., Wang, Y., Jiang, C., Xia, P., Gu, J., Liu, X., Bian, J., Yuan, Y., & Liu, Z. (2014). Calcium–calmodulin signaling elicits mitochondrial dysfunction and the release of cytochrome c during cadmium-induced apoptosis in primary osteoblasts. Toxicology Letters, 224(1), 1–6. https://doi.org/10.1016/j.toxlet.2013.10.009
[50] Liu, X., Gong, Y., Xiong, K., Ye, Y., Xiong, Y., Zhuang, Z., Luo, Y., Jiang, Q., & He, F. (2013). Melatonin mediates protective effects on inflammatory response induced by interleukin-1 beta in human mesenchymal stem cells. Journal of Pineal Research, 55(1), 14–25. https://doi.org/10.1111/jpi.12045
[51] Lu, X., Yu, S., Chen, G., Zheng, W., Peng, J., Huang, X., & Chen, L. (2021). Insight into the roles of melatonin in bone tissue and bone-related diseases

(Review). International Journal of Molecular Medicine, 47(5), 82. https://doi.org/10.3892/ijmm.2021.4915
[52] Lu, Y., Di, Y. P., Chang, M., Huang, X., Chen, Q., Hong, N., Kahkonen, B. A., Di, M. E., Yu, C., Keller, E. T., & Zhang, J. (2021). Cigarette smoke-associated inflammation impairs bone remodeling through NFκB activation. Journal of Translational Medicine, 19(1), 163. https://doi.org/10.1186/s12967-021-02836-z
[53] Luo, H., Gu, R., Ouyang, H., Wang, L., Shi, S., Ji, Y., Bao, B., Liao, G., & Xu, B. (2021). Cadmium exposure induces osteoporosis through cellular senescence, associated with activation of NF-κB pathway and mitochondrial dysfunction. Environmental Pollution, 290, 118043. https://doi.org/10.1016/j.envpol.2021.118043
[54] Lv, Y.-J., Wei, Q.-Z., Zhang, Y.-C., Huang, R., Li, B.-S., Tan, J.-B., Wang, J., Ling, H.-T., Wu, S.-X., & Yang, X.-F. (2019). Low-dose cadmium exposure acts on rat mesenchymal stem cells via RANKL/OPG and downregulate osteogenic differentiation genes. Environmental Pollution, 249, 620–628. https://doi.org/10.1016/j.envpol.2019.03.027
[55] Ma, Y., Ran, D., Shi, X., Zhao, H., & Liu, Z. (2021). Cadmium toxicity: A role in bone cell function and teeth development. The Science of the Total Environment, 769, 144646. https://doi.org/10.1016/j.scitotenv.2020.144646
[56] Majidinia, M., Sadeghpour, A., Mehrzadi, S., Reiter, R. J., Khatami, N., & Yousefi, B. (2017). Melatonin: A pleiotropic molecule that modulates DNA damage response and repair pathways. Journal of Pineal Research, 63(1). https://doi.org/10.1111/jpi.12416
[57] Masson, G., & Selye, H. (1943). Changes in the Accessory Sex Organs of the Male Rat after Administration of Estradiol in Combination with Progesterone or Desoxycorticosterone Acetate. The American Journal of Pathology, 19(1), 1–7.
[58] Mbalaviele, G., Sheikh, S., Stains, J. P., Salazar, V. S., Cheng, S.-L., Chen, D., & Civitelli, R. (2005). Beta-catenin and BMP-2 synergize to promote osteoblast differentiation and new bone formation. Journal of Cellular Biochemistry, 94(2), 403–418. https://doi.org/10.1002/jcb.20253
[59] McNeill, D. R., Narayana, A., Wong, H.-K., & Wilson, D. M. (2004). Inhibition of Ape1 nuclease activity by lead, iron, and cadmium. Environmental Health Perspectives, 112(7), 799–804. https://doi.org/10.1289/ehp.7038
[60] Meier, J. A., & Larner, A. C. (2014). Toward a new STATe: The role of STATs in mitochondrial function. Seminars in Immunology, 26(1), 20–28. https://doi.org/10.1016/j.smim.2013.12.005
[61] Miccadei, S., & Floridi, A. (1993). Sites of inhibition of mitochondrial electron transport by cadmium. Chemico-Biological Interactions, 89(2–3), 159–167. https://doi.org/10.1016/0009-2797(93)90006-k
[62] Misra, U. K., Gawdi, G., & Pizzo, S. V. (2003). Induction of mitogenic signalling in the 1LN prostate cell line on exposure to submicromolar concentrations of cadmium+. Cellular Signalling, 15(11), 1059–1070. https://doi.org/10.1016/s0898-6568(03)00117-7
[63] Morishima, A., Grumbach, M. M., Simpson, E. R., Fisher, C., & Qin, K. (1995). Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. The Journal of Clinical Endocrinology and Metabolism, 80(12), 3689–3698. https://doi.org/10.1210/jcem.80.12.8530621
[64] Müller, L., & Ohnesorge, F. K. (1984). Cadmium-induced alteration of the energy level in isolated hepatocytes. Toxicology, 31(3–4), 297–306. https://doi.org/10.1016/0300-483x(84)90110-0
[65] Nakade, O., Koyama, H., Ariji, H., Yajima, A., & Kaku, T. (1999). Melatonin stimulates proliferation and type I collagen synthesis in human bone cells in vitro. Journal of Pineal Research, 27(2), 106–110. https://doi.org/10.1111/j.1600-079x.1999.tb00603.x
[66] Nemmiche, S. (2017). Oxidative Signaling Response to Cadmium Exposure. Toxicological Sciences: An Official Journal of the Society of Toxicology, 156(1), 4–10. https://doi.org/10.1093/toxsci/kfw222
[67] Ou, L., Wang, H., Wu, Z., Wang, P., Yang, L., Li, X., Sun, K., Zhu, X., & Zhang, R. (2021). Effects of cadmium on osteoblast cell line: Exportin 1 accumulation, p-JNK activation, DNA damage and cell apoptosis. Ecotoxicology and Environmental Safety, 208, 111668. https://doi.org/10.1016/j.ecoenv.2020.111668
[68] Piters, E., Boudin, E., & Van Hul, W. (2008). Wnt signaling: A win for bone. Archives of Biochemistry and Biophysics, 473(2), 112–116. https://doi.org/10.1016/j.abb.2008.03.006
[69] Reiter, R. J., Manchester, L. C., & Tan, D.-X. (2010). Neurotoxins: Free radical mechanisms and melatonin protection. Current Neuropharmacology, 8(3), 194–210. https://doi.org/10.2174/157015910792246236
[70] Rodríguez, J., & Mandalunis, P. M. (2016). Effect of cadmium on bone tissue in growing animals. Experimental and Toxicologic Pathology, 68(7), 391–397. https://doi.org/10.1016/j.etp.2016.06.001
[71] Rozenberg, S., Al-Daghri, N., Aubertin-Leheudre, M., Brandi, M.-L., Cano, A., Collins, P., Cooper, C., Genazzani, A. R., Hillard, T., Kanis, J. A., Kaufman, J.-M., Lambrinoudaki, I., Laslop, A., McCloskey, E., Palacios, S., Prieto-Alhambra, D., Reginster, J.-Y., Rizzoli, R., Rosano, G., … Harvey, N. C. (2020). Is there a role for menopausal hormone therapy in the management of postmenopausal osteoporosis? Osteoporosis International, 31(12), 2271–2286. https://doi.org/10.1007/s00198-020-05497-8
[72] Shah, K. M., Stern, M. M., Stern, A. R., Pathak, J. L., Bravenboer, N., & Bakker, A. D. (2016). Osteocyte isolation and culture methods. BoneKEy Reports, 5, 838. https://doi.org/10.1038/bonekey.2016.65
[73] Smith, E. P., Boyd, J., Frank, G. R., Takahashi, H., Cohen, R. M., Specker, B., Williams, T. C., Lubahn, D. B., & Korach, K. S. (1994). Estrogen Resistance Caused by a Mutation in the Estrogen-Receptor Gene in a Man. New England Journal of Medicine, 331(16), 1056–1061. https://doi.org/10.1056/NEJM199410203311604
[74] Stevenson, J. (2023). Prevention and treatment of osteoporosis in women. Post Reproductive Health, 29(1), 11–14. https://doi.org/10.1177/20533691221139902
[75] Suzuki, Y., Morita, I., Ishizaki, Y., Yamane, Y., & Murota, S. (1989). Cadmium stimulates prostaglandin E2 synthesis in osteoblast-like cells, MC3T3-E1. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research, 1012(2), 135–139. https://doi.org/10.1016/0167-4889(89)90086-4
[76] Szczepanek, K., Chen, Q., Derecka, M., Salloum, F. N., Zhang, Q., Szelag, M., Cichy, J., Kukreja, R. C., Dulak, J., Lesnefsky, E. J., & Larner, A. C. (2011). Mitochondrial-targeted Signal Transducer and Activator of Transcription 3 (STAT3) Protects against Ischemia-induced Changes in the Electron Transport Chain and the Generation of Reactive Oxygen Species *. Journal of Biological Chemistry, 286(34), 29610–29620. https://doi.org/10.1074/jbc.M111.226209
[77] Tammineni, P., Anugula, C., Mohammed, F., Anjaneyulu, M., Larner, A. C., & Sepuri, N. B. V. (2013). The Import of the Transcription Factor STAT3 into Mitochondria Depends on GRIM-19, a Component of the Electron Transport Chain. Journal of Biological Chemistry, 288(7), 4723–4732. https://doi.org/10.1074/jbc.M112.378984
[78] Tarquini, B., Perfetto, F., Poli, R., & Tarquini, R. (1994). Daytime Circulating Melatonin Levels in Smokers. Tumori Journal, 80(3), 229–232. https://doi.org/10.1177/030089169408000313
[79] Tordjman, S., Chokron, S., Delorme, R., Charrier, A., Bellissant, E., Jaafari, N., & Fougerou, C. (2017). Melatonin: Pharmacology, Functions and Therapeutic Benefits. Current Neuropharmacology, 15(3), 434–443. https://doi.org/10.2174/1570159X14666161228122115
[80] Ursing, C., Bahr, C. von, Brismar, K., & Röjdmark, S. (2005). Influence of cigarette smoking on melatonin levels in man. European Journal of Clinical Pharmacology, 61(3), 197–201. https://doi.org/10.1007/s00228-005-0908-7
[81] Vandenput, L., & Ohlsson, C. (2009). Estrogens as regulators of bone health in men. Nature Reviews Endocrinology, 5(8), Article 8. https://doi.org/10.1038/nrendo.2009.112
[82] Wang, X., Liang, T., Zhu, Y., Qiu, J., Qiu, X., Lian, C., Gao, B., Peng, Y., Liang, A., Zhou, H., Yang, X., Liao, Z., Li, Y., Xu, C., Su, P., & Huang, D. (2019). Melatonin prevents bone destruction in mice with retinoic acid–induced osteoporosis. Molecular Medicine, 25(1), 43. https://doi.org/10.1186/s10020-019-0107-0
[83] Wang, Y., Fang, J., Leonard, S. S., & Rao, K. M. K. (2004). Cadmium inhibits the electron transfer chain and induces reactive oxygen species. Free Radical Biology & Medicine, 36(11), 1434–1443. https://doi.org/10.1016/j.freeradbiomed.2004.03.010
[84] Xie, Z., Chen, F., Li, W. A., Geng, X., Li, C., Meng, X., Feng, Y., Liu, W., & Yu, F. (2017). A review of sleep disorders and melatonin. Neurological Research, 39(6), 559–565. https://doi.org/10.1080/01616412.2017.1315864
[85] Xu, L., Zhang, L., Wang, Z., Li, C., Li, S., Li, L., Fan, Q., & Zheng, L. (2018). Melatonin Suppresses Estrogen Deficiency-Induced Osteoporosis and Promotes Osteoblastogenesis by Inactivating the NLRP3 Inflammasome. Calcified Tissue International, 103(4), 400–410. https://doi.org/10.1007/s00223-018-0428-y
[86] Youn, C.-K., Kim, S.-H., Lee, D. Y., Song, S. H., Chang, I.-Y., Hyun, J.-W., Chung, M.-H., & You, H. J. (2005). Cadmium Down-regulates Human OGG1 through Suppression of Sp1 Activity*. Journal of Biological Chemistry, 280(26), 25185–25195. https://doi.org/10.1074/jbc.M412793200
[87] Zisapel, N. (2018). New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. British Journal of Pharmacology, 175(16), 3190–3199. https://doi.org/10.1111/bph.14116