How does Alcohol effect Osteoporosis through the TRPV6 pathway

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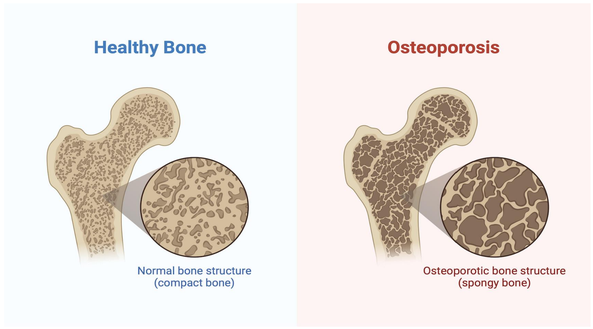
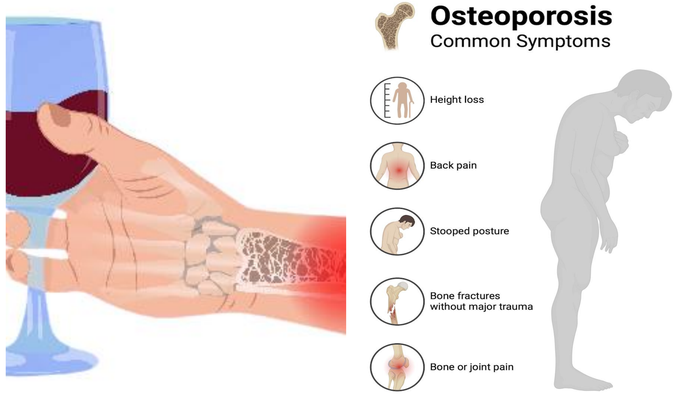
Bone Remodeling Imbalances & Osteoporosis



Current studies indicate that alcohol contributes to osteoporosis by causing a disruption in bone remodeling. This disruption comes from an imbalance in bone formation and bone resorption (1, 2)). Alcohol increases bone resorption by inducing oxidative stress and osteocyte apoptosis (1). Alcohol inhibits bone synthesis and cell proliferation by suppressing osteoblastic differentiation of mesenchymal bone marrow cells that are needed for bone tissue repair (3). Consequently, these disruptions/imbalances result in osteopenia via disruptions in modulation of proinflammatory cytokines and their mediators such as Wnt/ B-catenin, ERK/STAT3, NOX1,2,4, and IGF/PI3k/AKT/MTOR signaling (2, 16, 17, 18, 19,) and thereby increases osteoclast activity via RANKL cytokine proliferation (8). In turn, osteopenia can progress to osteoporosis. A majority of studies indicate that alcohol-induced osteopenia is mainly due to decreased bone formation rather than the increased bone resorption it may cause as well (1-5).

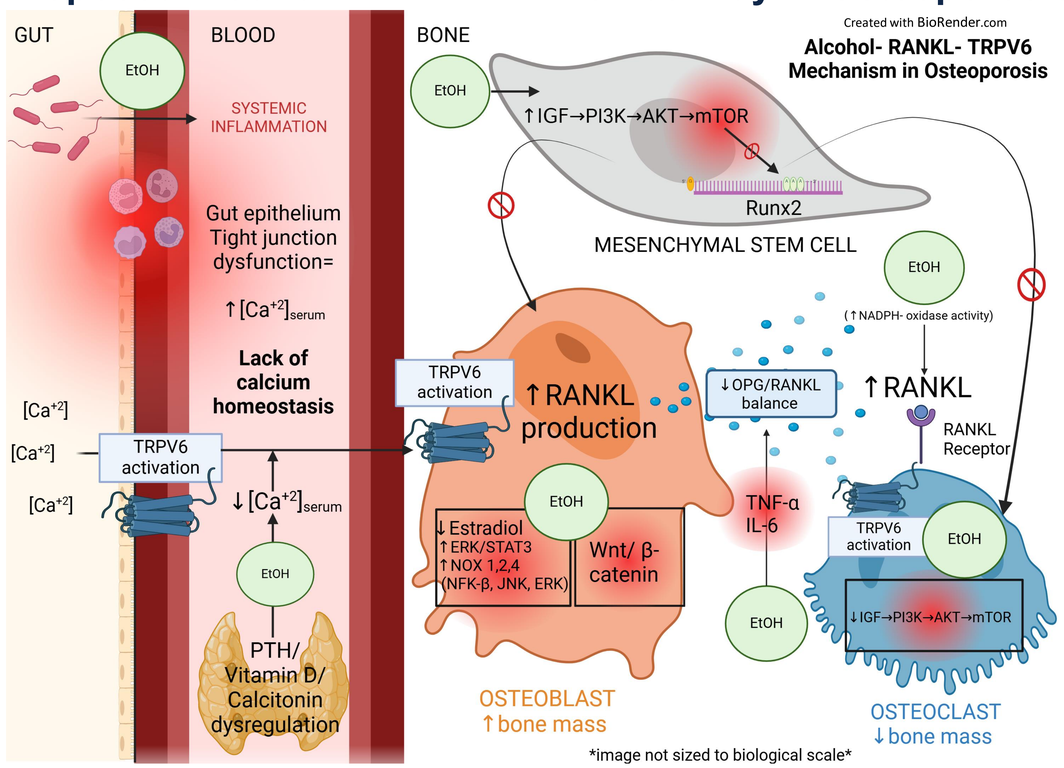


TRPV6 Pathway

Transient receptor potential vanilloid 6 (TRPV6), is a calcium-selective channel involved in calcium absorption in epithelial tissues and bone. Disruption of TRPV6 function can lead to imbalances in calcium absorption and signaling, potentially contributing to bone disorders like osteoporosis. (6) TRPV6-mediated calcium signaling pathways within bone cells regulate crucial processes such as osteoblast differentiation, proliferation, and apoptosis, ultimately impacting bone remodeling and mineralization (7).

Chronic alcohol consumption can interfere with TRPV6 function, resulting in reduced calcium absorption and increased bone density loss. Ethanol disrupts the tight junctions of the TRPV6 channel and affects TRPV6's ability to absorb calcium. The alcohol induced disturbances lead to endotoxemia, systemic inflammation, organ damage and can lead to increased bone-related disorders (8). The disrupted calcium absorption, coupled with the inflammatory effects of alcohol compromises bone integrity and contributes to accelerated bone density loss.

Proposed Alcohol-RANKL-TRPV6 Pathway in Osteoporosis



Methods

A comprehensive literature search was conducted to identify relevant studies examining the relationship between alcohol consumption, RANKL, TRPV6, and osteoporosis. Electronic databases including PubMed and Google Scholar were searched. Only studies published in peer-reviewed journals were included. Reviews, meta-analyses, conference abstracts, and non-English language studies were excluded.

Synthesis

Upon review, our proposed synthesis includes the following potential points of future investigation in studying the mechanism of osteoporosis related to alcohol consumption.

Alcohol consumption has profound impacts in multiple sources of pathology in osteoporosis. We propose that inflammation and upregulation of cytokines and their mediators (Wnt/ β-catenin, ERK/STAT3, NOX 1,2,4, NFk-β) due to alcohol mediated effects on osteoclasts, osteoblasts, mesenchymal bone stem cells, and gut epithelia have relational value between studies on RANKL cytokine osteoblast mediated osteoclast proliferation, TRPV6, and Calcium homeostasis related to PTH, Calcitonin, and Vitamin D (16, 17, 18 ,19).
Within this mechanism, a key player contributing to osteoporosis bone pathology is the disruption of calcium homeostasis via gut epithelium tight junction disruption, resulting in calcium ion influx, with simultaneous effect from PTH/ Calcitonin/ vitamin D alcohol related disruption that increases calcium ion concentration. This disruption in calcium homeostasis then contributes to decreased homeostatic balance between osteoclast and osteoblast activity, which thereby increases dysregulation of inflammatory cytokines and their mediators in bone. Alcohol's profound inflammatory effects are noted systemically, with infiltration of gut microbiota into circulation. Notably, alcohol has additional inflammatory effects that decrease mesenchymal stem cell differentiation within bone remodeling processes, thus inhibiting osteoblast/ osteoclast proliferation and diminishing bone repair leading to osteoporosis. However, RANKL proves to be a concurrent mediator of increased osteoclast number compared to osteoblasts and further heightens the overall inflammation response. Leading to cell death and pathology.

Implications/Future Directions

Current studies indicate that low alcohol intake has no effect or low beneficial effect to bone health of men and postmenopausal women (9, 10, 11, 12, 13, 14, 15). There appear to be differences in the type of alcohol consumed (beer, wine, liquor) and the impact on markers of bone health (14, 11, 13). Although low alcohol is a contributor to development of osteoporosis, more significant contributors include dietary calcium intake, weak muscle strength and low body weight (11). Binge drinking appears to contribute more heavily to osteoporosis development than low intake (10).

We proposed that additional studies be conducted to evaluate the impact of alcohol consumption on the development of osteoporosis and more specifically the alcohol- RANKL- TRPV6 pathway. This could be done with a prospective observational study in patients at risk for development of osteoporosis and in groups of no alcohol intake, moderate alcohol intake and high alcohol intake based on survey. We suggest following these patients yearly collecting information on bone density (DEXA Scans), osteoporotic fractures, TRPV6 and RANKL pathway activity markers, inflammatory pathway markers, signaling cascade proteins as well as alcohol consumption in additional to potential confounders like diet and physical activity.

There are concerns with patient self-report of alcohol consumption as a screening measure as there are questions about validity of questionnaires reliant on patient subjective reports.

Acknowledgements

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References

https://docs.google.com/document/d/1ns-9M153C_n-0U6rGfHwGC0VL3_Vj3Vk8KqJVCxPuTw/edit

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