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IMMUNOPATHOLOGY IN OSTEOPOROSIS

NeuroQuantology 2022

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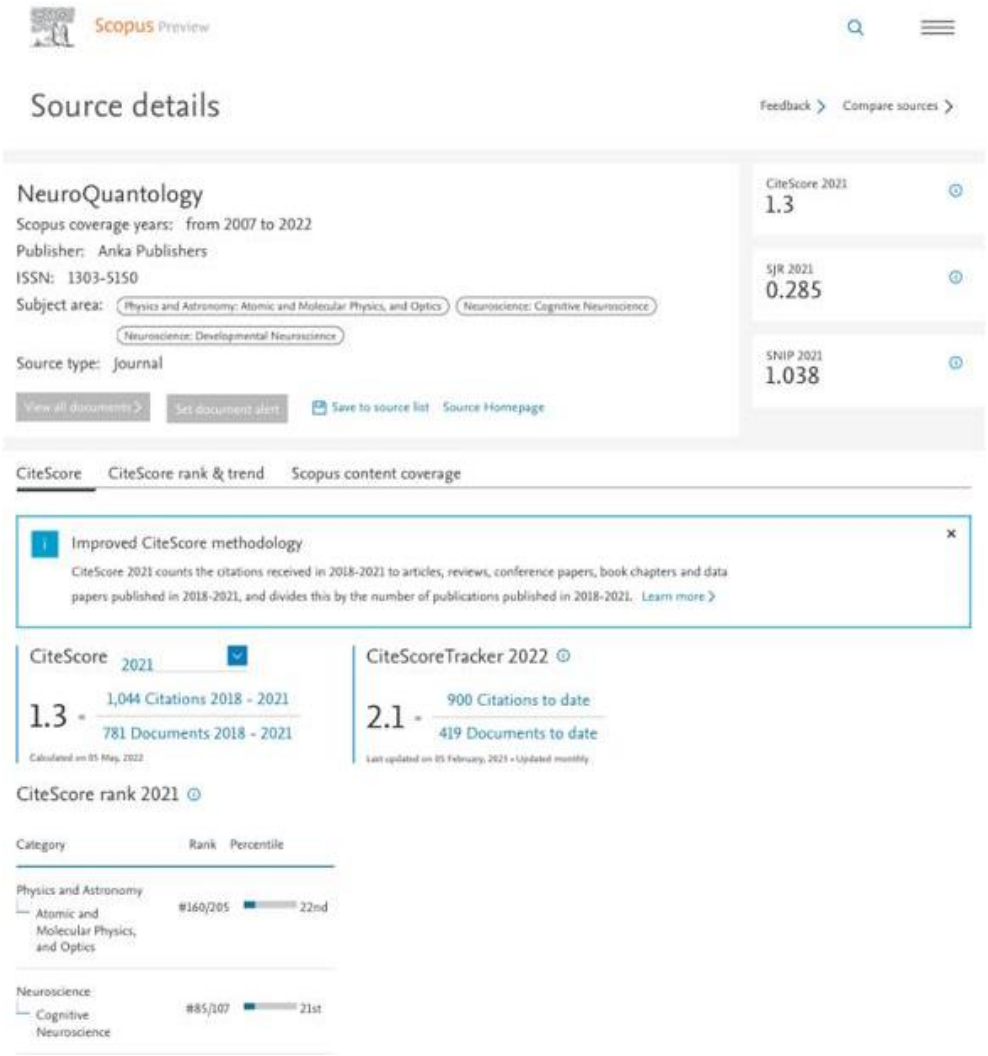

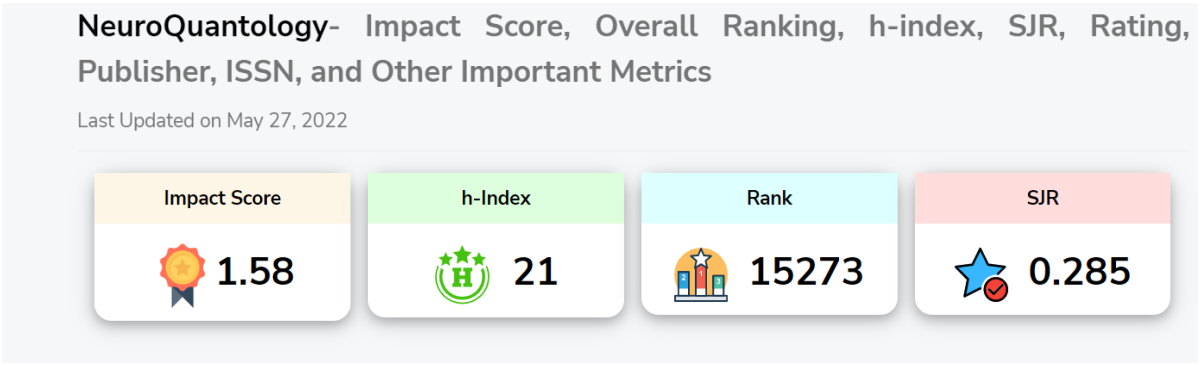

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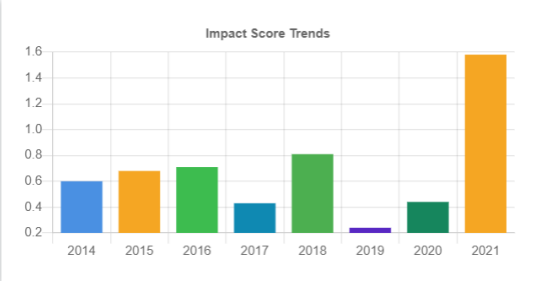

Year	Impact Score (IS)
2022/2023	Coming Soon
2021	1.58
2020	0.44
2019	0.24
2018	0.81

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NeuroQuantology

COUNTRY	SUBJECT AREA AND CATEGORY	PUBLISHER	H-INDEX
Turkey Universities and research institutions in Turkey Media Ranking in Turkey	Neuroscience Cognitive Neuroscience Developmental Neuroscience Physics and Astronomy Atomic and Molecular Physics, and Optics		21

PUBLICATION TYPE	ISSN	COVERAGE
Journals	13035150	2007-2021

SCOPE

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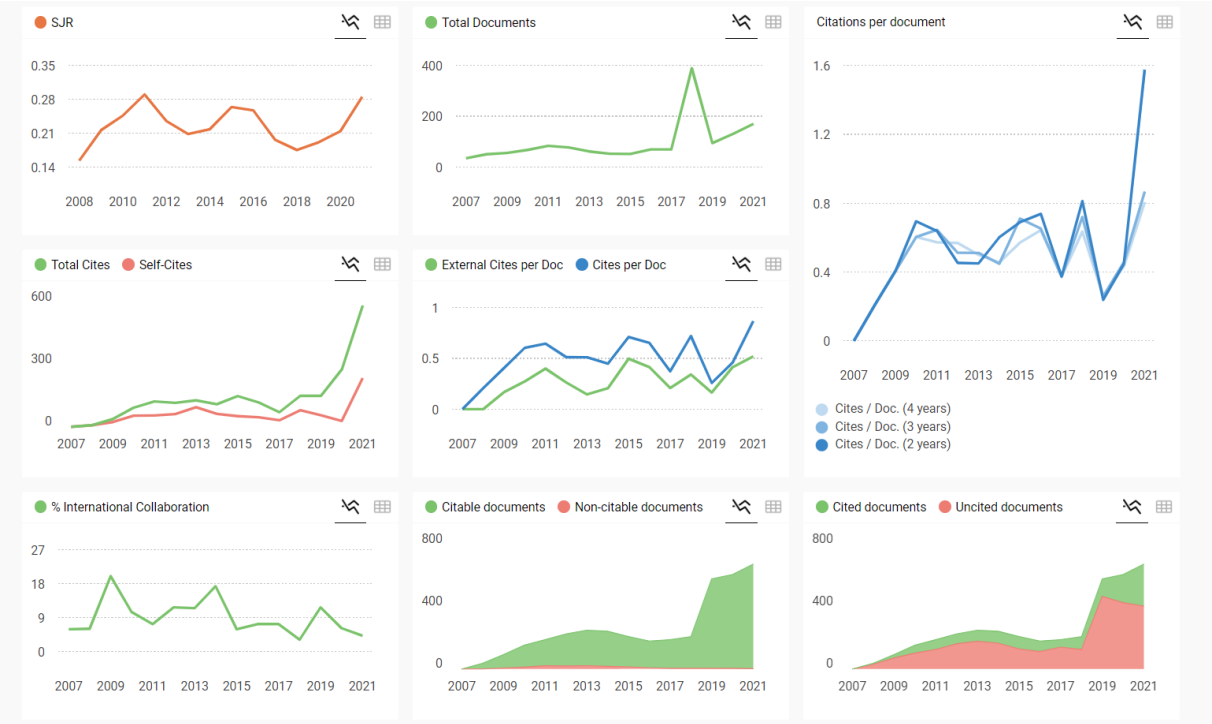

IMMUNOPATHOLOGY IN OSTEOPOROSIS

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Abstract:
Osteoporosis is a bone-damaging metabolic disorder. Reduced bone matrix causes damage to bone tissue microarchitecture due to aberrant bone turnover during the remodeling process, resulting in decreased bone mass and strength. Excess bone resorption and osteoporosis result from an imbalance of activity between osteoclasts and osteoblasts.Osteoporosis has a significant impact on a person's ability to carry out daily tasks. Falls and fracture complications are also more frequent. Increased osteoclast activity could be caused by a lack of estrogen, cytokine factors, or bone pressure, according to the hypothesis. The activity of pro-inflammatory mediators is inversely related to estrogen levels. Estrogen deficiency causes the release of cytokines and a decrease in the performance of T cells that support osteoclastogenesis, as well as an increase in B cells, pro-inflammatory, and pro-osteoclastogenesis interleukins.As a result, RANKL expression rises, and osteoclast proliferation occurs. TNF alpha is involved in the osteoclastogenesis stage and interacts with RANKL to activate osteoclasts indirectly. Other cytokines, such as IL-1, IL-6, and IL-7, can also promote osteoclastogenesis. Interferon-gamma, IL-4, IL-10, and IL-12 all suppress it. Understanding the pathophysiology of osteoporosis can lead to advances in treatment and prevention, lowering morbidity, and mortality in patients.

Keywords:bone remodeling,inflammatory mediators, osteoblasts, osteoclasts, osteoimmunology, osteoporosis

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INTRODUCTION

Osteoporosis is a metabolic disease characterized by a decreased bone matrix, which causes damage to the microarchitecture of bone tissue due to aberrant bone turnover during the remodeling process.[1] As a result, bone mass and strength weaken. Since the bones become easily fractured, this condition might lead to complications. The processes of bone formation by osteoblasts and resorption by osteoclasts occur continuously throughout human life. If there is an imbalance in activity between the two types of cells, where osteoclasts are more dominant than osteoblasts, bone turnover abnormalities develop, specifically the process of bone resorption is greater than the process of

bone formation, leading to osteoporosis.[2,3]

The relationship between bone and the immunological system is known as osteoimmunology.[4] Normal immune cell activity results in balanced mineralization and bone resorption, both of which are played by osteoblasts and osteoclasts.[5] The immune system can act as a protector for the body because it can differentiate between self-cells and foreign components. However, in certain circumstances the immune system is unable to distinguish and recognize foreign components, resulting in autoimmune diseases. Where the body's immune cells attack their cells because they are misinterpreted as dangerous foreign objects. In inflammatory and autoimmune cases, RANKL and inflammatory cytokines are formed due to the activation of T cell products that can induce RANKL expression in osteoblasts.[6] Several T-cell-derived cytokines, such as IL-12 and IL-18, can intermingle with the RANK signaling pathway, osteoclastogenesis, and osteoclast functions.[7]

Osteoporosis is divided into several classifications based on the cause: primary osteoporosis and secondary osteoporosis. Primary osteoporosis is divided into 2 types: primary osteoporosis type 1 occurs in post-menopause women, and type 2 osteoporosis occurs in elderly people (>70 years).[8]While secondary osteoporosis occurs due to other underlying diseases, for example, osteoporosis that occurs in patients with bone TB, osteomalacia, chronic rheumatoid arthritis, in addition to long-term steroid use, or hyperthyroidism.[9,10]Osteoporosis greatly impacts a person's ability to carry out daily activities. The risk of falls and fracture complications also increases. This will increase morbidity and mortality. Understanding the pathophysiology can be the basis for advances in therapy and prevention of osteoporosis.[11]

DISCUSSION

Several factors can contribute to increased osteoclast activity, which leads to excessive bone resorption. According to the theory, it could be linked to a lack of estrogen, cytokine factors, and the burden on the bones. Osteocytes are the most dominant bone-forming cells. Only 10% of bone components are not osteocytes.[12] The osteocytes produce sclerostin, which regulates bone matrix mineralization to prevent excessive bone formation by inhibiting canonical Wnt signaling so that it fails to increase the transcription of osteogenic genes during bone formation.[13,14]In the cytosol, osteoblasts have 2 estrogen receptors: alpha and beta estrogen receptors. However, in its work, the expression of beta receptors is 10 times stronger than that of alpha estrogen receptors. The normal bone should have a balanced expression of forming cells (osteoblasts) and absorbing cells (osteoclasts).[15]

The estrogen hormone in bone cells plays a role in reducing various proinflammatory cytokines from bone marrow stromal cells and mononuclear cells that can lead to increased differentiation and maturation of osteoclasts, such as IL-1, IL-6, and TNF-α, as well as triggering osteoblasts to reduce TGF-β release. Postmenopausal women experience a decrease in estrogen levels so that the work of osteoclasts increases both, directly and indirectly, eventually increasing bone resorption.[16]Estrogen deficiency will cause the release of cytokines that support the formation of osteoclasts. When estrogen is deficient, FSH levels are elevated, and osteoclasts and their precursors have FSH receptors. This condition results in increased osteoclast activity and bone remodeling activity in conditions of estrogen

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deficiency, one of which is menopause.[17]One type of osteoporosis is primary type 1, which occurs after menopause. Scientists have determined that estrogen replacement therapy can be used to treat osteoporosis in postmenopausal women.[18] Because estrogen can stimulate the expression of osteoprotegerin (OPG) and Transforming Growth Factor-B (TGF-β) in osteoblasts and stromal cells.

OPG is an inhibitor of osteoclastogenesis by inhibiting the binding between the Receptor Activator of Nuclear Factor Kappa-β ligand (RANKL) and Receptor Activator of Nuclear Factor Kappa-β (RANK).[19] RANKL is one of the TNF-alpha cytokines, it is binding to RANK will facilitate the occurrence of bone destruction.[20] RANKL and RANK are regulators of bone remodeling and importance in osteoclast development and activation. Interestingly, the RANKL/RANK interaction also regulates T cell, dendritic cell survival, and lymph node formation.[21,22] RANKL binds to the RANK expression on signal transduction activation of hematopoietic progenitors that cause osteoclasts differentiation. RANKL stimulates bone resorption activity in mature osteoclasts via RANK. When RANK is activated, the signal will be sent into the cell via Tumor Necrosis Factor Receptor-Associated Factors (TRAFs) receptors, especially TRAF6. RANK is important in the activation and differentiation of osteoclasts for bone resorption, and also acts as a link in the NF-kB, JNK/SAPK, p38, and Akt/PKB pathways.[23]

Osteoprotegerin (OPG) is an osteoclastogenesis inhibitory factor, that functions as a RANKL receptor that binds to RANK.[24] When the binding of RANK and RANKL is inhibited by OPG, there is no osteoclast formation and excessive bone resorption. OPG activity can increase triggered by IL-4, IL-10, IL-13, IL-18, and estrogen.[25] So that one of the mechanisms of osteoporosis in menopausal women is due to decreased estrogen and reduced OPG activity. Thus, the correlation between RANKL, RANK, and OPG makes a molecular link between bone remodeling, the immune system, and inflammation.[25]

Meanwhile, TGF-β is released from bone during active bone resorption as a feedback mechanism by upregulating OPG levels. TGF-β plays a role in the proliferation of osteoblasts and inhibits their apoptosis, on the other hand, osteoclast apoptosis increases,and excess bone resorption can be prevented.[26]

Estrogen also plays a role in regulating activity and increasing the number of T cells.[27] T cells maintain immune homeostasis, inhibit inflammation, and inhibit monocyte differentiation into osteoclasts.[28] Studies in mice with overexpression of T cells showed a high bone mass index, due to inhibition of osteoclasts activity in bone resorption.[29] Therefore, decreased estrogen levels in postmenopausal women cause decreased T-cell performance and increased osteoclasts, resulting in osteoporosis.[18]

In summary, a person who suffers from estrogen insufficiency will experience an increase in B cells, T cells, as well as pro-inflammatory and pro-osteoclastogenic interleukins. As a result, RANKL expression rises and osteoclast proliferation occurs.[30]

The performance of osteoblasts in bone formation is also enhanced by parathyroid hormone and vitamin D.[31] Vitamin D is one of the calciotropic factors (in addition to PGE2, IL-1, IL-11, TNF- and glucocorticoid factors) that induce RANKL expression in osteoblasts.[32] Vitamin D has anti-inflammatory properties and may influence the regulation of immune function, the proliferation, and differentiation of many cell types.[33]Studies revealed that the effects of vitamin D

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resulted in suppression of inflammation-related genes expression, including decreased TNF-α gene expression induced by intense exercise.[34,35]

Production of IL-1, IL-6, and/or TNF-α has shown a positive correlation with bone resorption or bone loss.[36] TNF-α, IL-1, IL-6, IL-23, IL-27, and all of the pro-inflammatory mediators may worsen the progression of osteoporosis by destroying cartilage and bone due to increased osteoclast activity.[37] These mediators are activated by macrophages. TNF α specifically plays a role in the osteoclastogenesis stage and indirectly engages with RANKL to trigger osteoclast activation.[38] However, this effect can be inhibited by IL-18 which is also secreted by macrophages, it also regulates Th1 and IFN-γ.[39]Interferon (IFN)-γ secretion T-cell-dependentenhances bone resorption, further supporting T-cell-dependent co-secretion of TNF-α and RANKL under estrogen deficiency and infection. This explains the pathophysiology of osteoporosis in association with chronic inflammatory disorders such as periodontitis in postmenopausal women. Osteoclasts are also activated by IL-23.[40]

Expression of RANKL in osteoblasts is also increased due to the production of cytokines that are activated by T cells.[41] Activation of T cells directly expresses and produces RANKL, induces osteoclast formation, and activates via specific receptors. There are several mechanisms and interactions by which cytokines regulate bone resorption. IL-6 contributes to the upregulation of RANKL in osteoblast cells. IL-1 and TNF-α may also not promote osteoclast development, but they stimulate mature osteoclasts to cycle through the resorption cycle by modulating RANKL activity.[42,43] IL-1 is widely involved in bone metabolism as well as an osteoblast activator function. IL-1 and IL-6 also directly increase osteoclast activity by a RANKL-independent mechanism. These molecules directly extend the lifespan of osteoclasts to inhibit osteoclast apoptosis. TNF-α and IL-1 inhibit collagen synthesis in osteoblasts and promote extracellular matrix degradation.[44]

RANKL activation will decrease due to suppression by IL-27 which is also able to increase Egr-2 expression to prevent osteoblast apoptosis.[45] The function of RANKL can be played by IL-1 directly, or IL-1 indirectly triggers RANKL expression. Therefore, IL-1 is known as an osteoclast activating factor.[46] But on the other hand, IL-1 also regulates the release of OPG which inhibits bone resorption by preventing the binding of RANKL to RANK, and in turn stimulates apoptosis of osteoclast cells.[47]

In malignancy, high levels of IL-1 can be a marker of bone metastases. Because IL-1 increases the formation of new blood vessels and stimulates more pro-inflammatory cytokines that support cancer cell growth and invasion into bone.[48] The process of osteoclastogenesis is inhibited by interferon-gamma, IL-4, IL-10, and IL-12. In contrast, osteoclastogenesis will be stimulated by the presence of Tumor Necrosis Factor (TNF), IL-1, IL-6, and IL-7.[49]Estrogen levels are inversely proportional to the activity of pro-inflammatory mediators.[50]

Conclusion

Bone and the immune system are two interrelated organ systems called osteoimmunology. In the pathophysiology of osteoporosis, the immune system is involved in a complex manner. The role of pro-inflammatory cytokines, hormones, and other factors greatly influences the balance of bone formation and resorption carried out by osteoblasts and osteoclasts. Understanding the pathophysiology of osteoporosis can lead to advances in treatment and prevention, lowering

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morbidity, and mortality of osteoporosis patients.

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