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# PAGET'S DISEASE

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**ABSTRACT**

Extramammary Paget disease, also known as EMPD, is a rare clinical disorder. The intervention is linked to numerous types of Paget disease. Paget disease of the bones prevents the body's normal recycling process, in which new bone tissue gradually replaces old bone tissue. As a result, bones tend to degrade and distort over time. The mutations that are responsible for Paget diseases are TNFRSF11A, SQSTM1, and TNFRSF11B. The long-term consequences of bisphosphonates on the progression of the disease are not well researched, but they have been proven to cure radiological abnormalities and restore normal histologically. In addition, bisphosphonate therapy is quite successful at slowing down bone turnover. Therefore, this article has been designed to review the diagnosis, histology, and treatment of Paget's disease.

**KEYWORDS:** *Paget's disease, bones, diagnosis, fracture, syndrome*

## INTRODUCTION

The clinical condition known as extramammary Paget disease, or EMPD, is extremely uncommon. There are several forms of Paget's disease. The body's natural recycling mechanism, in which young bone tissue progressively replaces old bone tissue, is hampered by Paget's disease of the bones. As a result, bones tend to deteriorate and deform over the period. The pelvis, head, spine, and limbs are the most frequently impacted areas (1).

Paget disease of the bones has an enigmatic origin. A combination of hereditary and environmental factors may cause the condition. Several genes seem to be connected to developing the condition. Paget's disease could be linked to a bone infection caused by a "slow virus," a condition that lasts for many years until symptoms manifest. Four genes which induce Paget's illness and associated disorders have mutations that have been found, suggesting that genetic factors play a significant role in this disease. Sequestosome 1 or SQSTM1, a scaffold enzyme in the nuclear factor-B (NF-B) signalling pathway, is the most significant of these (2). Patients with SQSTM1 mutations experience severe Paget's disease of the bones, which is very penetrant as they age. The early-onset variant of Paget's disease of bones is brought on by TNFRSF11A mutations (3). Bone remodeling is a typical process in which old bone is destroyed, and new bone is produced to replace it. The TNFRSF11A, SQSTM1, and TNFRSF11B genes are implicated in this process (4).

A chronic inflammatory disease condition called Paget's disease of the bone causes a rise in bone re-absorption (5). Environmental elements also have a role. Most studies have concentrated on paramyxovirus infections as a potential cause, but there is inconsistent data to support this idea. Insufficient intake of calcium and repeated mechanical stressing of the bones are two additional possible culprits. Inhibition of osteoclastic bone resorption, such as bisphosphonates, is the mainstay of medical care for Paget's disease of the bone. Patients who experience bone pain due to increased energy

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metabolism in afflicted bones should receive bisphosphonate medication (6). Paget disease of the bones is currently incurable but treatable. The sooner Paget's illness may be identified and treated, the lower the risk of problems developing from the condition. Before the age of 40, it is rare to be diagnosed; in most series, men make up the majority. Familial aggregation is found in most succession, and its distribution pattern is uneven, with pockets of high occurrence (7).

Research is currently being conducted to see if bisphosphonate intervention in asymptomatic people with early illness will stop development and avoid consequences, allowing a better diagnosis and understanding of the disease.

*Epidemiology*

Its geographic distribution is asymmetrical, with high prevalence in places where familial aggregation is frequently found in series. People of British ancestry are most frequently affected by Paget's illness. British immigrants to nations like New Zealand, Australia, and North America and European nations such as Germany, France, Spain, and Italy, are also susceptible to the illness (8). According to Poór et al. study, which examined the prevalence of the Paget disease of bone in eight European cities, Innsbruck, Austria, had the lowest high prevalence, 0.2%, among hospital patients under the age of 55 (9).

The disease can affect one or more places throughout the skeleton and is characterised by localised anomalies of accelerated bone turnover. Predominantly affecting the axial skeleton, the skull (42% of cases), pelvis (70% of cases), lumbar spine (53% of cases), femur (55% of cases), and tibia (32% of cases), are typical sites of involvement. Paget's disease is significantly more common as people age, and figures from the United Kingdom indicate that by the eighth decade of life, the condition affects roughly 8% of men and 5% of women (10). In addition, the frequency of the disease varies significantly by ethnicity and location. Paget's disease of the bones is most prevalent in the United Kingdom but also widespread in southern and western Europe and among British immigrants to South Africa, Australia, and New Zealand.

On the other hand, this illness is uncommon in the Indian subcontinent, Scandinavia, Japan, China, with other Southeast Asian nations. These findings imply that genetic factors play a significant role in disease susceptibility. However, evidence also points to the importance of environmental issues, given that the occurrence and medical severity of the disease have significantly decreased over the past 25 years in the United Kingdom (6).

*Diagnosis and clinical presentation*

In Paget's disease of bones, the diagnostic evaluation of bone measurements, a comprehension of the healthy skeletal dispersion, and the structure of cancellous bone have to be interpreted. Peripheral and axial assessment locations and small portions of both exhibit considerable variances, showing that the trabecular bone density at the femoral neck is denser in normal patients than at the lumbar region or the iliac crest. It is essential to notice that the iliac crest's trabecular microarchitecture systematically varies, with the anterior region having the largest bone mass and the middle and dorsal parts having lower amounts (11).

When patients are being evaluated for other conditions, incidental discovery of elevated serum alkaline phosphatase and abnormal radiography is a common manifestation of Paget's disease. Patients may also display particular characteristics, such as bone discomfort and deformity. This disease's bone pain is typically reported as being present during rest, at night, and when using an affected limb. However, in clinical settings, Pagetic bone pain is frequently challenging to identify from tertiary osteoarthritis pain and from concurrent musculoskeletal conditions such as degenerative spinal degeneration. Localisation over an afflicted location where there is pharmacological and scintigraphic evidence of ongoing metabolic activity is one of the clinical characteristics supporting a Pagetic origin.

Pain that is restricted to the joint instead of the bone and gets worse with the movement of the joint are characteristics that rule out a Pagetic aetiology. Pagetic aetiology is supported by the reduction of bone pain following a treatment trial of bisphosphonate medication (6).

If a patient has deformed weight-bearing limbs and experiences sudden, localised bone pain, they likely have a pseudofracture. The convex aspect of the bones in a malformed limb is where pseudofractures almost often occur and do not respond well to antiresorptive treatment. Bone deformities characterise severe Paget's disease, and in individuals with metabolically active illness, the temperature sensor may be elevated over the affected joints (12).

*Histology*

The iliac crest bone or the vertebrae have received the majority of attention in investigations on the histology of Paget's disease of bones. As previously indicated, Osteoclasts, the main cellular anomaly in Paget's disease of bones, are larger, more numerous, and have many more nuclei per cell than normal osteoclasts (13). In their histological analysis of Pagetic iliac crest samples by using Hamburger Bone Registry, Seitz et al. reported that trabecular bone seemed

predominantly solitary and had an ungainly composition. The authors also noted a typical appearance of extensive resorption lacunae with a swallowtail pattern. They also observed an increase in osteoblastic surfaces and activated cuboidal osteoblasts as indicators of faster bone development, and they noted that collagen fibres did not have a uniform dispersion indicative of collagenous fibres (14). Histologically speaking, these anomalies can result in a "mosaic look" or a combination of woven with lamellar bone. In Pagetic bone lesions, osteoclasts are larger and more numerous than in healthy bone, and they also have many more nuclei than is typical. Additionally, these osteoclasts include distinctive nuclear complexes, which are tiny, cylindrical formations that mimic virus particles in specific ways. These bodies have been observed in pycnodysostosis, osteopetrosis, and even macrophages from individuals with hereditary oxalosis, so they are not exclusive to Pagetic osteoclasts (15).

*Treatment*

Paget's disease of the bones is currently incurable but treatable. The sooner Paget's illness may be identified and treated, the lower the risk of problems developing from the condition. Treatment involves a long-considered standard of care. The primary sign that Paget's disease of the bones needs medical attention is localised bone pain that is believed to be caused by enhanced metabolic activity. Analgesics and non-steroidal anti-inflammatory drugs can also treat pagetic bone pain symptomatology. Bisphosphonates or calcitonin, which prevents osteoclastic bone resorption, are effective treatments for pagetic bone pain (16).

The bone disease Paget's can be treated with a variety of drugs. Bisphosphonates are the most prevalent kind. Zoledronate is the bisphosphonate that works the best. This medication frequently causes the condition to go into long-term remission with just one dose; however, it cannot treat bony deformities. Paget disease's bone problems can be treated or improved without surgery. Some operations include knee and joint replacements, realigning malformed bones, and facilitating improved bone fracture healing (7). Many clinicians believe that aminobisphosphonates, such as risedronate, pamidronate, and zoledronic acid, are recommended in Paget's disease because they are more efficient at lowering bone resorption than previous bisphosphonates, like etidronate and tiludronate (17).

Older patients with Paget's disease frequently have dietary calcium and vitamin D shortage; it is crucial to address this deficiency before beginning bisphosphonate medication to prevent problems like hypocalcemia, which is a danger following injectable bisphosphonate therapy. Patients who received injectable pamidronate for Paget's disease may also get focal osteomalacia, a side effect linked to etidronate therapy (17). Treatments with activated vitamin D metabolites cannot reverse this mineralisation problem, which appears to be a direct consequence of bisphosphonates rather than vitamin D insufficiency. There have not yet been any reports of mineralisation problems concerning treating individuals with Paget's disease of the bones with risedronate, tiludronate, alendronate, and zoledronic acid (18).

There is a considerable risk of delayed union when treating fractures conservatively in patients with Paget's disease. Patients with severe knee or hip osteoarthritis and Paget's disease frequently gain from unilateral surgical intervention. Rarely an osteotomy procedure is required to treat a long bone bending deformity. Neurosurgical treatment will be necessary for patients with a neurological condition of the spine who have not improved while taking bisphosphonates. Because of the increased vasculature of the diseased bone, surgery on pagetic bone is challenging; hence treatment with bisphosphonate and calcitonin must begin before any non-urgent procedure is carried out (19).

## CONCLUSIONS

The faster Paget's disease can be discovered and treated, the less likely complications may arise. Unfortunately, it is uncommon to be diagnosed before age 40, and in most studies, men predominate. Most successions have familial aggregation, which has an uneven geographical distribution with areas of high occurrence. The use of bisphosphonates in asymptomatic individuals with the early disease is now being studied to determine whether it can halt development and prevent negative effects; this will provide a more accurate diagnosis and comprehension of the condition. Additionally, it will make some alternative treatments to surgeries and incisions available.

*Conflict of interest*

The author declares that they have no conflict of interest.

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# PSYCHOLOGICAL ASPECTS OF THE PATIENT WITH RHEUMATOID ARTHRITIS

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## ABSTRACT

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease with risk factors of genetics, the female sex, and environmental factors. Lifestyle factors such as obesity, cigarette smoking, alcohol consumption, stress and low socioeconomic status may be implicated in the disease. RA patients have a reduced quality of life and are an economical and health burden for countries. Growing evidence shows that RA patients may present neurological disease with structural differences in the hippocampus and basal ganglia compared to individuals unaffected by RA. The disease involves the immune, nervous, and endocrine systems with physical and psychological discomfort. Emotional stress and anxiety make it a psychosomatic disease with organic damage aggravated by emotional factors. The constant fear and strong concern that afflicts the patient can lead to psychological, physical and mental discomfort. However, more studies need to be done on this topic to understand the real psychological state of the patient and how it is involved in RA. Here, in this article, we report some new evidence on the neurological state of the RA patient.

**KEYWORDS:** *neurology, rheumatoid arthritis, inflammation, immune system, psychological disorders, autoimmunity*

## INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease and a substantial global public health challenge. A recent study examining the worldwide incidence and burden of RA estimated approximately 20 million cases with 3.4 million daily adjusted life years globally (1).

Risk factors for the disease include genetic predisposition, the female sex, and environmental and lifestyle factors, including obesity, smoking, alcohol consumption, stress, and low socioeconomic status.

Patients with this systemic disease suffer from joint swelling and pain, with varying degrees of severity from patient to patient. In addition, RA is associated with various complications, including permanent joint damage that requires surgery, effects on the blood vessels with rheumatoid vasculitis, and Felty syndrome (2).

It is a chronic and progressive disease that begins to affect the small joints initially, followed by larger ones, and can progressively affect other systems such as the skin, eyes, heart, kidneys, and lungs. Bone, ligament, and cartilage damage is common, as well as deformities and severe pain.

RA may lead to compression and invasion of the spinal cord and peripheral nerves, which can cause myelopathy, radiculopathy, and entrapment neuropathies such as carpal tunnel syndrome. The cervical spine is frequently involved in

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RA and can be affected with diverse ranges of severity, with some studies indicating up to 80% prevalence in cases (3). The atlantooccipital joint, atlantoaxial joint, and subaxial joint can all be affected. There is inflammation and the synovial membranes of joints are affected, with the overproduction of synovial fluid that damages articular structures and ligaments (4). Consequently, there can be compression of the spinal cord, nerve roots, and cervical spine structural alterations. Spinal cord compression can affect the brainstem, spinal nerve roots, cranial nerves, and vertebral arteries (5).

Approximately 40% of RA patients have chronic pain (6) that has physical and psychological consequences, with patients having an increased risk for neurological disease and neuropsychiatric comorbidities. There is no cure for RA and the treatment aims to reduce pain and control joint damage.

RA patients have a reduced quality of life, impacted by the negative physical and mental effects of the disease (7). In turn, patients have an increased rate of use of healthcare resources (8) and psychological disorders such as major depression (9), anxiety (10), and additionally, an increased risk of developing neurodegenerative disease (11).

*Neurological disease and structural differences in the brain of RA patients*

In RA, the adaptive immune system and the innate immune system interact in a complex mode that involves T-cells, autoantibodies, myeloid cells, and proinflammatory cytokines. There is bidirectional communication between the peripheral and central immune responses that can lead to neuroinflammation and central nervous system (CNS) comorbidity in RA patients (12).

Research has shown structural differences in the brains of RA patients, with changes in the hippocampus and basal ganglia that are not present in healthy, non-arthritic individuals.

Insulin-like growth factor 1 receptor (IGF1R) signaling is enriched in microglia of the hippocampus, and abnormal IGF1R signaling was seen in experimental studies to be associated with hippocampal neurogenesis, reduced hippocampal size, and decreased mobility. Blocking IGF1R was seen to provide some improvement, indicating that hippocampal damage could be reversible to some extent (13).

Another study showed that RA patients with long disease duration had increased ventricle-to-brain ratios in addition to decreased midsagittal cerebellar areas, which may link cerebral and cerebellar atrophy to the disease (14).

Research has also shown changes in the subcortical grey matter of RA patients in the basal ganglia, an area involved in motor control, pain processing, and behavioural response to stimuli, which could be the consequences of chronic pain and defects in motor control of these patients (15).

Pain is strongly linked with cognition and emotion, and imaging studies have shown that the emotional and attentional state can alter cerebral pain pathways, with chronic pain sufferers displaying alterations in certain brain regions and showing amplified responses to nociceptive stimuli (15-17).

Chronic pain has been associated with structural changes in the brain, which has been documented in diverse studies (18-21).

*Emotional factors of RA*

Pain, fatigue, morning stiffness, and disability are often standard conditions for RA patients. Many patients feel constant fear and strong concern relating to pain and their condition, which leads to psychological and physical discomfort.

Chronic pain is characterized by significant emotional distress with feelings including anxiety, anger, frustration, and depressed mood. Somatization and catastrophizing are often common responses to chronic pain and these psychological responses can be destructive to the patient's well-being. These negative emotional states can hinder patient functioning in the presence of pain, fatigue, and other physical symptoms they are already experiencing.

RA patients are at increased risk for the development of neuropsychiatric comorbidities, including major depressive disorder (MDD) (9), anxiety (10), impaired cognitive performance (22), and neurodegenerative disease such as dementia (23). MDD is often involved, as the rate in RA patients is 17% (24). Studies have also shown conflicting results for the implication of RA in other neurodegenerative diseases such as Alzheimer's Disease (AD) (25) and Parkinson's Disease (PD) (26,27).

These psychiatric problems could be due to biological or inflammatory changes or psychological stresses that come with pain and the difficulty of living with medical adversity. But, most likely, it is a combination of these different factors that interact to produce neuropsychiatric comorbidity.

The anxiety, depression, and cognitive impairment that may affect RA patients are, in turn, harmful to their condition, as these disorders can affect responsiveness to treatment and are associated with greater disease activity.

## CONCLUSIONS

The chronic musculoskeletal pain experienced in RA is described as "chronic pain in the muscles, bones, joints, or tendons that is characterized by significant emotional distress (i.e., anxiety, anger, frustration, and depressed mood) or functional disability" (28). This pain is subjective and influenced by biological, psychological, and social factors (28).

RA is a multifactorial disease that involves the immune system, nervous system, and endocrine systems, in which patients experience physical and psychological discomfort. The emotional stress and anxiety form RA as a psychosomatic disease, with organic damage that is aggravated by emotional factors.

Chronic pain is implicated in psychological disorders, particularly depression and anxiety, in a bidirectional manner. Chronic pain can initiate and exacerbate depression and anxiety, conditions which, in turn, directly affect the pain level in a negative manner. Peripheral inflammation and sensitization, and central sensitization, can lead to persistent pain. In fact, it was found that patients' negative emotions relating to their RA state impacted the level of pain they were experiencing (29).

The immune system is also involved in pain regulation. Chronic inflammation and the release of proinflammatory cytokines contribute to pain. In turn, inflammation is also involved in depression and anxiety (24). Proinflammatory cytokines, including interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF) are seen to be increased in MDD (30). In the cerebrospinal fluid of RA patients, there are also increased levels of the proinflammatory cytokines IL-1, IL-6, and TNF, substances which have the potential to contribute to cognitive impairment, although more research is needed to elucidate the precise mechanisms (31-33).

Insulin sensitivity is also connected to inflammation, and RA patients have a high prevalence of insulin resistance, above 50%, which is associated with systemic inflammation and cytokine levels (34). Insulin receptors and IGF1R are implicated in neurogenesis and could be associated with neurological diseases, cognitive decline, and regional atrophy (35,36).

This evidence shows the psychosomatic nature of RA, involving psychological disorders, including depression and anxiety.

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*Letter to the Editor*

# VITAMIN E ACTIVITY IN THE CENTRAL NERVOUS SYSTEM

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**KEYWORDS:** *vitamin E, anti-oxidant, brain, alpha-tocopherol, Alzheimer's disease, Parkinson's disease*

## INTRODUCTION

Nutrients are necessary for the normal physiological function of humans and animals. Without the supply of vitamin E and mineral salts, no metabolic process in our body, including the brain, could work (1). Vitamins, identified for the first time in 1912, are organic compounds necessary for good health and lifestyle (2). However, long before it was known, foods were necessary for animal life. To date, 13 vitamins can be synthesized in a laboratory and introduced in a regular diet, although our body produces some vitamins (3).

Vitamins are classified into two large groups: water-soluble and fat-soluble (4). The fat-soluble vitamins are vitamin A or retinol; vitamin D or calciferol; vitamin E or tocopherol; and vitamin K (5). Water-soluble vitamins include: Vitamin B1 or thiamine; Vitamin B2 or riboflavin; vitamin B3 or PP and niacin; vitamin B5 or pantothenic acid; vitamin B6 or pyridoxine; vitamin B8 or H or biotin; vitamin B9 or folic acid; vitamin B12 or cobalamin, and vitamin C or ascorbic acid (6,7). Vitamin E is considered the primary fat-soluble antioxidant of all vitamins and is involved in lipid peroxidation damage (8-10). Peroxidation is a reaction involved in ageing processes and other neurodegenerative pathologies and is harmful to cells (11). High-dose vitamin E can induce nausea, headache, fatigue, double-vision, muscular weakness, and kidney issues in the central nervous system (12). Many studies on vitamin E note the effects of this antioxidant on brain tissues and memory, as it has been seen that it improves the brain-derived neurotrophic factor by antagonizing some harmful compounds (13,14). Furthermore, vitamin E in the central nervous system (CNS) prevents brain tissue oxidative damage (15).

## DISCUSSION

Vitamin E, or tocopherol, is a fat-soluble vitamin with antioxidant properties, fights free radicals, protects the body from the damage of pollution and cigarette smoke and protects against the onset of cancer (16). Peroxidation is a reaction involved in ageing processes and other pathologies, such as neurodegenerative ones and is harmful to cells (17). On the other hand, specific vitamins such as vitamin E are neuroprotective and relieve neurological diseases (18). While there are no treatments to halt the progression of neurodegenerative diseases, a healthy lifestyle and a diet rich in antioxidants

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can undoubtedly improve the health and function of our cells (19). On the other hand, poor nutrition or malnutrition can cause metabolic and nervous system disorders (20) (Table I). To date, n. 8 types of vitamins E, 4 tocopherols (a, b, g, and d) and 4 tocotrienols (a, b, g, and d) have been found in nature. Vitamin E is synthesized by plants that contain alpha-tocopherol in their leaves and is extracted as an oil (21).

**Table I.** *Deficiencies of some vitamins that can cause disorders to the central nervous system (CNS).*

| VITAMIN DEFICIENCY | CNS DISORDERS |
|---|---|
| Vitamin E | encephalopathy, nerve degeneration |
| Riboflavin | nerve degeneration |
| Thiamin | peripheral neuropathy anxiety, psychosis |
| Niacin | depression, dementia, dizziness, irritability, tumors |
| Vitamin D | tetany, demineralisation, bone deformation |
| Vitamin A | ataxia |
| Vitamin B12 | irritability, peripheral neuropathy, nerve degeneration |

Alpha-tocopherol comes from the diet, is not produced by our body, and is a fat-soluble molecule. Vitamin E administration is absorbed from the small intestine and is important for the diet (22). In experimental animals, it has been seen that vitamin E taken in high doses can damage bone mineralization, reduce hepatic storage of vitamin A, and cause coagulopathy. Several lines of evidence support that vitamin E circulates with chylomicrons and participates in the metabolism of very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Mice genetically lacking HDL have lower alpha-tocopherol levels and impaired brain function, demonstrating that vitamin E is closely related to HDL. In addition, alpha-tocopherol can cross the endothelial cells and arrive at the brain's glial cells, which are expressed in different brain regions and made available.

It has been seen that vitamin E is essential for the health of neurons, even if its transport and regulation in the brain remain unclear at the moment (23). Vitamin E deficiency has been observed in several neurological diseases. After being taken, it crosses the blood-brain barrier, guaranteeing a fundamental nutritional contribution to the CNS.

Vitamin E is involved in ataxia, oxidative stress, Alzheimer's disease, and Parkinson's disease, where levels are low. It is unclear whether these diseases can improve after administering vitamin E (24).

Vitamin E modulates endothelial cells' function in the brain and regulates immune cell migration. Vitamin E administration is absorbed from the small intestine and is important for the diet. When given in high doses to experimental animals, a dysfunction of bone mineralization has been observed, and reused hepatic storage of vitamin A can also give a coagulopathy. Vitamin E has excellent antioxidant effects with action on both inflammation and the immune system by inhibiting the effects of tumor necrosis factor (TNF) and cellular invasiveness. Vitamin E protects against LDL oxidation and promotes anti-inflammatory responses by binding to protein kinase Cα by decreasing NF-κB activation and reducing pro-inflammatory cytokine and chemokine synthesis. This effect can occur in the brain of patients with neurological diseases. The accumulation of oxidative stress raises the levels of reactive oxygen species (ROS), which damage the mitochondria and counteract the cellular antioxidant defense mechanisms, damaging the metabolism of neurons and cerebral energy deficit. The lack of energy due to the mitochondria dysfunction leads to cell death (apoptosis), caused by an increase in the proapoptotic protein Bcl-2 Bax and Bak in the mitochondrial membrane (Fig 1).

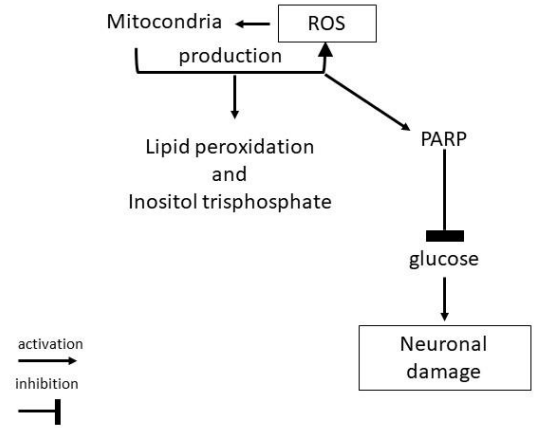


**Fig. 1**. *Reactive oxygen species (ROS) are generated by mitochondria but can also be produced by them under stress. The production of ROS causes lipid peroxidation and inositol trisphosphate stimulation, and ROS activate PARPs which inhibit mitochondrial glucose with neuronal damage.*

Many studies report that vitamin E, an antioxidant capable of eliminating ROS, is neuroprotective against cellular neurodegeneration. ROS are implicated in brain damage and stroke and can suppress the antioxidant defenses exerted by vitamin E, causing cell death, apoptosis, and necrosis. Many studies on vitamin E concern the effect of this antioxidant on brain tissues and also the effect on memory, as it has been seen that it improves the brain-derived neurotrophic factor by decreasing some harmful compounds (13).

## CONCLUSIONS

In light of these observations, we can undoubtedly say that the daily intake of vitamin E at recommended doses can represent a preventive strategy against brain diseases, impaired-cell-mediated immunity and ageing and may alleviate the pathological state of the patient affected by cellular degeneration. On the other hand, low vitamin E levels with reduced alpha-tocopherol intake can lead to long-term central nervous system damage, and treatment of neurological patients deficient in vitamin E should be considered. However, further studies are required to establish the exact function of vitamin E in the brain.

*Conflict of interest*

The author declares that they have no conflict of interest.

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# INFLAMMATION AND DEPRESSION: THE INVOLVEMENT OF CYTOKINES

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## ABSTRACT

Major depressive disorder (MDD) is a frequent, debilitating psychiatric condition characterized by low mood and functional burden. It is a heterogeneous disorder, with a complex pathophysiology that includes genetic, environmental, biological, and psychosocial factors. Inflammation is often associated with MDD as well, with elevated levels of proinflammatory cytokines, such as IL-1, IL-6, and TNF, repeatedly presenting in combination with depression. Increasing evidence promotes the "inflammation hypothesis" of MDD, suggesting that acute and chronic inflammation contributes to depression pathophysiology and affects neurological processes. An activated immune response and the release of proinflammatory cytokines could affect neural plasticity, neuroendocrine function, and neurotransmitter metabolism, and ultimately, cytokines could serve as indicators for risk, as well as treatment, of certain subsets of depression.

**KEYWORDS:** *depression, major depressive disorder, inflammation, cytokine, IL-1, IL-6, TNF, immunity, neurological disease*

## INTRODUCTION

Major depressive disorder (MDD) is a frequent and disabling psychiatric condition and public health issue that is characterized by low mood and functional burden. The World Health Organization describes depression as "sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration" (1). As of 2015, it was estimated that 322 million people worldwide were living with depression (1). It is one of the primary causes of worldwide disability and has a high lifetime prevalence rate (2). MDD can have symptoms ranging from mild to severe, can be periodic or long-lasting, and can severely impair the functioning of daily life for an individual. In addition, sufferers have a higher risk of suicidality, and ultimately, suicide (3).

MDD is a heterogeneous disorder with a complicated pathophysiology, involving environmental and hereditary factors, and increasing evidence implicates the involvement of the immune system. Proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF) are seen at increased levels in MDD (4) and are associated with the occurrence of depression-like symptoms (5). Immune activation and the subsequent continual release of proinflammatory cytokines can raise cortisol levels by affecting the hypothalamic–pituitary–adrenal (HPA) axis (6-7).

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Chronic stress can lead to continual elevation of cortisol levels and desensitization of glucocorticoid receptors, resulting in decreased hippocampal neurogenesis (8).

As biomarkers, proinflammatory cytokines such as IL-1, IL-6, and TNF, may be able to indicate risk for certain subsets of depression and could be useful in therapeutic treatment (9). In addition, inhibition of proinflammatory cytokine levels could be curative.

*Depression Pathophysiology*

The monoamine-deficiency theory has been a predominant explanation of depression pathophysiology since the 1950s (10). It posits that a deficiency in levels of neurotransmitters in the central nervous system (CNS), such as serotonin, norepinephrine, and dopamine, is associated with MDD development (11). However, this theory cannot explain the pathophysiology of MDD, as it is a heterogenous disorder with diverse etiologies, stemming from genetic, environmental, biological, and psychosocial factors. The pathophysiology is complex, likely involving multifactorial mechanisms that work together. In fact, there is a high rate of treatment resistance with antidepressants, between 30-50% (12), which suggests there may be other untargeted factors involved.

Genetic and environmental factors play a role in the development of MDD. There is a familial component, with a proposed 30-40% heritability based on family and twin studies (13). Individual-specific environmental factors such as history of abuse, trauma, relationship problems, and chronic or severe stress, also increase the risk of developing MDD (14-16).

In some studies, volume loss has been observed in brain regions, particularly in the hippocampus, of those with MDD (17-20). Hippocampal atrophy appears to be associated with the length of depression and can be limited with the use of antidepressants (20). However, the etiology of this phenomena is unknown and is has been suggested that stress (21), cortisol elevation, glutamatergic pathways, genetics (22), and increased cellular density may play a role (23-24). Interestingly, as inflammation becomes increasingly suspected in the pathophysiology of MDD, studies have shown an association between inflammatory biomarkers and reduced hippocampal volume (25-26). Environmental stress has been correlated to inflammatory effects, with increased inflammatory markers and loss of volume in the hippocampus (26).

Recently, research has begun to indicate the role of inflammation in MDD pathophysiology, which has led to an "inflammation hypothesis". It is hypothesized that inflammation may play a central role in the development and persistence of MDD in some subsets of people. Acute and chronic inflammation can affect neurobiological pathways and alter neurocircuitry by decreasing neurotransmitter metabolism and neurogenesis and increasing glutamate excitotoxicity (27).

*The inflammatory hypothesis of MDD*

The innate immune system initiates acute inflammatory activation in response to foreign pathogens or tissue damage. Microglia are the innate immune cells of the CNS that have functions similar to macrophages. Activated microglia release proinflammatory cytokines, small proteins which regulate cell signaling, mediating immune responses (28). With recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), granulocytes congregate to the site and inflammatory mediators are produced, including cytokines, which are involved in repairing and clearing cell damage. Inflammation can subside after repair and clearance or can become chronic and result in the hyper-activation of cells and sustained production of proinflammatory cytokines, reinforcing the inflammatory state.

Brain-immune interactions may be involved in the development of MDD. The brain and the immune system are connected by neural communication pathways, and proinflammatory cytokines can mediate behavioral effects by acting as neurotransmitters and neuroregulators (29). These behavioral effects are similar to those seen in MDD, as well as those associated with depression in late life and following illness (30).

Chronic inflammation, and abnormal immune activation, is at the base of diverse autoimmune, neurodegenerative, metabolic, and vascular diseases, in addition to cancer (31), and depression following disease is a common occurrence (32). The co-morbidity of illness and depression suggests there is a causal relationship involving the pathophysiological processes of disease, which could be related to inflammation and the involvement of proinflammatory cytokines (29,33).

The release of inflammatory cytokines such as IL-1, IL-6, and TNF following immune activation causes "sickness behavior" with characteristics similar to depressive-like symptoms, producing fever, malaise, fatigue, and alterations in lipid and protein metabolism (34-35).

Studies have shown that some anti-inflammatory therapies, in combination with conventional antidepressants, improved depressive symptoms in patients (36-37), further implicating the role of inflammation in MDD and suggesting that immune-targeted therapies could be useful in treating the disorder.

Strong evidence indicates that inflammation does play a role in initiating depressive symptoms in certain individuals. Furthermore, the diverse peripheral inflammatory biomarkers observed in MDD, and evidence so far, suggests the possibility of other causal pathways, such as depression causing and maintaining inflammation, inflammation leading to depression, or the combined relationship of both (4). However, further research is necessary to elucidate the relationship between inflammation and MDD.

*Cytokines and Depression*

An activated inflammatory response causes the release of proinflammatory cytokines, which can access the brain and alter behavior, affecting neural plasticity, neuroendocrine function, and neurotransmitter metabolism (38). Studies have shown that MDD is associated with higher circulating C-reactive protein (CRP) concentrations and elevated levels of proinflammatory cytokines such as IL-1, IL-6, TNF, and interferon-gamma (INF-γ) (which increases in viral infection) (4,39-41). This is in line with replicated reports from other studies, suggesting an inflammatory state accompanying MDD. One study showed that 75% of medically healthy MDD subjects had elevated levels of diverse proinflammatory cytokines, including MCP-1, IL-1α, IL-1β, IL-2, IL-6, IL-8, and IFN-γ (42). IL-1 and IL-6 are strongly indicated in depression and IL-6 is considered a peripheral biomarker. The combination of IL-6 with other cytokines could be useful for the classification of MDD subtypes and identifying treatment options (9).

Inflammation of the CNS with increased peripheral blood inflammatory biomarkers and elevated levels of proinflammatory cytokines has been seen in individuals with neurodegeneration and depressive symptoms such as sleep disturbances, low mood, fatigue, and anhedonia (41,43,44). Increased IL-6 has been linked with sleep deprivation and dysregulation (44,45). Childhood maltreatment also predicted elevated levels of CRP and IL-6 in adulthood and could be correlated with reduced hippocampal volume (25), although other interindividual factors of vulnerability may likely be involved as well.

Interestingly, both medically healthy and ill patients with MDD show classic features of inflammation, with increased cytokines and other inflammatory markers (46). Treatment with cytokines has been shown to induce mood and cognitive changes similar to those in depression (5). For example, subcutaneous and intravenous injections of IL-2, which is a T-cell growth factor and induces inflammation, were seen to initiate depressive symptoms (47), and TNF administration in mice creates depression-like behavior (48). Interferon-α (IFN-α) is used in therapy for various infectious diseases and cancer, but IFN-α frequently produces depressive-like symptoms, anxiety, anhedonia, and changes in cognitive function (49,50), to the extent that 20-50% of patients undergoing treatment with IFN-α are diagnosed with depression (51,52). Interestingly, this IFN-α therapy-induced depressive state improves with antidepressant medication (52). Depression was also seen to be more prevalent following immunotherapy with IL-6, IL-8 and IL-10 (53,54).

What are the mechanisms by which cytokines could induce depression? Inflammatory cytokines can affect the body's stress-regulation system, affecting the HPA axis. The HPA axis is closely linked to stress and its malfunction is associated with diverse mental diseases, including depression. Glucocorticoids are important for regulating homeostasis during stressful challenges that affect neuroendocrine and immune responses. Proinflammatory cytokines may raise cortisol, which is an anti-inflammatory immunosuppressor, and maintain hypercortisolemia. IL-1 was seen to elevate corticotropin-releasing hormone (CRH), adrenocorticotropic hormone, and corticosteroid levels, activating the sympathoadrenal system and HPA axis. Cytokines can interfere with glucocorticoid receptor signaling and response, which could lead to glucocorticoid resistance and the release of CRH (55), and eventually, decreased hippocampal neurogenesis.

Regarding the classic monoamine theory of MDD, there is evidence supporting cytokine influence on the noradrenergic and serotonergic systems (11) by synthesis, release, and reuptake of different neurotransmitters (56). Animal studies show that cytokine administration affects monoamine metabolism (57), likely via the enzyme indoleamine 2,3 dioxygenase (IDO) in glial cells, which can be activated by cytokines through inflammatory signaling pathways (58). Ultimately, IDO activation is associated with low levels of serotonin (59).

Additionally, in the event of sustained inflammation, cytokines can affect neural plasticity by diverse mechanisms, including decreased neurogenesis, reduced neurotrophic support, glutamatergic activation, apoptosis in astrocytes and oligodendrocytes, and oxidative stress, amongst others (56,60-62).

*Inflammation in depression and oral health*

It is clear from a literature review that there is a statistically significant correlation between depression and pathologies of the oral cavity. Specifically, a pathological situation at the level of the oral cavity's immune system can induce depressive symptoms through neuroimmune interactions that are relevant to depression (63).

It is clear to date that periodontal disease is a multifactorial pathology that does not only have a bacterial origin, but rather the immune system plays a fundamental role in the etiogenesis (63). Specifically, mast cells appear to mediate the transition between gingivitis and periodontitis through the activation of T lymphocytes and the release of chemokines and cytokines that mediate the destruction of periodontal tissue. In patients with chronic diseases or disabling conditions (64-67), this mechanism is amplified by both internal factors of cytokine dysregulation and external factors such as poor oral hygiene habits due to the limiting pathology. The role of inflammation mediators has now been clarified to the extent that they are targeted by immunomodulatory therapies such as laser or, to a greater extent, photobiomodulation (68).

Some authors point out that the same inflammatory cytokines are involved in periodontal disease and depression and that they have a bidirectional correlation between them.

Therefore, a multidisciplinary approach including the dental team could be useful for patients with depression to improve oral health and thus contribute to the overall improvement of the patient's systemic health. Experimental studies should be carried out to help define a specific protocol for the most common manifestations at the level of the oral cavity of individuals suffering from depression to intercept the pathology early and to provide specific, aimed oral health care.

## CONCLUSIONS

MDD continues to be a public health concern and cause severe impairment for large numbers of individuals around the world. As time progresses, it becomes increasingly apparent that traditional approaches are not sufficient and a unified hypothesis of MDD does not exist, as it is a multi-system, heterogeneous disorder with complex mechanisms of interaction between diverse components (69).

Continuing research suggests the involvement of the immune system in contributing to the pathophysiology of MDD, with repeated studies showing elevations of proinflammatory cytokines in depressed individuals, the majority of which include IL-1, IL-6, and TNF. These cytokines interact with diverse pathophysiological processes involved in depression, leading to the inflammatory hypothesis of MDD. This hypothesis could lead to important findings for the evaluation and treatment of MDD. Inflammatory biomarkers can be useful for identifying subsets of depression and appropriate treatments for these individuals.

Strong evidence has suggested that inflammation is present with depression, likely involved in causation for some individuals. However, the process of inflammation resulting from depression itself must be investigated further. This could describe further mechanisms of the pathogenesis, indicate biomarkers, and improve therapy options.

*Conflict of interest*

The authors declare that they have no conflict of interest.

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*Letter to the Editor*

# AUTISM SPECTRUM DISORDER – NEW FRONTIERS

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## INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that includes autistic, pervasive developmental and Asperger's disorders. It is a common developmental disability that is diagnosed in early childhood, within the first three years of life. ASD manifests with dysfunctional social interaction and communication, repetitive behaviors, sensory and learning defects. Early diagnosis and developmental and behavioral intervention is critical to improve quality of life and social impairments present in those with ASD. Family history of ASD is a risk factor for development, as well as the combination of genetics and environmental factors acting together. Children with ASD may also present with immune dysfunction and inflammation in the brain which could also contribute to development, with IL-37, IL-18, and TNF seen to be increased in the amygdala and dorsal lateral prefrontal cortex of ASD patients.

## DISCUSSION

ASD is defined by the Centers for Disease Control and Prevention as "a developmental disability caused by differences in the brain" (1). ASD is heterogeneous, highly heritable, and can co-occur with other conditions (2). It includes autistic, pervasive developmental and Asperger's disorders and the category was created for containing a broad spectrum of social communication deficits.

ASD is frequently diagnosed in early childhood and is a common neurodevelopmental disorder. Over the past 20 years, the rates of diagnosis have increased drastically, with the modern prevalence rate in diagnosed children between 1.5%-2% (3,4). ASD is more frequent in males, with a ratio of 4 boys to every affected girl (5,6).

The disorder manifests with dysfunctional social communication and interaction, repetitive behaviors, attention, cognitive, learning, and sensory defects (7). There can be varying levels of intellectual disability. Psychiatric and neurological disorders can often occur with ASD and include anxiety, depression, epilepsy, and attention-deficit/hyperactivity disorder (ADHD).

ASD is a developmental disorder, with the onset of symptoms in the first three years of life. In some cases, symptoms are apparent within a child's first year of life, while in others, development can be normal and then switch to delay in the acquisition of new skills or their loss (7). Diagnosis is based on behavioral and developmental presentation, with clinical

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specifiers such as language, intelligence, comorbidity, and support taken into consideration. A reliable diagnosis can be made by the age of two years old. Early intervention is critical to enhancing communication skills.

*Risk factors*

Those who have a family history of ASD, have older parents, were born at very low birth weight, or have particular genetic conditions such as Down or Fragile X syndrome, have a higher risk of ASD (8). In the majority of ASD cases, the exact etiology is unknown, although development may be affected by the combination of genetics and environmental aspects acting together (9). Recent twin studies have suggested 40-50% variance of environmental factors in ASD (10-12).

Prenatal, natal, and postnatal environmental risk factors have been identified, although they are not causal, being considered reactive or contributory at best (2,13). Advanced parental age, small gestational age, pregnancy and birth complications, gestational diabetes mellitus, and the use of valproate during pregnancy are some of these risk factors.

*Inflammation*

So far, the pathogenesis of ASD is unknown, but it is hypothesized that some immune and autoimmune inflammatory diseases are involved. We recently reported that in children with ASD there is a presence of immune dysfunction and inflammation in the brain (14). In fact, we found that the anti-inflammatory cytokine IL-37, and pro-inflammatory cytokines IL-18 and TNF, are increased in the amygdala and dorsal lateral prefrontal cortex of children with ASD, demonstrating that inflammation is important in this disease (14). In addition, IL-37 inhibits neurotensin, stimulated secretion and gene expression of IL-1β and cytokine CXCL8.

The elevation of IL-37 in the brain of ASD could signify a defensive strategy for fighting the pro-inflammatory IL-1 family members which are potent mediators of inflammation and are harmful to the brain.

*Genetics*

Genetics have a strong influence on ASD, with a 50% risk for development (15), and a wide range of genetic variation is involved. The most common genetic abnormalities are synaptic gene mutations (16,17), which are also seen in other neuropsychiatric disorders (18). Mutations reported in synaptic genes include neurexin (NRXN) families, neuroligins (NLGN), SH3 and multiple ankyrin repeat domains (SHANK), and contactin-associated protein-like 2 (CNTNAP2) (19) and indicate that ASD may result from synaptic plasticity abnormalities.

## CONCLUSIONS

Different neurodevelopmental disorder theories have been proposed to explain the pathophysiology of autism, for example, the theory of mind and social motivational deficit theories, and are helpful for clinicians and cognitive behavioral therapy (2). It is believed that different causes of ASD act together to affect a person's development (1). MRI studies seem to show the disruption of neural pathways in the brains of children before behavioral symptoms are presented (20,21).

Early developmental and behavioral intervention is important in ASD to improve impairments in social communication and interaction. Some approaches include parent-mediated interventions and the Early Start Denver Model, an intensive therapist-guided intervention that instructs parents on the usage of beneficial modes of communication and interaction. Therapy continues with school-based strategies and then aims to promote independence in adults with ASD. Medication is primarily used to treat associated symptoms such as agitation and irritability, and the common mental health conditions that accompany ASD, such as ADHD.

Quality of life (QoL) has been reported as lower in adults with ASD when compared to the general population (22). Being female, having a co-current mental health condition, and experiencing severe autism symptoms tend to lower QoL, while employment, relationships, and support tend to raise QoL (23).

Autism research continues to evolve with genetic and neurobiology studies, as the numbers of diagnosed children have risen steadily over the last two decades, increasing from a diagnosis of 1 in 150 children in 2000 to 1 in 44 children at present. This drastic rise in numbers most likely stems from an increase in awareness and diagnoses of ASD.

Currently, there is no therapy for ASD and new research is needed to further our understanding of the disease and improve the QoL for patients.

*Conflict of interest*

The author declares that they have no conflict of interest.

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