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VITAMIN D DEFICIENCY AS A CONTRIBUTING FACTOR IN CHRONIC LOW BACK PAIN AND SCIATICA: MYTH OR REALITY?

Muhammad Mohtashim[1], Aruba Saeed[2], Bushra Munir[3], Shahzada Khurram Syed[4], Qanbar Abbas[5], Rehana Shaheen[6], Naveed Munir[*7], Imtiaz Mahmood Tahir[8], Zahed Mahood[9], Muhammad Jahangeer[10]

[1,9]*Department of Biochemistry, Government College University Faisalabad, Faisalabad, Pakistan*
[2]*Faculty of Rehabilitation Sciences, Lahore University of Biological and Applied Sciences, Lahore, Pakistan*
[3]*Department of Biochemistry, University of Sargodha, Sargodha, Pakistan*
[4]*Department of Clinical Services, School of Health Sciences, University of Management and Technology, Lahore, Pakistan*
[5]*Department of Zoology, Quaid-i-Azam University, Islamabad, Pakistan*
[6]*Department of Life Sciences, School of Science, University of Management and Technology, Lahore, Pakistan*
[*7]*Department of Biomedical Laboratory Sciences, School of Health Sciences, University of Management and Technology, Lahore, Pakistan*
[8]*College of Allied Health Professional, Directorate of Medical Sciences, Government College University Faisalabad, Faisalabad, Pakistan*
[10]*Office of Research, Innovation and Commercialization, Lahore University of Biological and Applied Sciences, Lahore, Pakistan*

[*7]naveed.munir@umt.edu.pk

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Corresponding Author: *
Naveed Munir

Abstract

Vitamin D which is linked to musculoskeletal function in our bodies, and its insufficiency is a worldwide health issue. Low back pain (LBP) and sciatica are important health problems in terms of low quality of life, loss of work power, and cost of diagnosis and treatment approaches. Vitamin D relation with chronic back pain and sciatica is very important because of limited research and data material on back pain and specially sciatica. The purpose of this study is to investigate the relationship between vitamin D deficiency with back pain severity and sciatica leg pain in patients who are suffering from these diseases. Vitamin D insufficiency raises the chance of developing LBP thus researchers are looking into the potential function of vitamin D deficit in the prevention of LBP. Different management strategies should be implemented with patients having chronic pain such as certain mediation, physical therapy, exposure of the sunlight, and NSAIDs to investigate the crosstalk between vitamin D deficiency and LBP. There is a significant relation between back pain and leg pain namely sciatica while the link between the vitamin D deficiency and sciatica is still under study. Vitamin D affects lumber disc herniation, disc slip, and lumber spin due to its significant role in nerve and bones health. Although sciatica is often caused by the compression or irritation of the sciatic nerve or its nerve roots in the lumbar spine, often due to disc herniation, spinal stenosis, or other spinal issues but there is contravention in the link between vitamin D level and sciatica. So, this review article has been compiled to determine any link among vitamin D deficiency, LBP

Frontier in Medical & Health Research

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and sciatica.

INTRODUCTION

Vitamin D which was initially classified as vitamin in the twentieth century, but it is now classified as a prohormone. Vitamin D is a fat-soluble seco-steroid chemically. The major purpose of Vitamin D to keep blood calcium levels within a restricted limit. Vitamin D is required for bone growth, maintenance, or remodeling, along with muscular function. Of particular interest the role it might play in improving neuromuscular function, slow down the process of inflammation, or lowering the hazard of numerous chronic disorders, including as malignancies, autoimmune disorders, viral diseases, and cardiovascular diseases (Brannon, 2012). Vitamin D has been found to have hormonal, neurological, anatomic or immunological effects on pain expression, suggesting that it may play a role in the etiology of pain (Jesus et al., 2013).

Pain is the sensation that human experience. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience linked with existing or potential tissue damage, or characterized by the patient in terms of such harm". Primarily pain is a particular perceptual feeling. The sensation of pain begins with the receptor nociceptors that belong to CNS but its sensation is felt in conscious part of the brain. The pain has two major kinds that are acute nociceptive pain which functions by indicating initial warning sign or pathological chronic pain that is effectively a constant false alarm (Woolf & Ma, 2007). Acute pain is a feeling that is produced following intense activation of several tissues that belongs to the body. The process of nociception relates to many biochemical or neurological modifications that arise in reaction from noxious stimuli. This stimulation generates movement potentials in number one sensory neurons referred to as nociceptors. These nociceptors are triggered via high-threshold stimuli to transfer excitatory indicators to the sensory mobile our bodies in the dorsal root ganglion (DRG) thru the dorsal roots and subsequently into the spinal column (Porreca, 2015). In the spinal cord, these initial one sensory nerve fibers produce neurotransmitters consisting of glutamate and neuropeptides that spark off 2d-order neurons. The 2d-order neurons transmit information through specific pathways that attain the thalamus when the sensation of pain gradually increases to a certain level. Third-order neurons linking the thalamus to the somatosensory cortex are engaged, ensuing in the feeling of pain (Shipton & Shipton, 2007).

Nociceptors are observed in maximum tissues inside the frame, including skin, corneas, mucosa, muscle, bladder, joints, and visceral organs. There are in particular two varieties of nociceptors concerned within the torment pathway, namely, C fibers and A-delta fibers. The skinny, myelinated A-delta fibers are fast transmitting; they're prompted by each mechanical and thermal stimulus. The unmyelinated C fibers reply to chemical, thermal, and mechanical stimuli. C fibers within the viscera are notable in that they reply to unpleasant stimuli which include the stretching of empty organs. The chronic pain defined by IASP is as "pain that has persisted beyond normal tissue healing time." This is considered (in lack of additional requirements) to be three months. Nevertheless, certain chronic pain conditions are defined by repeated brief acute events and exacerbations for example trigeminal neuralgia or arthritis. Chronic pain can produce after damaging of nerve, after inflammation or injury in the tissues, and after disturbance in the normal functioning of neurons. In the nervous system chronic pain may result many structural, functional or many chemical alterations (Seifert & Maihöfner, 2011). The knowledge of neuroplasticity (ability of brain to alter its structure or function) could be a beneficial revision for functional loss; in matter of pain, it seems maladaptive (Siddall, 2013). The Persistent pain changes the neural system to create impulsive pain that develops without any obvious peripheral stimulation as well as a hypersensitivity to peripheral stimuli. Hypersensitivity in the pain can rise in hyperalgesia (a condition in which extreme pain sensation develops) and allodynia (a sensation of pain that comes from non-painful process).

Chronic low back pain (CLBP) is characterized as a torment present between the costal edges and the mediocre gluteal folds for ≥ 90 days and it could be

Frontier in Medical & Health Research

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related with torment in legs or tangible and engine deficiencies according to nerve root involvement (Dionne et al., 2008). There are two symptomatic classes of Low Back Pain (LBP): vague LBP and the other is explicit LBP with or without radiculopathy. Vague CLBP is portrayed by low back torment with no clinical or analytic proof of a particular reason, similar to, injury, circle herniation, contamination, spondyloarthritis, spinal stenosis, and harm. About 80% of the patients introducing in the outpatient office with grumble of LBP have vague LBP (Maher et al., 2017). Several elements like advanced age, female sex, overweight or fat body habitus, smoking, unfriendly perspective, and requesting actual work have been related with CLBP (Engstrom et al., 2012). In the treatment of CLBP regularly self-treatment with nonprescribed over the counter agony executioners are utilized, or physiotherapy and different methods of elective medications have been used. In spite of quite possibly the most widely recognized foundations for interviews to clinical OPDs, discovering a reason to LBP is frequently troublesome and surprisingly more severe in treating it medicinally. CLBP causes huge impedance in personal satisfaction and occupation execution, consequently prompting a prominent inability and financial burden (Hoy at al., 2014).

Radiating leg pain is usually referred to as sciatica. Inflammation or compression of the lumbo-sacral nerve roots (L4-S1) that comprise the sciatic nerve causes it (Valat et al., 2010). Sciatica can cause a lot of pain and make it difficult to do things. The significance of conservative therapy for sciatica has been highlighted in recently updated clinical guidelines in Denmark, the United States, and the United Kingdom (Stochkendahl et al., 2018). Radiculopathy is a condition in which the nerve root is involved, resulting in neurological deficits such as weakening or numbness. Sciatica is characterized by agonizing and severe leg pain that radiates below the knee and into the foot and toes (Ropper & Zafonte, 2015). The pain might come on suddenly or gradually, and it can be mild or severe. Low back discomfort is often reported by most people. Strömqvist et al. (2017) found that disc herniations impacting the L5 or S1 nerve root are more prevalent and produce discomfort in the back or side of the leg, as well as in the foot and toes. The discomfort is confined to the front and lateral side of the thigh if the L4 root is damaged. Other signs of nerve root involvement include tingling or numbness, as well as a decrease of muscular strength in the same limb. The most frequent cause is disc herniation as a result of age-related degenerative changes, and in rare cases, trauma (Konstantinou et al., 2018).

The inflammatory reaction causes the herniated disc material to resorb, which is considered to explain why most patients recover without surgery. Other reasons include animal stenosis and, less frequently, soft tissue stenosis caused by cysts, tumors, or extraspinal disease. Extra-spinal disease in the lumbosacral nerve plexus, such as tumor, trauma, infection, or gynecological disorders, or muscle entrapment, such as piriformis syndrome, can occasionally resemble disc herniation symptoms (Ailianou et al., 2012). According to a recent systematic review (eight studies), smoking, obesity, and manual labor are modifiable risk factors for the first episode of sciatica, suggesting the possibility of prevention (Cook et al., 2014). There is much of debate over linking persistent LBP with levels of vitamin D. Study revealed 82.30 percent patients with nonspecific CLBP to be Vitamin D deficient whereas in 19.68 percent instances Vitamin D levels were normal. The research done by Bahinipati J et al. and Al Faraj et al. in patients with chronic LBP revealed the majority of patients were having low Vitamin D level, and its insufficiency was recognized as one of the key causes for chronic LBP (Bahinipati and Mohapatra, 2020). Few researches have examined the relationship between vitamin D with the severity of persistent back pain. As per the research done by Lotfy et al., Gokcek, E., & Kaydu (2018), and Xu et al., serum 25 (OH) D levels connect substantially with the pain severity (Xu et al., 2020).

Synthesis, Absorption and Metabolism of Vitamin D

Vitamin D which is mostly produced from the skin and food sources in the human body following UV light exposure. More than 90% of systemic Vitamin D comes through the skin, with the remaining 10% coming from diet (Holick, 2008). Vitamin D comes in a variety of forms, the most prevalent of which are Vitamin D_2 or Vitamin D_3. Calciferol is the name

Frontier in Medical & Health Research

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given to each of these substances. Vitamin D_3 is produced in human skin and eaten in the diet through the consumption of animal-based foods, primarily fish oils, whereas vitamin D_2 is obtained from plant sources, is not predominantly human-made, and is added to meals (Zanuy & Carranza, 2007). Only the side chain structure of vitamins D_2 and D_3 differs (Figure 1). The changes have no effect on metabolism (i.e. activation), and both types perform the same function as a prohormone. Vitamin D received from the sun, diet, and supplements is physiologically inactive (either vitamin D_2 or vitamin D_3) and must be activated by two enzymatic hydroxylation processes in the liver and kidney (Figure 1C). Vitamin D (D_2 or D_3) is generally absorbed along with other dietary lipids in the small intestine (Silva & Furlanetto, 2018). When lipids are present in the lumen, bile acids are released, causing emulsification and the production of lipid-containing micelles, which then diffuse into enterocytes (Mulligan & Licata, 2010). Exogenous vitamin D is packed into chylomicrons and delivered to the liver once absorbed. Adipose tissue and skeletal muscle can absorb a portion of the vitamin D present in the chylomicron. Once the leftover chylomicrons reach the liver, a particular carrier protein called vitamin D binding protein (DBP) allows them to enter hepatocytes and then transport them to the many tissues that require them. Vitamin D_3 can be photosynthesized in the skin endogenously.

When exposed to ultraviolet B (UVB) light, 7-dehydrocholesterol (provitamin D_3) is transformed to pre-vitamin D_3 (pre-calciferol). In the epidermis, it can then undergo heat isomerization to vitamin D_3 (Figure 1). Pre-vitamin D_3 can also be photoconverted to inactive molecules like tachysterol and lumisterol, which have distinct biological effects (Cisneros et al., 2017). Vitamin D_3 is produced in the skin as a result of the amount and quality of UVB light that reaches the dermis, as well as the availability of 7-dehydrocholesterol and the skin's properties.

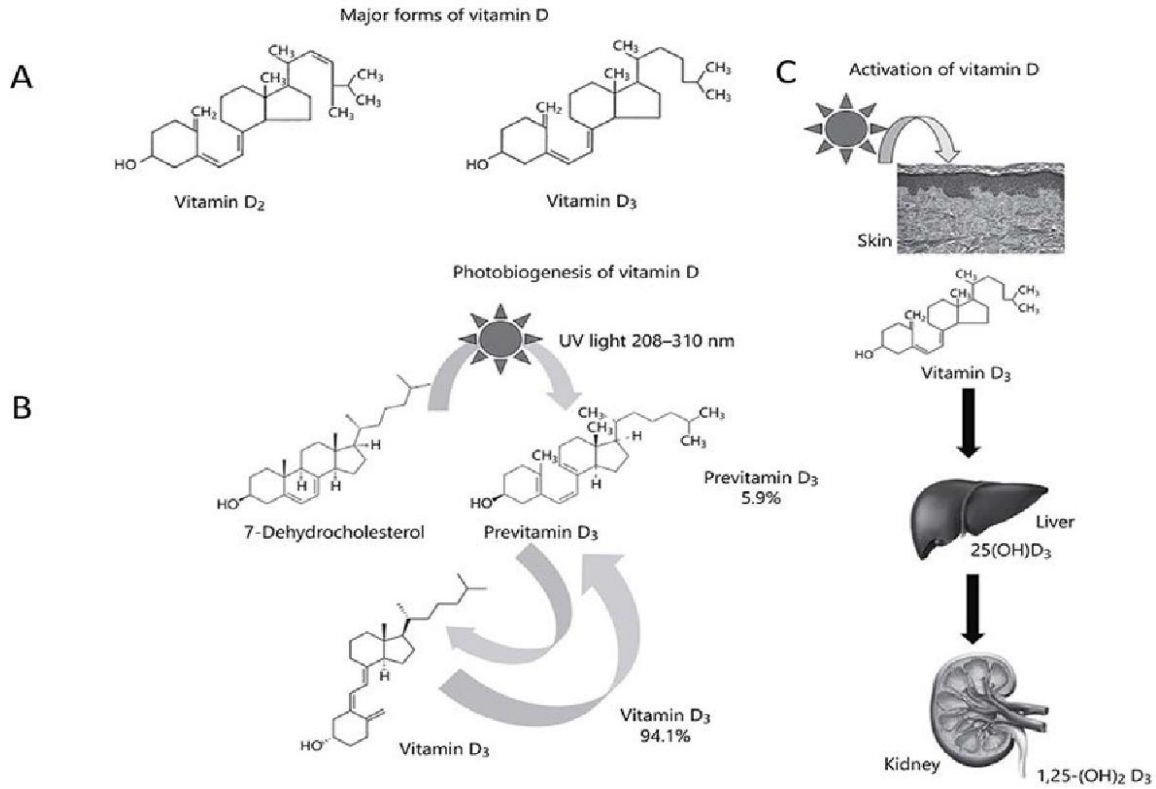

Figure 1: Structure and activation of Vitamin D (A) Different forms/ structures of vitamin D (B) synthesis of Vitamin D under the influence of sun light (C) activation of vitamin D.

Frontier in Medical & Health Research

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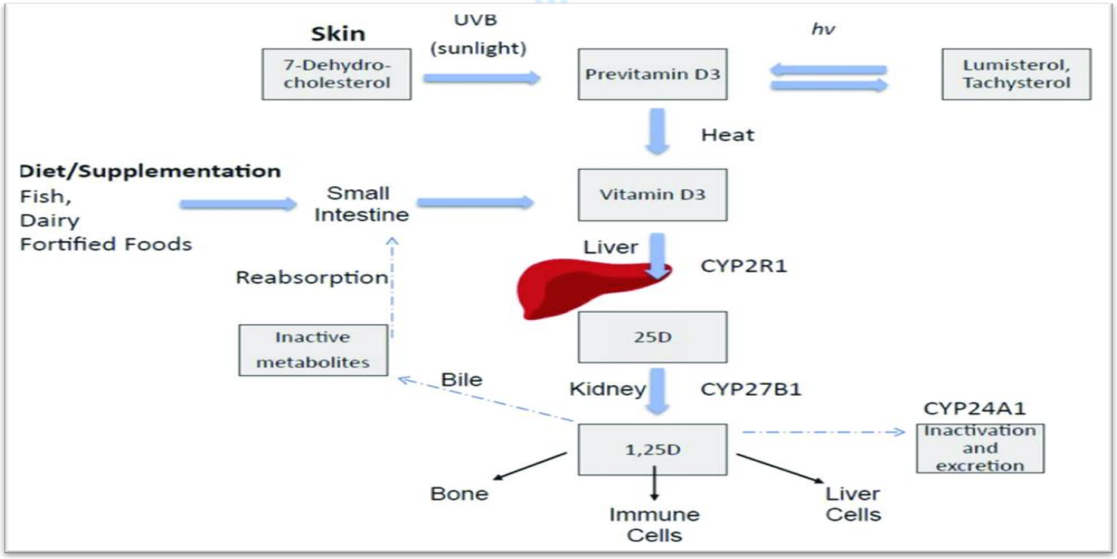
The three major stages in the metabolism of Vitamin D are 25-hydroxylation, 1-alpha-hydroxylation, and 24-hydroxylation are carried out by cytochrome P450 mixed-function oxidases (CYPs). These enzymes can be found in the endoplasmic reticulum (ER) (e.g., CYP2R1) or the mitochondria (e.g., CYP2R1). The electron donor of ER enzyme is P450 reductase, which relies on reduced nicotinamide adenine dinucleotide phosphate (NADPH). Ferredoxin and coenzyme ferredoxin reductase make up electron donor chain for mitochondrial enzymes. They aren't particular to a single CYP; rather, they're specific to the CYP itself. Although only enzyme of ER such as CYP2R1 and the enzyme of mitochondria CYP24A1 have been crystallized among the CYPs involved that take part in the metabolism of Vitamin D, these enzymes are expected to share a number of structural characteristics. Twelve helices (A-L) and loops, as well as a common prosthetic group, the iron-containing protoporphyrin IX (heme), are linked to cysteine thiol. Above heme, helix I pass through the core of the enzyme, and catalytic activity requires a pair of thr (ser) and asp (glu) (Sugimoto and Shiro, 2012).

The hydroxylation of Vitamin D in the liver is done by P-450 which is catalyzed by 25(OH)D and encoded by the gene CYP27A1 (Brannon, 2012). The majority of flowing 25(OH)D and the dynamic Vitamin D types, particularly 1,25-dihydroxyvitamin D [1,25(OH)2D], which is attached to Vitamin D restricting protein (80–90%) and egg whites (10–20%) in the blood, with just small fraction remaining free or else unbound. The two mechanisms is used for the absorption process of calcidiol: dispersion of free calcidiol across the cell layers all over the body or albumin D-box binding protein (DBP) receptor-mediated endocytosis by the cubulin and megalin coreceptors. It gives the notion that some behavioral and physiological determinants may influence endocytic transit (Willnow & Nykjaer, 2010). The effect of DBP on free against bound 25(OH) D might affect the amount of free 25(OH)D available for return. The predilection for DBP is the most important factor in determining how long a Vitamin D metabolite will be accessible for usage. More research is needed to understand the guidelines for activating 25(OH)D from lipid accumulating pools in relation to health benefits. Vitamin D, then again, might be hydroxylated to 25(OH) D in every single substantial tissue, coming about in autocrine creation of 25(OH)D in these tissues (Hollis and Wagner, 2013).The synthetic 25-hydroxyvitamin D-1 alpha-hydroxylase (CYP27B1) changes 25(OH)D over to its dynamic construction, 1,25-dihydroxyvitamin D [1,25(OH)2D3], which is in this manner used in the kidneys and maybe in a wide scope of extra renal tissues. Vitamin D works by controlling quality articulation after it has been confined to VDR.



Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Figure 2: Mechanism of the Synthesis of Vitamin D under the influence of ultraviolet radiations in the skin and absorbed from different dietary sources.

Relationship between Vitamin D deficiency and low back pain

Vitamin D, one of the fat-soluble vitamins, is a group of sterols that are hormones and hormone precursors due to its ability to be produced endogenously (Richard et al., 2005). Deficiency or insufficiency of vitamin D has been linked to a variety of chronic illnesses in recent years (Holick, 2008). To determine the status Vitamin D, the serum level 25(OH) D should be tested. It is widely believed that if serum level of 25(OH)D is greater than 30 ng/mL, the level of Vitamin D is acceptable; if it is 20 to 30 ng/mL, there is Vitamin D inadequacy; if it is 20 ng/mL, there is a deficiency of Vitamin D; and if it is 10 ng/mL, there is a severe deficiency of Vitamin D. Due to the insufficiency of Vitamin D containing foods, only a tiny percentage (10%–20%) of this vitamin is taken with meals. UVB rays are responsible for a substantial part (80–90%) of its synthesis in the skin. Direct sunlight contact on the skin is necessary for synthesis. The angle of sunlight that comes toward the surface of earth helps in the production of vitamin D. When the entire body is exposed to sunshine and becomes bright pink at opportune periods during the summer, about 20,000 IU Vitamin D synthesis occurs at a level comparable to the Vitamin D dose (Wacker & Holick, 2013). It was found out that vitamin D levels in young female of LBP patients were lower than in men, although this alteration in the discovery was not statistically verified. The relation between Vitamin D with LBP has been studied, and it has been discovered that patients with LBP have lower serum 25(OH)D levels and are more prevalent in younger women (Zadro et al., 2017). There was little research exploring the link between D vitamin and pain severity when we conducted a literature study. There was a substantial connection between serum 25(OH)D and pain severity in certain trials (Lotfi et al., 2007). However, in several investigations, the relationship between serum 25(OH)D and pain intensity was not shown to be significant (Babita et al., 2015). LBP and vitamin deficiency are the most frequent health issues in the world. Sunlight influences the production of more than 90% of Vitamin D in the body. When consumed with meals, vitamin D does not make a substantial impact, especially if a supplement is not taken. Seasonal and regional variations are unavoidable in the vitamin D production in human body since sunshine is the key production source.

Vitamin D supplementation with chronic low back pain

By exerting anatomic, hormonal, neurological, and immunological impacts on pain expression, vitamin D plays an important part in genesis and development of many chronic pain syndromes and associated chronically (Jesus et al., 2013). Muscle weakness and discomfort are caused by low level of vitamin D that effect humans of all age (Hans et al., 2011). Vitamin D has also been demonstrated to have immunomodulatory properties. Vitamin-D supplements have linked to improvement in density of bones or musculoskeletal complaints. Its supplementation may lower the production of inflammatory cytokines while increasing the production of anti-inflammatory cytokines. Vitamin D insufficiency can affect people of all ages and may be a contributing cause to unexplained musculoskeletal discomfort. It is a potentially curable condition, and supplementation can be used as an adjunctive treatment for musculoskeletal discomfort (Muir and Montero-odasso, 2011).

Reduced vitamin D levels have been linked to increased cerebral susceptibility to mechanical stimulation in chronic pain sufferers (Von Känel et al, 2014). It has a significant function in astrocyte detoxification pathways and hence has a neuroprotective effect. Improved vitamin-D levels may aid in astrocyte detoxification pathways in the neuropathic pain component of CLBP patients. In astrocytes and microglia, vitamin D inhibits tumor necrosis factor alpha (TNF-), macrophage colony-stimulating factor (M-CSF), and inducible nitric oxide synthase. TNF- has been firmly linked to pain sensitivity at both the peripheral and central levels. MCSF is a cytokine that promotes monocyte and macrophage proliferation, differentiation, and survival. Many inflammatory mediators can be released by macrophages, including proinflammatory cytokines, notably TNF- and interleukin-1 beta (IL-1),

Frontier in Medical & Health Research

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nerve growth factor (NGF), nitric oxide (NO), and prostanoids. Reduced sun exposure is cited as the primary reason of decreased vitamin-D production (Holick et al., 2011). According to Holick et al, persons with naturally dark skin tones may require 3 to 5 times the amount of sun exposure to synthesis the same amount of vitamin D as people with lighter skin tones. Vitamin D supplementation raises plasma 25(OH) D3 levels, possibly addressing the consequences of vitamin D insufficiency (Straube et al., 2015). Straube et al. conducted two recent meta-analyses that found disparities in the outcomes of randomized clinical trials (RCTs) and non-RCTs. Vitamin D supplementation was shown to be beneficial in treating chronic pain in 10% and 95% of RCTs and non-RCTs/observational studies, respectively.

Chronic pain associated with Vitamin D and central hypersensitivity

Vitamin D levels in individuals with persistent pain that satisfied preliminary diagnostic ACR criteria for fibromyalgia in connection to markers of central hypersensitivity, mainly mechanical pain sensitivity. The cutoffs for distinguishing between deficient and inadequate vitamin D levels, as well as sufficient and normal calciferol level, was not universally mentioned in the literature and, moreover, rely on what is considered an acceptable level for the index illness under investigation (Holick et al., 2011). To our knowledge, there is no consensus evidence on sufficient level of calciferol in the patients having chronic pain; nonetheless, in clinical settings, it may appear fair to designate values of calciferol insufficiency is less than 50 nmol/l and higher than 75 nmol/l are considered normal. We discovered that nearly three-quarters of our patients were vitamin D deficient, with another fifth showing vitamin D deficiency. To put it another way, just around ten percent people have normal value of calciferol who has suffered from disease. Other research that performed with patients suffering from chronic pain with primary or tertiary care centers has found a similar low frequency of normal level of calciferol.

Approximately half of the general inhabitants of the world is anticipated to have usual level of calciferol. As a result, doctors should know the fact that less than usual level of calciferol are more than norms that it should expected from people suffering from chronic pain. The researchers discovered a strong inverse relationship between sensitivity of pain with continuously observed calciferol level. This conclusion is consistent with animal experiments on sensitivity of ache mechanism. It was reported that a reduction of calciferol about 100 nmol/l correlated to increase of two units in pressure pain intensity on a numeric rating scale ranging from 0 to 10. This effect size has been demonstrated to be clinically significant for self-information of impulsive persistent musculoskeletal pain. Despite statistical adjustments for a variety of potentially confounding factors, including particular groupings of various agony medicines, the substantial relationship between low level of calciferol and increased mechanical sensitivity of agony always remained (Iqbal et al., 2025).

Chronic Back pain associated with Vitamin D deficiency in postmenopausal women's

Chronic low back pain is a relatively prevalent problem among postmenopausal women. It is becoming more noticeable that in most situations, the specific cause of pain cannot be determined and that a wide range of psychological and social variables might be implicated in this illness. As a result, the patient's unpleasant predicament worsens as he or she grows older. Similarly, the risk is 1.5 to 2.5 times higher in smokers than in nonsmokers (Mattila et al., 2008). It is also more prevalent in women who have had two or more pregnancies. Obesity is likely related with an increase in chronic LBP, even if the research is inconclusive. Even if it is disputed, vitamin D insufficiency may be an underlying component in untreated adult musculoskeletal pain and is a possible curable cause (Lewis, 2005). Many researches have recently been conducted on the relationship between vitamin D and persistent LBP (Hicks et al., 2008). In a case-control study, vitamin D insufficiency was found to be an independent risk factor for persistent LBP in postmenopausal women. These findings are consistent with previous research. Hicks and colleagues found that elderly women with vitamin D insufficiency were nearly twice as likely to have moderate or severe back pain. In Saudi Arabia, 83

Frontier in Medical & Health Research

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percent of 150 patients with low back pain with no clear reason for more than six months had an unusually low vitamin D level. Clinical improvement in symptoms was observed in all of individuals who had a low starting vitamin D concentration after therapy with vitamin D supplements (Al Faraj & Al Mutairi, 2003).

Mechanism of action of Vitamin D on pain processing

After an injury in the peripheral nerve, there are several processes that involved in the improvement of neuropathic pain. These processes contain ectopic excitability in the sensory type of neurons, alternation in the expression of the genes, and sensation of sensory neurons in the spinal cord region (Moalem & Tracey, 2006). These processes are affected by a range of organic and psychological variables. Neurotransmitters together with glutamate, serotonin, and GABA along with irritation of the glial are essential for the recklessness and inhibition impact on the process of ache. The process of neuropathic pathway of ache and inflammatory processes might also depend upon the activity of numerous cytokines or many factors such as transcription or presence of several molecules such as CGRP. Because steroid materials affect the plasticity of the human nervous system, those drugs play a vital role in the regulation of pain sensation (de Abreu et al., 2009).

Vitamin D with prostaglandins

The activity of prostaglandins is affected by decreasing expression of COX-2 and by increasing 15-PGDH expression by Vitamin D (Feldman et al., 2007). The degradation of prostaglandins or inhibition of Prostaglandins-e2 receptor and prostaglandin-f2 alpha receptor are all done by the enzyme 15-PGDH. Prostaglandins have a direct impact on sensory neurons by means of decreasing the firing threshold, growing the quantity of motion potentials evoked with the aid of a singles for the depolarizing mechanism, and boosting SP and CGRP release. The prostaglandins facilitate the pathway of pain including neurons inside spinal cord through depolarizing the molecule PGE2 BY extensive variety of neurons (Moalem & Tracey, 2006).

Vitamin D as a neuroactive steroid

Like other neuroactive hormones, Vitamin D can alter neuronal excitability (Kalueff & Tuohimaa, 2007). This comprises spontaneous regular firing, action potential length, intrinsic excitability, and neurotransmitter sensitivity as well as neurotransmitter receptors such as the GABA receptor and the N-methyl-D-aspartate (NMDA) receptor (Mensah-Nyagan et al., 2009). Steroid chemicals change the electrical movement of various neurons and powerhouses by influencing the replication of their particle channels and synapse receptors, or by altering the action of their channels and receptors through other molecules. As a synapse steroid, nutrient D animates various sign transduction components. The appearance of calcium particles, the arrival of calcium particles from intracellular capacity, the guideline of adenylate cyclase, phospholipase C (PLC), protein kinase C, protein kinase D, and mitogen actuated protein (MAP) kinases, and fast development. RAF kinase is the example (Calberg & Capbell, 2013). Vitamin D, like a steroid, also influences brain neurotransmitters such as dopamine or serotonin.

Vitamin D with Neurotrophins

The increased production of neurotrophins such as NGF, NT3, and GDNF and decreased production of NT4 are all done by vitamin D (Figure 3). Vitamin D has the ability to influence the growth, maintenance, and survival of neurons via this mechanism. NGF is a well-known inflammatory mediator. It acts directly on the ending of sensory neurons that causing condition hypersensitivity, amplification the signals of sensory neuron, and increased innervation of damaged tissue (Mckelvey et al., 2013). Vitamin D administration has been found to enhance NGF production and prevent neurotrophic deficiencies in the diabetic neuropathic pain paradigm. There is some evidence that vitamin D has neuroprotective properties through reducing the effects of glucocorticoids and regulating neuronal calcium ion homeostasis (Harms et al., 2013). VDRs have been found in both neurons and glial cells. In brain cells, genes encoding enzymes involved in Vitamin D metabolism are expressed. Because $1,25(OH)2D_3$ induces cell death and re-differentiation pathways in glioma cells, it has been proposed that local

Frontier in Medical & Health Research

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production of 1,25(OH)2D_3 by microglia might drive an antitumor response.

Effects of Vitamin D on Inflammatory Pathways

Vitamin D has been shown to affect various inflammatory processes related to the onset and duration of chronic pain. Vitamin D stimulates the production of transforming growth factor 1 (TGF1) and interleukin 4 (IL4) in astrocytes and microglia (Garcion et al., 2002). TGF1 inhibits the effects of many cytokines, including interferons, TNF, and T cells, such as interleukin 1 (IL1) and interleukin 2 (IL2). It has the ability to reduce the function of immune cells. By inhibiting cytokine receptors (such as IL2 receptors). Vitamin D in astrocytes and microglia inhibits TNF and macrophage colony stimulating factor (MCSF). MTNF is closely related to increased awareness at the peripheral and central levels (Leung and Cahill, 2011). MCSF is a sort of cytokine that promotes several processes such as proliferation of different molecule, differentiation of different cells, survival mechanism of monocytes or different macrophages stages. Different mediators involved in the process of inflammation are produced by macrophages, including pro-inflammatory cytokines such as TNF and IL1, NGF, prostaglandins and nitric oxide. Vitamin D can inhibit the pain pathway by lowering MCSF.

Vitamin D with Nitric Oxide Synthase

The production of iNOS is blocked by the Vitamin D, this is the enzyme which is responsible for the production of nitric oxide or macrophages which is responsible for the activation mechanism of microglia and several astrocytes in mRNA and different proteins. NO is an essential neurotransmitter involved in the nociceptive process; it contributes to the development of central sensitization in the dorsal horn of the spinal cord (Cury et al., 2011). Astrocytes play an important part in detoxification pathways in the CNS, where nitric acid is removed by the glutathione. The activity of gamma-GT, a key enzyme involved in the metabolism of GSH, has been found to be controlled by 1,25(OH)2D3, which induces the process of apoptosis. Vitamin D's suppression of iNOS is a possible method for decreasing sensation of pain or damage in the neurons following injury or any sort of illness for example AIDS, Parkinson's disease (Marchand et al., 2005).

Vitamin D with T-Helper Cells

Different type of immune cells plays a role in the development of peripheral neuropathy and the pain in the pathway of neuropathy. Mostly, cells are produced by the nerves that are damaged; they seem to inhibit neutrophil and monocyte recruitment in the wounded nerve, hypothetically decreasing the synthesis of various chemokines and different mediators' molecules. Vitamin D inhibits neutrophil activity (Takahashi et al., 2002). Neutrophils generate a variety of inflammatory agents, including lipoxygenase products or cytokines. Great numbers of neutrophils produced during tissue damage and have been related to the development of neuropathic pain sensations. NGF's hyperalgesic effects appear to be somewhat dependent on neutrophil accumulation (Marchand et al., 2005). Vitamin D suppresses T-helper cell activation and is crucial in the prevention of autoimmune disorders.

VDR with 1α-Hydroxylase

Many regions of the human central nervous system contain VDR which is receptor of vitamin D and 1 alpha hydroxylase [enzyme that transforms 25(OH)D to the active form 1,25(OH)2D_3 via the hydroxylation process]. Prefrontal cortex, amygdala, raphe, cerebellum, thalamus, and hypothalamus are among them (Kalueff & Tuohimaa, 2007). Both the receptor and the enzyme have been shown to be present in neuronal and glial cells. VDR has been recognised in axonal predictions in the lateral portion of hypothalamus of rats (Jirikowski et al., 2009). The existence of different VDRs, 1 alpha-hydroxylase, and VDR protein in hypothalamus has been proposed a mechanism through which calciferol insufficiency is linked in the pathophysiology of different diseases that relates with head (Prakash et al., 2010).

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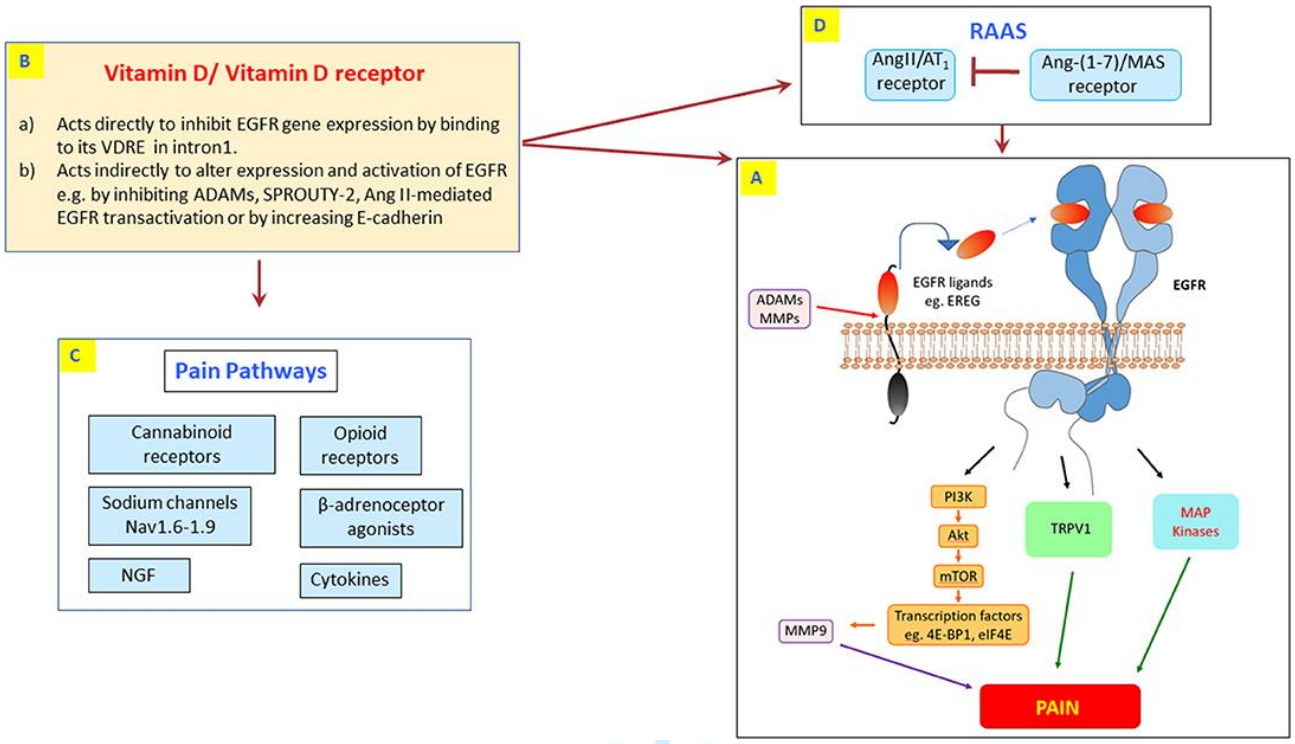

Figure 3: Interplay of Vitamin D and pain mechanism at molecular level**.**

Improvement of chronic back pain with Vitamin D repletion

The level of vitamin D is restored from baseline in an individual that suffer from osteomalcia resulted a full pain relief after 28 days (Ghose, 2005). Back discomfort and weakness have also improved in people with osteomalcia. Patients with persistent, common LBP or who have undergone unsuccessful surgery of the back results a deficiency in the level of vitamin D (Heath & Elovic, 2006). Infection and smoking are main factors for the tenacity or reappearance of LBP following surgery. Low vitamin D levels are a less prevalent cause. Repletion with thousand IU/day increases vitamin D fame by around 20-25 nmol/L, whereas two thousand IU/day improves levels by 40-50, except in those with darker complexion, which require substantially more. The patients whose suffering from back pain and decrease in calciferol level may benefit from a screening test such as repletion therapy and calciferol level. Muscle pain is prevalent in individuals with vitamin D insufficiency, as well as myopathy, and it generally improves faster than bone pain (which may take up to 1 year to resolve). Physicians should have a high index of suspicion for low vitamin D levels in LBP patients, and assessing vitamin D status may be crucial in these patients. Repletion of vitamin D may provide remarkable benefits in situations of vitamin D insufficiency/deficiency. Before and after performing back surgery it is essential to determine calciferol level and repletion in body. In this study, the best reacted patients are those who took 4000 and 5000 IU per day of vitamin D_3 (Schwalfenberg, 2009).

Treating vitamin D deficiency and insufficiency in chronic back pain

Vitamin D supplementation is also beneficial in individuals in which the blood level of vitamin ranging in between twenty to thirty ng/mL. For therapy of patients that suffering with chronic pain such as neck or back or different sorts of muscular spasm low level of vitamin D level is cricial. The mechanism behind this connection is yet unknown, necessitating more investigation. However, as documented by historical study data, it might be connected to a deficit or unbalanced homeostasis of intracellular and/or extracellular electrolytes, including calcium, magnesium, and phosphorus, as a result of vitamin D insufficiency (Haussler et al., 2012). According to recent studies, calciferol

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

receptor serves critical part in transduction of signals in cellular basis or immune response mediation. Vitamin D insufficiency has become widespread in the contemporary age for a variety of causes, attracting widespread public attention (Kahn et al., 2011). Recent interventional studies have revealed that vitamin D supplementation has a positive effect on cancer pain and muscle pain, but only in individuals who have low vitamin D levels before they begin treatment. Anti-inflammatory effects mediated by decreased cytokine and prostaglandin production, as well as impacts on T-cell responses, are possible pathways for vitamin D in pain treatment (Helde-Frankling & Björkhem-Bergman, 2017). To spread the awareness of chronic pain that occurs due to the deficiency of calciferol level is crucial among different people especially sportsman since it is readily preventable and treatable.

Relationship between lower back pain and sciatica

The IASP advises back pain is that "pain in the lower limb should be clearly characterized as either referred pain or radicular pain." When in doubt, no implication should be made, and the discomfort should be characterized as lower-limb pain." According to Lundborg, continuous nerve compression has three clinical stages: In stage one there are intermittent paresthesias and deflects of sensory neurons that occur at night. In stage two there is a distinguishing between more severe symptoms such as numbness that fail to decide during the sun time; and in stage three there is a differentiation between many neurological changes that results in inferable pain that will not disappear. Physical treatments and pain or inflammation control may often be used to treat stage I problems, but in more severe diseases in stage three and stage two, surgical intercession may be necessary (Flanigan & DiGiovanni, 2011).

Mentioned pain arrangements involving the low back and limbs might be caused by the lumbar facet joints. The pain distribution from the lumbosacral facet joints was reported by Gellhorn (Gellhorn et al., 2013). Frustration in the facet joints in healthy helpers results in a pattern of pain which resembles sciatica. Facet blockade or denervation with anesthetic can provide pain relief. The sacroiliac joints involve as a solitary reason from the leg in the lower portion; however, it might be part of the muscles of piriformis stated pain that is reported by Freiberg. Entrapments in the peripheral nerve ending of the lower extremities are uncommon and comprise a diverse range of nerve diseases. The most frequent entrapment neuropathy of the lower leg is peroneal nerve palsy, which is caused by compressive disease at the level of the fibular head (Poage et al., 2016). External variables for example squatting for a long time, crossing of legs time after time and wearing bracelets or big and long shoes due to short height have been linked to peroneal nerve compression, as have internal ones such as different exercises, abnormalities in the vascular nerve, traumatic and injuries in the nerve.

Pro-inflammatory mediators have been discovered inside the disc and perineural tissue of individuals having surgical procedure for lumbar disc disorder (Shamji et al., 2010). It has also been proposed that an immune response to nerve tissue has a role within the pathophysiology of both acute and chronic sciatica. With the appearance of state-of-the-art spinal imaging, starting with pc tomography (CT) within the 1970s and the first record displaying the capacity to pick out herniated lumber discs in 1979, attention has shifted to radicular syndrome as the number one source of ache referring from the returned to the leg. This can be seen as early as 1988, while Frymoyer wrote on sciatica and most effective covered radicular elements that had been relevant to this scientific entity. According to Smyth, "Sciatica necessitates mechanical and inflammatory stimulation to the anterior number one rami of lumbar nerve roots." More recent publications have nearly absolutely identified the nerve root because the source of returned and leg pain, a situation known as sciatica (Deyo & Mirza, 2016).

Vitamin D and Lumber spine

Low vitamin D levels can be caused by a variety of factors, including malabsorption, insufficient ingestion, and poor hydroxylation due to decreased hepatic or renal function (Bouquegneau et al., 2016). Minimum level of calciferol in healthy people is 30 ng/ml. When considered in the context of surgical intervention, the final effect of mineralization of the bone leads to the severe form of osteomalacia but visual inapparent deficiencies also have additional

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negative consequences. Because calciferol is essential for healthy bones and its deficiency leads to the weakening and fractures in the bone (Maier et al., 2015) and also have long lasting effects on patients that undergo the process Lumbar spine fusions, which are more common in the elderly population whose suffer from the calciferol level overall. A wide range of problems, including non-union, pseudarthrosis, infection, revisions, and hardware failures, should be fairly predicted. All of these can be attributed to low rate of healing process and slow mechanism of mineralization in the bones. Our hypothesis was that individuals with low blood vitamin D levels would be more prone to problems such as failure of heart, different infections and orthopaedic surgery.

We opted to investigate its impact on postoperative consequences that undergo lumbar fusion surgery. The major goal of our study is to look into the impact of calciferol on the occurrence of postoperative problems in individuals having lumbar fusion surgery. Many additional research suggests that the risk of fracture in the early age that suffers with hypovitaminosis D, but few investigations look the impact of different sorts of supplements of calciferol, its deficiencies and the impact of these in healing bones (Sprauge et al., 2016). Given the intricate interaction of various regulatory systems, our findings imply that vitamin D shortage may not be a danger factor for post lumbar fusion problems on its own. There are several homeostatic systems that regulate the level of Ca and P, and their mechanisms can endure a significant deficiency of exogenous or endogenous vitamin D before clinically obvious osteomalacia is identified. The overall picture of Ca and P homeostasis calls for additional research into which regulatory deficits are more strongly linked to postoperative consequences.

Treatment of lumber disc herniation with Vitamin D receptor

Because of its defensive function towards neurotoxicity and detoxifying pathways, as well as its receptors in many areas of the relevant nervous machine, vitamin D has known to have a role as neurosteriod (Harms et al., 2011). The spinal twine, nerve roots, roots of dorsal side of ganglia, and glial cells all include vitamin D receptors (Smolder et al., 2011). The polymorphism of the VDR gene has a feature within the development of herniation and degenerative mechanism in the lumber disc. Discs are primarily made of avascular tissue this is extremely touchy to dietary supply and waste product excretion, and the balance among these two processes is a vital component which can make contributions to disc degeneration. Active diet D metabolites were investigated in nucleus pulposus and annulus fibrosus cells (Colombini et al., 2012). In vitro, nutrition D inhibits and decreases monocyte chemoattractant protein 1, thrombopoietin, vascular endothelial increase factor, and angiogenin production with the aid of human annulus cells. As previously stated, vitamin D influences detoxifying mechanisms which are crucial in disc cellular nutritional equilibrium.

Calciferol has characteristics as a regulation in the immune system which allows it to suppress proinflammatory cytokines while increasing anti-inflammatory cytokines (Hewison, 2011). Vitamin D has antioxidant capabilities that protect cells against free radicals, species of oxygen that is reactive, and glutamate. Vitamin D performs a function in pain by means of (1) unswervingly downregulating inflammatory cytokines which has a purpose to cause pain, (2) exciting the receptors of the body that initiate pain, (3) start anti-inflammatory process of cytokines that will work to fight against inflammation, (4) its function in metabolites that has a role to eliminate material that is harmful, or (5) dramatically accumulative the pool of anti-toxins. It additionally impacts neurons that is sensory to control ache, modulates excitabilities in the neurones, and capabilities within the sensory notion method on the substantia gelatinosa and spinal ganglion stages. Furthermore, its state influences ache sensitivity and opiate pastime. The involvement of the diet D receptor in skeletal muscular tissues and its consequences on muscular energy and function were found (Garcia et al., 2013). We suggest a unique function for nutrition D within the treatment of discogenic ache and sensory deficits associated with this pathology, based totally on the inflammatory nature of disc herniation and the immunomodulatory effects of nutrition D, as well as the life of vitamin D receptors in diverse parts of regions which might be affected within the

Frontier in Medical & Health Research

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procedure of disc herniation. We anticipated that vitamin D_3 has a position in reducing the depth of discogenic ache and that diet D_3 can ameliorate sensory impairments related to discogenic ache.

Conclusion

Our findings suggest a link between Vitamin D insufficiency and the intensity of pain in LBP patients. The broad screening of Vitamin D levels in people with LBP should be considered since it is a low-cost, safe, and manageable form of the symptoms for doctors. Prospective studies are required to establish the link between LBP and Vitamin D deficit, as well as to evaluate if Vitamin D insufficiency increases the risk of developing LBP and the possible function of Vitamin D deficiency in the prevention of LBP. Different screening tests should be implemented with patients with chronic pain. Our finding also suggests a relation between back pain and leg pain which is sciatica but not a significant relation between vitamin D with sciatica was found.

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