THE NEW ARMENIAN MEDICAL JOURNAL
Vol.10 (2016), No 1, p.24-31

Review Article

NEUROPATHIC AND CHRONIC PAIN AND VITAMIN D DEFICIENCY

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Received 3/03/2015; accepted for printing 15/01/2016

Abstract

Pain is the most common reason for physician consultation in most developed countries. Pain is considered as a devastating symptom in many medical conditions, which reflects on human quality of life and social economic activity. Despite of devastating nature the pain by itself has become an independent target for research, however, the methods of pain assessment and management of patients with pain syndrome are still poorly studied.

One of the actual problems of modern medicine is metabolic syndrome related particularly to vitamin D deficiency. Recent literature data and clinical observations prove the presence of strong correlations between neuropathic and chronic pain and severity of vitamin D deficiency. Moreover, it was revealed, that supplementation of vitamin D was beneficial for all observed patients in both pain reduction and improvement of well-being.

Thus, prioritization of further investigations in this field and possible inclusion of low cost safe medicine are necessary for effective management of the pain.

Keywords: *neuropathic pain, chronic pain, vitamin D deficiency.*

Pain itself is an unpleasant distressing feeling, with strong evolutionary background of most powerful alert. The International Association for the Study of Pain states a widely used definition for pain concept: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". In medical practice pain is both a diagnosis in terms of neuropathic origin and a pathognomic symptom in others. Evolutionary pain stimulates the individual to withdraw from potentially damaging situations, then to protect a damaged tissue while it heals, and later to avoid similar experiences in the future.

Pain is the most common reason for physician consultation in most developed countries. It is a major devastating symptom in many medical conditions, and can seriously interfere with a person's quality of life.

It is well known, that usually pain disappears once the noxious stimuli are removed and the damaged tissue is healed, but in some cases it may persist despite removal of the stimulus and apparent healing of the body. In some cases pain arises in the obvious absence of any detectable stimulus, damage or disease.

Classification. Despite of widely accepted classification of the pain as dividing to regions and length of appearance, such approach has been widely criticized by practicing doctors as inadequate during the treatment. Woolf suggests three classes of pain: nociceptive pain, inflammatory pain, which is associated with tissue damage and the infiltration of immune cells, and pathological pain, which is a disease state caused by the damage of the nervous system or by its abnormal function (e.g. neuropathic pain, fibromyalgia, irritable bowel syndrome, tension type headache, etc.) [*Woolf C et al., 1998*]. The latter one is the most devastating and less manageable.

Chronic pain. Pain, as experienced by everyone, is usually transitory, lasting only until the noxious stimulus is removed or the underlying damage or pathology has healed, but some painful conditions, such as rheumatoid arthritis, peripheral neuropathy, cancer and neuropathic pain, as well as complex regional pain syndrome, may persist for years.

Pain that lasts a long time is called chronic or per-

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sistent, and pain that resolves quickly is called *acute*. Traditionally, the distinction between acute and chronic pain has relied upon an arbitrary interval of time from onset; the two most commonly used markers being 3 months and 6 months since the onset of pain, though some theorists and researchers have placed the transition from acute to chronic pain at 12 months [*Eisenberger N, Lieberman M, 2005*].

The International Association for the Study of Pain defines chronic pain as "pain that has persisted beyond normal tissue healing time" that takes (in absence of other criteria) for 3 months [*Merskey H, Bogduk N, 1994*]. However, some chronic pain disorders are characterized by recurrent short acute episodes and exacerbations such as trigeminal neuralgia and rheumatoid arthritis.

Chronic pain can be produced after tissue damage (or inflammation), nerve damage, and after alteration of normal neural function. Chronic persistent pain leads to chemical, functional, and anatomical changes throughout the nervous system (in the periphery, spinal cord, and brain) [*Woolf C, 1996; Coda B, Bonica J, 2000; Turk D, Okifuji A, 2001; Thienhaus O, Cole B, 2002*]. In chronic pain states, the nervous system is altered to produce spontaneous pain that arises without any apparent peripheral stimulus as well as a hypersensitivity to peripheral stimuli [*Woolf C et al., 1998; Merskey H, Bogduk N, 1994*]. Pain hypersensitivity potentiates hyperalgesia (the exaggerated and prolonged response to noxious stimulation) and allodynia (pain resulting from a stimulus that is normally non-painful) [*Treede R et al., 2008*]. Reduced descending inhibition in the central nervous system results in increased peripheral noxious signals that provide messages to the brain, and an increased experience of pain [*Paice J, 2003; Woolf C, 2011*].

Neuropathic pain. It's well known for now, that neuropathic pain is pain caused by damage or disease affecting the somatosensory nervous system [*Torrance N et al., 2006*] and may result from disorders of the peripheral nervous system or the central nervous system. Thus, neuropathic pain may be divided into peripheral neuropathic pain, central neuropathic pain, or mixed (peripheral and central) neuropathic pain. Neuropathic pain may be associated with abnormal sensations called dysesthesia or pain from normally non-painful stimuli (allodynia). So, neuropathic pain is caused by damage or disease affecting any part of the nervous system involved in bodily feelings (the somatosensory system).

Peripheral neuropathic pain is often described as "burning", "tingling", "electrical", "stabbing", or "pins and needles". It may have continuous and/or episodic (paroxysmal) components. The latter resemble stabbings or electric shocks, which are typical, for example, for trigeminal neuralgia. Common qualities include burning or coldness sensations, "pins and needles" sensations, numbness and itching, as in diabetic polyneuropathy. Current studies testify that up to 7-8% of the European population is affected, and in 5% individuals it may be severe [*Torrance N et al., 2006*].

Central neuropathic pain is found in spinal cord injury, multiple sclerosis, and some strokes [*Foley P et al., 2013; Urch C, Suzuki R, 2008*]. Aside from diabetes and other metabolic conditions, the common causes of painful peripheral neuropathies are herpes zoster infection, HIV-related neuropathies, nutritional deficiencies, toxins, remote manifestations of malignancies, immune mediated disorders and physical trauma to a nerve trunk [*Portenoy R, 1989*]. Neuropathic pain is common in cancer as a direct result of cancer on peripheral nerves (e.g., compression by a tumor), or as a side effect of chemotherapy (chemotherapy-induced peripheral neuropathy), radiation injury or surgery [*Tzatha E, DeAngelis L, 2016*]. Neuropathic pain can be very difficult to treat with only some 40-60% of people achieving partial relief [*Dworkin R et al., 2007; Urch C, Suzuki R, 2008*].

Favored treatments are certain antidepressants, anticonvulsants (pregabalin and gabapentin), and topical lidocaine. Opioid analgesics are recognized as useful agents but are not recommended as first line treatments [*Paice J, 2003*].Despite of the fact that opioids are not considered first line treatments in neuropathic pain they remain the most consistently effective class of drugs for this condition. Due to the risk of addiction or diversion, opioids must be used only in appropriate individuals and under close medical supervision.

Botulinum toxin type A (BTX-A) is best known by its trade name, Botox. Local intradermal injection of BTX-A is helpful in chronic focal painful neuropathies. The analgesic effects are not dependent on changes in muscle tone. Benefits persist for at least 14 weeks from the time of administration. The utility of BTX-A in other painful condi-

tions remains unproven [*Dworkin R et al., 2007*].

Topical agents. In some forms of neuropathy, especially post-herpetic neuralgia, the topical application of local anesthetics such as lidocaine is reported to provide relief. A transdermal patch containing lidocaine is available commercially in some countries.

Repeated topical applications of capsaicin are followed by a prolonged period of reduced skin sensibility referred to either desensitization or nociceptor inactivation. Capsaicin not only depletes substance P but also results in a reversible degeneration of epidermal nerve fibers. Nevertheless, benefits appear modest with standard (low) strength preparations, and topical capsaicin can itself induce pain [*Nolano M et al., 1999; Dworkin R et al., 2007*]. That's why current treatment of neuropathic chronic pain is far beyond of perfection and demands further researches directed to the elucidation of mechanisms underlying the pain induction with the aim of conducting further effective management.

Vitamin D. There appears to be a worldwide trend towards nutritional vitamin D deficiency that is causing a serious health concern [*Adams J, Hewison M, 2010*]. Estimates of vitamin D deficiency vary across the world and within countries themselves. It has been estimated that a wide range (20-100%) of elderly men and women living in the community in the United States, Canada, and Europe are vitamin D deficient [*Holick M, Chen T, 2008*].

The major cause of vitamin D deficiency is decreased sun exposure that limits the synthesis of vitamin D [*Holick M et al., 2011*]. This could occur through stringent application of sunscreen, or active avoidance of the sun for presumed health reasons [*Sinha A et al., 2013*]. Women who cover themselves for cultural or religious reasons are at risk of vitamin D deficiency as well [*Glerup H et al., 2000*]. People with naturally dark skin tone appear to require at least three to five times longer sun exposure to make the same amount of vitamin D as a person with a white skin tone [*Holick et al., 2011; Sinha A et al., 2013*]. People with dark-colored skin who live far from the equator are at high risk of developing a vitamin D deficiency. However, there is also evidence that dark-skinned people can be at risk even in sunny climate, such as Australia, in a large sample of women in residential care in three of the states, mean vitamin D3 serum level was below 50 *nmol/L,* and in high-level care – below 31.4 *nmol/L* [*Sinha A et al., 2013*]. Age, gender, and race can be factors associated with risk of vitamin D deficiency. In the United States, serum levels of 25-hydroxyvitamin D (OH) (*nmol/L*) among 15 adult participants more than or equal to 18 years of age were evaluated [*Zadshir A et al., 2005*]. White men and women (83.0 and 76.250 *nmol/L,* respectively) had higher mean serum levels of 25(OH)D than Hispanic men and w omen (68.3 *nmol/L* and 56.7 *nmol/L*, respectively; $p<0.0001$), and had higher mean serum levels of 25(OH)D than black men and women (52.2 and 45.*3 nmol/L*, respectively; $p<0.0001$) as well. The prevalence of both mild to moderate and severe deficiency of 25(OH)D was higher among women ($p<0.0001$) and in minority populations ($p<0.0001$). However, even amongst white men, 34% were found to have low vitamin D3 levels [*Zadshir A et al., 2005*].

The elderly are particularly at risk as the body's ability to synthesize vitamin D in the skin decreases with aging [*Holick M et al., 2011*]. Being less mobile and often confined indoors, their exposure to sunlight can be limited. This applies particularly to institutionalized individuals [*Zadshir A et al., 2005*]. Neonates may be deficient due to low serum maternal vitamin D3 levels caused by multiparity and by dark maternal skin with restricted sun exposure. Exclusively breast-fed infants, particularly if dark skinned with little exposure to sunlight, are at risk as well [*Wagner C et al., 2008*].

A number of studies have suggested a link between low levels of 25(OH)D and the incidence of both acute and chronic pain. Non homogenous clinical studies of vitamin D supplementation in patients with known vitamin D deficiency have shown mixed results in improving pain scores. Vitamin D is cheap and has relatively only few adverse effects. Its use in chronic pain could therefore be advocated even if the effectiveness wasn't significant [*Atherton K et al., 2009; Shipton E, Shipton E, 2015*]. Vitamin D is a fat-soluble secosteroid, the most common forms of which are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol), which are collectively known as calciferol. It can be produced endogenously by humans in the skin from a precursor 7-dehydrocholesterol which is converted to vitamin D3 after exposure to ultraviolet light. Vitamin D can also be obtained

from a limited number of dietary sources; vitamin D2 from plant origins and vitamin D3 from animal origins. However, there is no food able to accomplish dietary need of calciferol.

It is established, that vitamin D exerts hormonal, immunological, as well as neuroanalgesic influences on pain manifestation, thereby potentially playing a role in the etiology and maintenance of chronic pain states and associated comorbidities. Calcitrol (1.25(OH)2D3) is an active vitamin D metabolite. It plays an important role in many biological processes, especially in bone metabolism and muscle function. Vitamin D supplementation has been found to improve bone density and musculoskeletal symptoms [*Gloth F et al., 1995; Shipton E, Shipton E, 2015*]. Vitamin D deficiency causes muscle weakness and pain in children and adults. Low bone density and osteopenia appear to contribute to chronic pain in patients with cystic fibrosis, and are related to low vitamin D3 levels [*Hayes M et al., 2011*]. Low vitamin D levels have been found to be related to heightened central sensitivity (particularly augmented pain processing) upon mechanical stimulation in chronic pain patients [*Von Kanel R et al., 2014*]. Migraine and fibromyalgia represent a central neural hypersensitivity [*Woolf C, 1996; Bartley J, 2009*]. Activated microglia, astrocytes, and spinal glia release a variety of neuroexcitatory substances (nitric oxide, excitatory amino acids, proinflammatory cytokines, and mediators) that potentially initiate and maintain the neural hypersensitivity state seen in chronic pain states [*Woolf C, 1996*]. As a neuroactive steroid, vitamin D can modulate neuronal excitability including spontaneous regular firing, action potential duration, intrinsic excitability and sensitivity to neurotransmitters (gonadotropin-releasing hormone, opioidergic neurons) as well as to neurotransmitter receptors such as gamma-aminobutyric acid and N-methyl-d-aspartate [*Mensah-Nyagan A et al., 2009*]. Vitamin D plays a fundamental role in astrocyte detoxification pathways, and thereby exerts a neuroprotective effect [*Garcion E et al., 2002*]. Vitamin D suppresses tumor necrosis factor alpha, macrophage colony-stimulating factor, and nitric oxide synthase in astrocytes and microglia. Macrophage colony-stimulating factor is a cytokine that stimulates proliferation, differentiation, and survival of monocytes and macrophages. Macrophages can release many inflammatory mediators, including proinflammatory cytokines, particularly tumor necrosis factor alpha and interleukin-1 beta, nerve growth factor, nitric oxide and the prostanoids [*Marchand F et al., 2005*]. By limiting macrophage colony-stimulating factor, vitamin D has the potential to inhibit pain pathways. The presence of vitamin D receptors, 1α-hydroxylase, and vitamin D binding protein in the hypothalamus is suggested as the mechanism by which vitamin D deficiency is implicated in the pathophysiology of various primary headache disorders. Vitamin D upregulates the synthesis of neurotrophins such as nerve growth factor, neurotrophin 3, and glial cell line-derived neurotrophic factor, whereas neurotrophin 4 is down-regulated [*Marchand F et al., 2005; Leung L, Cahill C, 2010*]. Through this system, vitamin D can potentially affect the development of neurons, as well as their maintenance and survival. Nerve growth factor is a well-established inflammatory mediator and has direct effects on the sensory nerve endings causing hypersensitivity, amplification of sensory input signals, and enhanced innervation of injured tissue [*Woolf C, 1996; Prakash S et al., 2010*].

Now it is proven, that people who take anticonvulsants, glucocorticoids, antidepressants, rifampicin, or highly active antiretroviral drugs are at higher risk of developing vitamin D insufficiency [*Sinha A et al., 2013*], because these drugs enhance the catabolism of 25(OH)D and of 1.25(OH)2D3 [*Holick M et al., 2011*].

Clinical supplementation with vitamin D

Vitamin D supplementation increases 25(OH)D serum levels and can therefore potentially correct the effects of vitamin D deficiency [*Straube S et al., 2009*]. The impact of dietary intake on vitamin D metabolism and the reversibility of chronic pain with normalization of serum 25(OH)D levels remain unclear at present. Variation in vitamin D dosing schedules could have a profound effect in the outcome of clinical trials because of the short circulating half-life of intact vitamin D [*Hollis B, Wagner C, 2013*]. The cellular accessibility of the parent compound vitamin D, as well as that of 25(OH)D, is important when considering supplementing with vitamin D in a clinical trial. 25(OH)D and vitamin D can be internalized by cells through one of two mechanisms. Free 25(OH)D can enter the cell by diffusion across the cell mem-

brane or by the vitamin D-binding protein receptor-mediated endocytosis by the coreceptors of megalin and cubilin [*Brannon P, 2012*]. Most circulating vitamin D and 25(OH)D are transported in the blood bound to vitamin D-binding protein. The 25(OH)D is tightly bound to vitamin D-binding protein. The amount of vitamin D-binding protein and its effect on free versus bound 25(OH)D could inversely affect the free 25(OH)D available for uptake by diffusion into cells [*Brannon P, 2012*]. A wide variety of schedules have been used in published clinical trials [*Vieth R et al., 2001; Trivedi D et al., 2003; Holick M, Chen T, 2008*]. However, clinical research studies have shown that supplementary doses (less than 1000 *IU* per day) of vitamin D results in only modest increases in serum levels of 25(OH)D that may be inconsequential for achieving optimal serum levels of 75 *nmol/L* [*Holick M, Chen T, 2008*]. It has been suggested that optimal benefits from vitamin D supplementation would be achieved through a daily dose of vitamin D to ensure stable circulating serum levels over time [*Hollis B, Wagner C, 2013*].

Once-daily dosing appeared to be more effective than monthly or 3-monthly dosing in prevention of respiratory tract infections [*Bergman P et al., 2013*]. However, poor adherence with daily dosing of medications and supplements is widely appreciated. Thus, higher and longer interval dosing is likely to result in better adherence. Weekly dosing would be preferable over month due to the 3-4 week half-life of 25(OH)D [*Binkley N et al., 2011; Shipton E, Shipton E, 2015*]. Recent studies have revealed, that supplementation with either 1200 *IU* daily or 50.000 *IU* weekly of vitamin D for 3 months has improved the serum 25(OH)D level in both groups by almost 40%, but the difference in improvement was not statistically significant between the subgroups [*Binkley N et al., 2011*]. Four-monthly vitamin D supplementation has also resulted in positive outcomes [*Hollis B, Wagner C, 2013*]. Studies have shown that time to equilibrium for vitamin D supplementation is generally 3 to 6 months [*Shipton E, Shipton E, 2015*].

Vitamin D has relatively few adverse effects. Excessive inputs of vitamin D potentially produce renal stones, and renal calcification, with kidney failure, and oftimes death. Excessive vitamin D intake (over 50.000 *IU* per day) is rarely associated with hypercalcemia. Doses of 10.000 *IU* of vitamin D3 per day for up to 5 months have not been found to cause toxicity [*Vieth R, 2004; Heaney R, 2008*].

Evaluation of clinical studies regarding the use of vitamin D for the treatment of chronic pain was previously undertaken by a series of authors. A review of randomized double-blind trials of vitamin D supplementation compared with placebo was published in 2009. The aim was to determine the efficacy of vitamin D in the treatment of chronic pain conditions. Only four studies (with a total of 294 participants) were included; eleven trials were excluded due to poor methodological design, or because not all participants received a clearly defined chronic pain diagnosis [*Straube S et al., 2009; 2010*; *Shipton E, Shipton E; 2015*]. Patients were supplemented with varying amounts and formulations of vitamin D for periods ranging from 16 weeks to 12 months. In summary, out of the four trials reviewed, the benefit of using vitamin D in chronic pain treatment was only shown in one trial. In the other three trials, there was no significant beneficial effect of vitamin D over placebo. Adverse effects of treatment were infrequent, and occurred at the same rates in vitamin D and placebo groups [*Shipton E, Shipton E; 2015*].

It should be mentioned, that the studies were conducted with randomized double-blind trials only in 5 cases from 22 scientific publications during the analysis of modern literature data referring to the results of treatment with vitamin D in patients with chronic diseases associated with pain syndrome. Vitamin D treatments involved monthly equivalent doses between 1200 and 400.000 *IU*. Fourteen studies were in musculoskeletal pain, five in chronic widespread pain or fibromyalgia, one in diabetic subjects with neuropathic pain, one addressing an unusual hyperesthetic pain syndrome, and one case in various conditions. Duration of treatment was from a few days to 12 months, although most studies lasted 2 months or more. Treatment studies included 733 patients. Randomized double-blind trials involved 229 patients, of whom only 22 (10%) were in a trial with a significant improvement in treatment with vitamin D, and then only on a pain mobility measure. Analgesic effect was absent in 207 patients during treatment with vitamin D [*Shipton E, Shipton E, 2015*]. There was also no apparent correlation between significant improvement in pain with vitamin D and with a particular preparation. There was no persuasive evidence of lower levels of 25(OH)D in those with chronic pain than

in the control populations. There was a striking contrast in treatment effects between randomized, double-blind trials that minimized bias and those with designs known to be subjected to bias. Only 10% of patients were in trials showing a benefit of vitamin D treatment in previous case; in the latter – 93% [*Straube S et al., 2009*]. Present study highlighted the need for further randomized double-blind placebo-controlled trials.

The interest to vitamin D deficiency and pain was strongly influenced by the severe pain syndrome in particular old female patient, who was diagnosed with Alzheimer disease and severe osteoporosis, in 2013. By that time in Armenia the measurements of vitamin D level in blood were not demanded and clinical laboratories did not perform it in their routine practice. Performed abroad analyses of vitamin D in this patient found extremely low levels, and effective treatment with vitamin D supplementation was started. Currently at least five independent laboratories in Armenia are performing vitamin D measurement.

The data of about 1000 patients, collected during the last three years, suggest that despite of solar nature of the country with estimated average of 2700 hours of sunlight a year, a quite low level of vitamin D is observed in specific group of individuals (within the *14 nmol/L*; SD +/- *12 nmol/L*). Patients with pain syndromes show lower levels of vitamin D (8 +/- 6 *nmol/L*, compare to general population). Due to limited possibilities, patients previously treated with anticonvulsants, steroids or antidepressants were not divided into cohorts. The data of quantitative parameters of pain reduction in patients after supplementation with vitamin D weren't processed, however general state of the patients significantly improved, that was also manifested in reduction of the number of pain killers and subjective pain sensation.

It is noteworthy, that despite of many studies, there is insufficient high-quality evidence for a definitive effect of vitamin D in neuropathic or chronic pain. However, a trend appears in a positive direction indicating a beneficial effect of vitamin D over placebo in chronic pain.

Significant improvement of sleep, mood, pain levels, well-being, and various aspects of quality of life with vitamin D supplementation have been shown [*Shipton E, Shipton E, 2015*]. Whilst there is a growing body of both clinical and laboratory evidence pointing to a potential relationship between low levels of 25(OH)D and chronic pain, it is not possible to state conclusively that vitamin D deficiency is directly linked to the etiology or maintenance of chronic pain states. The scientific evidence for the use of vitamin D as a treatment option for chronic pain is limited at present due to low-quality designs, and due to the lack of randomized controlled trials.

A number of questions remain with regard to supplementation of vitamin D in patients with chronic pain [*Coda B, Bonica J, 2000*]. Metabolism of vitamin D action needs to be further elucidated including extra-renal activation and catabolism, distribution and mobilization from body pools, and its interaction with relevant genetic polymorphisms. There remains some debate over the precise definition of vitamin D deficiency or insufficiency based on the serum levels of 25(OH)D. The influence of age and body weight on the variability of the response of serum levels of 25(OH)D to intake needs to be clarified [*Brannon P, 2012*]. More focused research is necessary involving larger double-blind randomized controlled trials. These need to be stratified by baseline 25(OH)D levels, type of pain, and the use of adequate doses of vitamin D based on serum levels. The optimal dose and length of time for supplementation need to be assessed as well.

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