

Effects of vitamin B₁₂ supplementation on pain relief in certain diseases – a literature review

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Based on current scientific reports, vitamin B₁₂ (cobalamin), used in the treatment of pernicious anemia, may be used as a pain reliever. It has been shown to be effective in the treatment of different sorts of pain, including diabetic neuropathic, musculoskeletal, abdominal, back and spine ones, but also pain in Alzheimer's disease and pain ailments resulting from the development of neoplasms. In addition, it helps regeneration of the sensory nerves and relieves pain in eye diseases, for example in dry eye syndrome. This review summarizes recent research reports on pain-relieving properties of vitamin B₁₂.

Key words: vitamin B₁₂, methylcobalamin, pain pharmacology

Received: 20 December, 2021; **revised:** 25 January, 2022; **accepted:** 18 March, 2022; **available on-line:** 22 April, 2022

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Acknowledgements of Financial Support: Monika Stompor-Goraćy acknowledges support from the National Science Centre NCN Poland, Grant SONATA 16 number: 2020/39/D/NZ9/02023.

Abbreviations: CMP, cytidine monophosphate; CRPS, complex regional pain syndrome; ET1, DED, dry eye disease; ET1, endothelin 1; HC, haptocorrin; IL-1 β , interleukin 1 β ; IL-6, interleukin 6; IL-8; interleukin 8; UTP, uridine-5'-triphosphate; RCT, randomized controlled trial; TCBS, transcobalamins; TNF- α , tumor necrosis factor α , TRPV1, transient receptor potential vanilloid 1; VAS, Visual Analogue Scale

INTRODUCTION

Due to the increasing development of lifestyle diseases, the daily diet ingredients, vitamins and plant antioxidants are at the center of interest of the researchers all over the world, who look for effective substances with anti-inflammatory and analgesic properties (Stompor *et al.*, 2021; Su *et al.*, 2021). There are known pain-relieving properties of plant secondary metabolites, such as flavonoids (also in combination with metronidazole – clinical trials) (Rabelo *et al.*, 2021) or quinazolines (Ranni & Bathula, 2015).

Vitamin B₁₂ (C₈₈H₈₈O₁₄N₁₄PCo) known also as cobalamin or by the common name “red vitamin” is a water-soluble vitamin that is consumed with food. It is essential for the process of erythropoiesis, synthesis of DNA and RNA in erythroblasts and for normal functioning of the nervous system. Cobalamin functions as a cofactor for methionine synthase and methylmalonyl-CoA mutase. Vitamin B₁₂ was discovered during the search for an effective drug against the pernicious anemia (Julian *et al.*, 2020). It belongs to the group of corrinoids, which structures consist of four conjugated pyrrole rings joined into a macrocyclic ring. The pyrrole rings are connected to each other by methine bridges. The first ring is directly conjugated with the fourth one by the C α -C α bond.

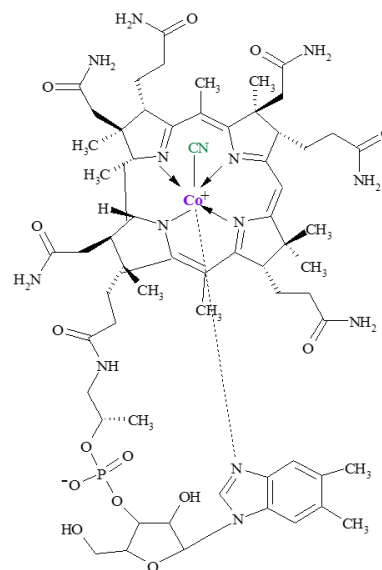


Figure 1. Chemical structure of vitamin B₁₂.

The system is bound to the centrally located cobalt atom in the +3-oxidation state. Above the macrocyclic system there is a cyano group in the perpendicular orientation, and beneath there is a 5,6-dimethylbenzimidazolyl (5,6-dimethylbenzimidazolyl-ribofuranosyl-3'-phosphate) group. Both ligands coordinate to the cobalt atom. In nature vitamin B₁₂ is found in the form of deoxyadenosylcobalamin (coenzyme B₁₂) and methylcobalamin. A stable form of vitamin B₁₂ is cyanocobalamin, which is produced on an industrial scale and cannot be found in nature.

Biochemically, vitamin B₁₂ is known to have a regulatory function in metabolism of carbohydrates, proteins and lipids. In addition, it plays a vital role in the production of healthy red blood cells, preventing anemia (Didangelos *et al.*, 2021). It has influence on the level of homocysteine, which elevated concentration in blood may lead to atherosclerosis (Celik *et al.*, 2018). It has been shown that an 8-week adjuvant therapy with vitamin B₁₂ in patients after replantation of severed fingers effectively improved the recovery of neurological functions in fingers, restoring sense of touch and pain perception in over 80% of the patients (Yu *et al.*, 2018).

Due to the fact that the excess of vitamin B₁₂ is stored in the liver and in muscles, its deficiency is rarely observed. The symptoms include anemia and neurological disorders (Buesing *et al.*, 2019), which may lead to development of neurodegenerative diseases, such as

Alzheimer's disease (Oh & Brown, 2003) and to megaloblastic anemia, resulting from malabsorption caused for example by enteritis (Fukuda *et al.*, 2020). It was demonstrated that bacterial infections, e.g., *Helicobacter pylori*, are risk factors for vitamin B₁₂ deficiency (Civan 2020). Moreover, deficiencies in testosterone and vitamin B₁₂ are often observed in patients with chronic testicular pain (Cui & Terlecki, 2018). When the deficiencies were corrected, over 80% of patients reported pain relief. An important role of vitamin B₁₂ was also indicated in etiology of such diseases as atherosclerosis, heart disorders and multiple sclerosis. According to Gang and others (Gang *et al.*, 2016) methylcobalamin combined with lidocaine may be an effective method to treat acute ophthalmic herpetic neuralgia and to improve cutaneous healing of the affected area.

Hypervitaminosis B₁₂ (hypercobalaminemia) is also harmful to human body, leading to acute or chronic hematological diseases, liver disorders, renal failure or eosinophilia (Zulfıqa *et al.*, 2019). The nutrient requirements for vitamin B₁₂ depend on age and health of individuals. The recommended daily intake of cobalamin in adults for normal body functioning is estimated to be 2.4 µg/day. In pregnancy it is 2.6 µg/day, and in lactating women 2.8 µg/day (Shipton *et al.*, 2015). It was as early as in the 50th of 20th century when the possibility of using vitamin B₁₂ to relieve pain (not only related to cobalamin deficiency) was studied (Pavlov *et al.*, 2019).

The majority of hypercobalaminemia (high serum vitamin B₁₂ levels, defined by a rate above 950 pg/ml (701 pmol/l)) cases pathophysiologically involve a qualitative and/or quantitative disorder of transcobalamins (TCBs) – the proteins belonging to the haptocorrin (HC) superfamily, which play the key role in tissue and hepatic uptake of vitamin B₁₂.

The vitamin B₁₂ malabsorption syndrome may be also caused by mutations in the genes coding for either of the subunit's receptors like a cubilin.

According to the Couderc and others (Couderc *et al.*, 2020) hypercobalaminemia may be potential marker in older cancer patients. Similarly, the elevation of serum cobalamin levels of myeloid malignancies and a lymphatic malignancy was described by Dekker and others (Dekker *et al.*, 2020).

Pain is one of the first symptoms that cause anxiety in patients and motivate them to visit their physicians (Siler *et al.*, 2019). This is the complex interplay between nerve endings and the central nervous system (Lee *et al.*, 2020, Żylicz & Krajnik, 2003). Pain causes great somatic discomfort, which is followed by an emotional reaction (Wang & Mullallay, 2020). There are various types of pain. The most common include acute, chronic and neuropathic pains. The range of pain intensity depends on the type of disability and current and previous diseases. Persistent pain is often associated with oncological diseases, also after the oncological therapy is finished. In this case patients suffer from nociceptive pain (including visceral one) and neuropathic pain (Kurtin & Fuoto, 2019). Nociceptive pain is caused by activation of sensory receptors (Bennett *et al.*, 2019), whereas neuropathic pain results from lesion or disease affecting the somatosensory system.

Neuropathic pain described in this review concerns the pain associated with cancer diseases, diabetes and alcoholism (Julian *et al.*, 2020). All these diseases decrease the level of vitamin B₁₂ in the body (Milić *et al.*, 2010). Neuropathic pain can be sudden (paroxysmal) and spontaneous. It is estimated that it occurs in 10% of population. One of the methods of relieving pain associated

with chronic diseases that require long-term treatment is vitamin B₁₂ supplementation. Moreover, vitamin B₁₂ deficiency is related to chronic ocular pain, for example in dry eye disease (DED), which occurs due to changes in the eye sensory system. Topical or parenteral vitamin B₁₂ supplementation may improve corneal epithelialisation and reinnervation and alleviate neurosensory symptoms (Ozen *et al.*, 2017).

The aim of this review is to summarize results of the research on effect of vitamin B₁₂ supplementation on the treatment of various kinds of pain, such as isotretinoin-induced musculoskeletal pain, low back pain, pain associated with aphthous stomatitis, pain associated with Alzheimer's disease and complex regional pain syndrome.

MATERIALS AND METHODS

A systematic literature review was prepared using PubMed database and other available research papers found in databases such as *Scopus*, *Web of Science* and others. The review comprises the research papers concerning the efficacy of vitamin B₁₂ supplementation as a safe method of pain relieving. The databases were searched using the following key words: „vitamin B₁₂”, „pain”, „pain pharmacology”, „deficiency”, „neuropathy”. The articles were chosen according to the following acceptance criteria: they should describe the role of vitamin B₁₂, consequences of its deficiency and methods of its supplementation in the treatment of pain associated with certain diseases. The literature included the results of clinical trials in humans, written either in English or in Polish. We have taken into consideration only the articles that have at least their abstracts available. The review was based on papers published in the past. No ethical questions are raised by this review.

DATA ANALYSIS

Treatment of diabetic peripheral neuropathy using vitamin B₁₂

Treatment of pain associated with diabetic neuropathy is still a challenge to modern palliative medicine. Diabetic neuropathies are complications of diabetes that affect nervous system. The most common is diabetic peripheral neuropathy, referring to damage in fibers of sensory nerves located in the skin and muscles. Diabetic peripheral neuropathy is associated with such symptoms as foot pain, tingling and numbness of the limbs. An important aspect in preventing neuropathic disorders is proper supplementation with vitamins B because their absorption is often impaired due to coexisting diseases.

In an open-label randomized controlled trial (RCT) in patients with diabetic neuropathy the treatment with vitamin B₁₂ administered twice a week at a dose of 2000 µg to a group of 50 patients was compared with daily administration of 10 mg oral nortriptyline to the same number of patients. After three months of the trial the pain was assessed using Visual Analogue Scale (VAS). It was observed that the change in the group treated with vitamin B₁₂ was significantly greater compared with the nortriptyline group. In neither group any side nor adverse effects were observed (Julian *et al.*, 2020).

In another trial in 10 patients suffering from uraemic diabetic neuropathy vitamin B₁₂ was administered intravenously three times a week for six months. After this time, a certain improvement in pain grading scale was

observed within this group, compared with patients with polyneuropathy secondary to uraemia and diabetes who were subjected to haemodialysis (Julian *et al.*, 2020).

Whereas Aftab and others (Aftab *et al.*, 2019) conducted the study in 310 patients suffering from diabetic peripheral neuropathy, diabetes and other metabolic disorders, who were subjected to a four-week combination therapy involving vitamins B₁ (100 mg), B₆ (100 mg) and B₁₂ (200 mcg), administered orally twice a day. The treatment proved effective in over 86% of patients.

The preclinical *in vivo* studies in rats carried out by the research team of He *et al.*, (2020) showed that vitamins B₁, B₆ and B₁₂ administered intraperitoneally at the doses of 10, 100 and 2 mg/kg, respectively, significantly reduced streptozotocin-induced neuropathic pain without affecting the level of blood glucose. In addition, the treatment suppressed neurochemical alterations: expressions of P2X₃ and TRPV1 in nociceptive neurons of dorsal root ganglion and decreased levels of spinal pro-inflammatory cytokines such as IL-1 β and TNF- α .

The research group of Didangelos and others (Didangelos *et al.*, 2021) measured the levels of vitamin B₁₂ in diabetic neuropathy with a Cobas e 602 analyzer. The patients taking part in the study were treated with oral antidiabetic drugs such as metformin along with insulin analogs. The participants were randomly assigned to a group of 44 patients receiving vitamin B₁₂ orally and a control group of 46 patients receiving placebo. The drugs were administered to both groups daily for 12 months. In the actively treated group, the level of vitamin B₁₂ increased from 232.0 to 776.7 pmol/L. In addition, it was observed that sural nerve conduction velocity, sural nerve action potential, pain score and quality of life significantly improved in the treated group. Also, the other clinical studies that metformin affects cobalamin level in patients were confirmed (Aroda *et al.*, 2016).

In a similar study vitamin B₁₂ combined with carnitine, superoxide dismutase and α -lipoic acid were evaluated as pain-relieving therapeutics. The patients were randomized to a treated group (43 patients) and a control group (42 patients) receiving placebo. The treated group received a combination of four medicines in one tablet. After 12 months of the treatment significant improvement in pain and the rest of indices of peripheral neuropathy was observed in the treated group (Karlafti *et al.*, 2020).

The effectiveness of gabapentin Plus B Complex (B₁/B₁₂) *versus* pregabalin for treating painful diabetic neuropathy was studied by Alvarado and Navarro (Alvarado & Navarro, 2016).

Vitamin B₁₂ as an effective method to treat alcoholic polyneuropathy

Alcoholic polyneuropathy is a disorder caused by the long-term alcohol abuse, leading to the loss of vitamins and micronutrients that are necessary for normal functioning of the body. These results in nerve damage and demyelination, which affect transmission of nerve impulses. The first symptoms of the disease include numbness and tingling in limbs, tactile and pain sensory impairments.

In a randomized controlled trial (RCT) participated 84 patients, who were divided into three treatment groups. The first group received vitamin B₁ (40 mg), the second one vitamin B₆ (90 mg) and vitamin B₁₂ (250 μ g) and the third one placebo. All three groups showed improvement in pain measured by the McGill pain questionnaire,

however with no significant differences between them (Julian *et al.*, 2020).

Whereas, in the other study a significant difference was observed between the placebo group C (85 patients) and the groups which for 12 weeks, three times a day received as follows: group A (83 patients) – vitamin B₁ (250 mg), vitamin B₂ (10 mg), vitamin B₆ (250 mg), and vitamin B₁₂ (250 mg); group B (88 patients) – the same medications as group A plus folic acid (1 mg). Pain intensity was assessed using the McGill pain questionnaire. In groups A and B significantly greater reduction in pain was observed compared to group C (placebo). Addition of folic acid in group B had no significant effect – in groups A and B the results were similar (Julian *et al.*, 2020).

Vitamin B₁₂ in complex regional pain syndrome (CRPS)

Complex regional pain syndrome (CRPS) is a rare disease which manifests as pain and swelling of a limb, disturbed blood flow in the affected area, skin trophic changes and osteoporosis (Bruehl 2015). This is a chronic limb disease that proceeds with exacerbations and belongs to algodystrophic syndromes (Giannotti *et al.*, 2016). Its symptoms include burning pain and swelling in the distal part of the affected limb, skin changes and contractures in the joint area.

The study was performed in a group of 5 patients with diagnosed complex regional pain syndrome, suffering from such symptoms as motor disturbances in the upper extremities, along with hyperalgesia and allodynia. The main symptom of this disease was pain, diagnosed as the neuropathic pain. In the conventional therapy non-steroidal anti-inflammatory drugs are usually used. The intensity of pain was measured by the visual analog scale (VAS). The patients taking part in the study developed symptoms of the disease (CRPS) after synovectomy, osteotomy, rhizarthrosis and carpal tunnel syndrome. During the period from January 2018 to September 2019 the pain in patients with CRPS was successfully reduced. Physical therapy along with TIOBEC® and B-group vitamins, including Vitamin B₁₂ and C-group vitamins alleviated pain and decreased oedema, and also alleviated such symptoms as erythema, sweating and stiffness (Fernández-Cuadros *et al.*, 2020).

Treatment of musculoskeletal pain with vitamin B₁₂

The study was conducted in 6 patients with acne vulgaris, suffering from musculoskeletal pain after the treatment with isotretinoin, which is reported to have harmful effects on the skeletal system and in some cases leads to osteoporosis. The cause of this disease is hyperhomocysteinemia, induced by retinoids, which are vitamin A derivatives, and it is suggested that vitamin B₁₂ and folic acid supplementation can lower the level of homocysteine in plasma. Four of the patients reported back pain and two reported leg pain. Two of the patients who were treated with isotretinoin in the past discontinued that treatment due to musculoskeletal pain. There was no other past history for all of the patients. In this study the patients were administered 1 mg of folic acid daily and vitamin B₁₂ twice a week for six months. After six weeks of the treatment the musculoskeletal pain disappeared (Feily, 2019).

Table 1 presents the treatment and evolution of patients. The study showed that supplementation with vitamin B₁₂ and folic acid reduced hyperhomocysteinemia and musculoskeletal pain.

Table 1. General data and patient test results, patient treatment and evolution in musculoskeletal pain – Author's own elaboration based on (Sil *et al.*, 2018)

Patient	Sex/Age (yrs)	Follow-up	Area of musculo-skeletal pain	Time of the pain after starting isotretinoin	History of pain after taking isotretinoin	Response to vit B ₁₂ and Folic acid
1	F/18	8 months	Back	Around 20 days after starting isotretinoin	Negative	Positive
2	F/21	6 months	Leg	Around 20 days after starting isotretinoin	Negative	Positive
3	F/24	8 months	Back	Around 45 days after starting isotretinoin	Positive	Positive
4	M/20	6 months	Back	Around 30 days after starting isotretinoin	Negative	Positive
5	F/29	8 months	Leg	Around 20 days after starting isotretinoin	Positive	Positive
6	F/22	6 months	Back	Around 20 days after starting isotretinoin	Negative	Positive

Tamaddonfard *et al.*, (2018) suggested that opioid receptors and cyclooxygenase pathway may be involved in antinociceptive activity of vitamin B₁₂. Vitamin B₁₂ (1.25, 2.50, 5.00 and 10.00 µg per rat) and diclofenac (12.50 and 25.00 µg per rat) significantly reduced a biphasic formalin-induced pain in rats. Significant antinociceptive effects were observed after combined treatment with diclofenac (6.25 and 12.50 µg per rat) and vitamin B₁₂ (0.63 and 2.50 µg per rat), respectively. Prior intracerebroventricular injection of naloxone (10.00 µg per rat) prevented vitamin B₁₂ (10.00 µg per rat) and diclofenac (25.00 µg per rat) induced antinociceptive effects.

Whereas Campbell and others (Campbell *et al.*, 2018) demonstrated that sublingual administration of vitamin B₁₂ (2500 mcg for 90 days) reduced pain and improved quality of life of women with breast cancer receiving endocrine therapy with aromatase inhibitors and suffering from musculoskeletal symptoms.

Vitamin B₁₂ in low back pain

In a randomized controlled trial (RCT) one group of patients received vitamin B₁₂ intramuscularly once a day at a dose of 1000 µg, while the second group received placebo. In both groups pain relief was noted, however in the group with vitamin B₁₂ supplementation a significant decrease in pain was observed (by 87%) (Buesing *et al.*, 2019).

In a similar study the treated group received 500 µg of methylcobalamin intramuscularly three times a week for 14 days and the control group received placebo. In both groups pain improvement was observed, but in the placebo group the result was insignificant, whereas in the treated group reduction of pain by 31% and functional improvement by 27% was reported (Scott Buesing *et al.*, 2019).

Vitamin B₁₂ supplementation in the treatment of aphthous stomatitis

Patients suffering from aphthous ulcers were divided into two groups and the test group received vitamin B₁₂, regardless of the initial vitamin B₁₂ levels in plasma, whereas the control group received placebo. After 2 days of the treatment pain reduction by 94% was observed in the test group, whereas no significant pain decrease

was noted in the control group (an average reduction by 65%) (Buesing *et al.*, 2019).

Vitamin B₁₂ in the treatment of abdominal pain in patients addicted to oral opioids

The cause of abdominal pain in patients taking part in the study by Sherkatbazazan and others (Sherkatbazazan *et al.*, 2019) was addiction to oral opioids. Too frequent use of opioids may lead to intestinal dysfunction, narcotic bowel syndrome and ileus. Vitamin B₁₂ effectively protects neurons from the opioid-induced damage through nerve regeneration. In a double-blind randomized clinical trial in patients addicted to oral opium 136 participants were divided into two groups. The first group received 75 µg of fentanyl intravenously, the second one 1 g of vitamin B₁₂ intramuscularly and 75 µg of fentanyl intravenously. The intensity of pain was measured using a visual analog scale (VAS) over the course of 120 min. The results showed that in the group receiving the combination of fentanyl and vitamin B₁₂ the abdominal pain improved permanently. The mean pain severity decreased from 7.94±1.24 to 6.62 after 10 minutes and to 1.52 after 120 min. It is worth noting that the patients in this group suffered from more intense pain at the onset of testing than in the group receiving fentanyl alone, where the mean pain severity was 7.13±1.11 (Sherkatbazazan *et al.*, 2019).

Vitamin B₁₂ in Alzheimer's disease

Alzheimer's disease is a worldwide disease associated with a decline of cognitive functions, affecting mainly elderly people. The patients suffer from psychotic symptoms and pain. It has been demonstrated that in Alzheimer's disease there are changes in the levels of cytokines, which are glycoproteins produced by the immune system to combat inflammatory disorders. The aim of the study was to evaluate the effect of vitamin B₁₂ combined with antipsychotic drugs such as risperidone and quetiapine on pain reduction and modulation of cytokines expression in patients with Alzheimer's disease. In addition, their effect on serum levels of IL-6 and IL-8, transforming growth factor TGF-β, tumor necrosis factor TNF-α and endothelin ET-1 were evaluated. The evaluation was done in healthy controls and in Alzheimer Disease Patients (test group). The pain intensity was

measured using VAS scale. It was demonstrated that antipsychotic drugs may affect cytokine levels. In patients with psychotic symptoms the treatment vitamin B₁₂ in combination with quetiapine decreased the pain (Vakilian *et al.*, 2018).

Vitamin B₁₂ in the treatment of spinal pain

Low back pain often arises from strains to the muscles in the lumbar region. It is associated with injuries and poor body mechanics. Naslauský Mibielli and others (Mibielli *et al.*, 2020) studied the effect of nucleotides in combination with vitamin B₁₂ or other B vitamins on pain alleviation. The pain was measured by the VAS method. The patients were divided into two groups. The first group (group A, 317 patients) received nucleotides with vitamin B₁₂, the second one (group B, the same number of patients) received B vitamins (B₁, B₆, B₁₂). The trial lasted for 60 days. After 30 and 60 days of the treatment a significant reduction in the VAS score was observed in both groups, but in group A the score reduction was greater and less cases of adverse side effects were noted (Naslauský Mibielli *et al.*, 2020).

Vitamin B₁₂ deficiency and shingles symptoms

Pain and itching are the main symptoms of shingles, which may lead to development of herpetic pain. As a result, patients suffer from sleeping disorders, depression, loss of weight and chronic fatigue syndrome. The level of vitamin B₁₂, which is used for neuropathic pain treatment and is responsible for peripheral nerve regeneration, was evaluated in order to establish whether its deficiency is associated with herpetic itching and pain. 53 patients with diagnosed shingles took part in the study, whereas 27 patients were included to the control group. It was found that vitamin B₁₂ levels in patients with herpetic pain were lower than in patients with herpetic itch and in the control group. These indicate that vitamin B₁₂ deficiency is associated with herpetic pain, but not with herpetic itch.

In the other randomized clinical trial, the efficacy of methylcobalamin in alleviation of pain associated with subacute ophthalmic herpetic neuralgia was studied. The ophthalmic branch of the trigeminal nerve is the site where significant neurotrophic activity of *Varicella zoster* is observed, the virus affecting mainly elderly people. The pain comes along with blistering rash. 105 patients took part in the study, with the pain intensity of 4 or more in the VAS scale. They were divided into three groups of 35 people each, depending on the way of administration of vitamin B₁₂ and lidocaine. The first group received a combination of methylcobalamin and lidocaine *via* local injections, the second one intramuscular methylcobalamin and local lidocaine injection and the third one oral vitamin B₁₂ and lidocaine local injection. The treatment lasted for 4 weeks. A significant reduction of pain was observed in 91% of patients receiving vitamin B₁₂ and lidocaine in local injection, which allowed reduction of painkillers administered to the patients. In the other groups alleviation of pain was reported in 66% of patients receiving intramuscular vitamin B₁₂ and local lidocaine injection and in 57% of patients who received oral vitamin B₁₂ and lidocaine local injection. Therefore, it was demonstrated that local injection of methylcobalamin results in significant pain relief in patients with subacute ophthalmic herpetic neuralgia and is superior to systemic administration.

Table 2. VAS pain scores before and after treatment (Han *et al.*, 2017).

Group	n	Before therapy	After therapy
Met+Acu group	49	5.57 ± 0.257	3.23 ± 0.170***ΔΔ
Control group	49	5.50 ± 0.244	4.25 ± 0.197***

****P* < 0.001, compared before and after therapy | ΔΔ*P* < 0.01, compared between the Met + Acu and control groups. Table – Author's own elaboration based on source (Han *et al.*, 2017).

Table 3. Effect of vitamin B₁₂ on worst and average pain at baseline and after treatment

Pain score difference	Baseline Mean (SD)	Post-intervention %Δ Mean (SD)	Mean diff (95% C.I.)	<i>P</i> -value
WPS	7.73 (1.74)	5.61 (2.56) -23.03	2.25 (2.73, 4.40)	.0003
APS	6.78 (1.44)	4.36 (2.12) -33.78	2.55 (2.15, 3.46)	<.0001

SD, Standard deviation; %Δ, Percent difference; WPS, Worst pain score; APS, Average pain score. Bold values are statistically significant. Table – Author's own elaboration based on source (Campbell *et al.*, 2018)

Methylcobalamin and acupuncture in multiple myeloma

Multiple myeloma is one of the most frequent hematologic cancers. Chemotherapy-induced peripheral neuropathy is a common side effect, which affects 30–60% of patients. The symptoms include excessive pain, walking impairment, dysesthesia, muscle weakness and atrophy, disappearance of deep tendon reflexes. Whereas the symptoms associated with autonomic nervous system include bradycardia, arrhythmia and orthostatic hypertension. A group of 98 patients participated in a clinical study aimed to evaluate the effectiveness of the treatment with vitamin B₁₂ in combination with acupuncture in relieving pain. The control group (49 patients) received methylcobalamin alone in a dose of 500 μg (intramuscular injections every second day, altogether 10 injections, followed by 500 μg oral methylcobalamin administration three times a day for two months). The second group was treated with vitamin B₁₂ used in the same way as above, accompanied by acupuncture. After 84 days of the treatment the pain was significantly alleviated in both groups (lower VAS scores), however a significantly higher decrease was observed in the group treated with methylcobalamin in combination with acupuncture – 85.5% of the patients. Whereas, in the control group a decrease in pain intensity was reported by 77.6% of the patients.

Vitamin B₁₂ in women with early stage breast cancer

Aromatase inhibitors are necessary medications in the treatment of breast cancer in postmenopausal women. However, for many patients this hormone therapy brings about unwanted side effects, such as musculoskeletal pain or joint pain and stiffness. In a phase II study 36 patients were receiving 2500 mcg of sublingual methylcobalamin daily for 90 days. Some adverse effects associated with taking vitamin B₁₂ were observed in the course of the study, which included nausea, diarrhea and dry mouth. Whereas pain was not considered as the side effect of methylcobalamin supplementation. Average pain scores improved by 34% after three months of the treatment. Moreover, an improvement by 23% in the worst pain was noted. The patients finished the chemotherapy

2.4 years earlier, which diminished the risk of the chemotherapy-related pain. However, they may have suffered from other diseases.

DISCUSSION

The research results presented above lead to the conclusion that vitamin B₁₂ consumed daily with food may support the treatment of many diseases or medical complications. Its deficiency or malabsorption may cause neurological, neuropsychological and hematological disorders (Pavlov *et al.*, 2019). In one of the studies a 62-year-old Japanese woman was diagnosed with vitamin B₁₂ deficiency, anemia and polyneuropathy due to chronic radiation enteritis. She suffered from such somatic symptoms as abdominal pain, diarrhea and small-bowel obstruction.

It has been proved that cobalamin deficiency may cause radiation enteritis, because this vitamin is absorbed exclusively in the terminal ileum. Vitamin B₁₂ injections improved such symptoms as anemia and numbness (Fukuda *et al.*, 2020). In another randomized trial effects of different dosages of vitamin B₁₂ on serum cobalamin levels in patients with peripheral neuropathy were studied. It was observed that patients receiving 500 µg of methylcobalamin three times a week demonstrated two times better results than those receiving 1500 µg of methylcobalamin once a week (Sil *et al.*, 2018). In the study with the participations of palliative care patients in Warnow-Klinik (Germany) the effects of deficiency of vitamins B (B₁, B₆, B₁₂), vitamin C, D and folic acid on pain and other deficiency symptoms, such as weakness, shortness of breath and loss of appetite were studied. Most of the palliative care patients suffered from cancer and most often the deficiency of vitamin D in blood was diagnosed. Vitamin B₁₂ deficiency was noted in 19 out of 31 patients, whereas its elevated level was observed in 7 patients. Vitamin B₁₂ was administered mainly to the patients with anemia and with cancer. The deficiency led to hyperhomocysteinemia and elevated levels of C-reactive protein (CRP). It was found that vitamin B₁₂ supplementation is effective in the treatment of general debility (Vollbracht *et al.*, 2019).

Special consideration is needed for people on a vegan diet, which eliminates the products of animal origin, being the source of vitamin B₁₂. People on such a diet should take cobalamin as dietary supplement in the form of capsules, so as to avoid serious consequences of its deficiency. However, it was found that in pregnancy vegan diet may have positive health effects, on condition that it is strictly controlled by a physician and, when appropriate, changes are made to improve maternal nutrition (Karcz *et al.*, 2019). Hypervitaminosis in the case of vitamin B₁₂ does not cause systemic toxicity and only very high doses may lead to allergic reactions. Elevated level of methylcobalamin is rarely met because its excess is excreted with urine. The most recent research revealed that there is a correlation between elevated vitamin B₁₂ levels and risk of mortality in elderly people. However, it is worth noting that the patients who died had also lower calcium and sodium levels and a medical history of chronic liver disease.

Pain is a subjective sensation with evolutionary biological utility. It is the reason that we can diagnose damage to the organism. Currently we use a number of psychiatric medications to alleviate pain (Niculescu *et al.*, 2019). Vitamin B₁₂ is proposed as a non-pharmacological method of pain management, free from adverse and side ef-

fects. There are several initial studies which focus on its potential efficacy in pain relieving. Hopefully, the results will be most successful, because as St. Augustine once said – “The greatest evil is physical pain” (Niculescu *et al.*, 2019).

Mibielli and others (Mibielli *et al.*, 2020) reported the results of a 60-day oral treatment of low back pain using a combination of nucleotides, UTP, CMP and vitamin B₁₂, in comparison to a combination of vitamins B₁, B₆ and B₁₂. After 30 days of the treatment pain intensity reduction (according to the VAS scale) was greater in the group receiving the nucleotides plus vitamin B₁₂.

CONCLUSION

In summary, vitamin B₁₂ belonging to the water-soluble vitamins is consumed with daily diet by the majority of people. At the beginning it was discovered to prevent pernicious anemia, but afterwards it found application also in the treatment of pain associated with other diseases, being highly efficient and not causing any unexpected complications. Current research confirms that vitamin B₁₂ is an effective pain-killer.

Low intake of vitamin B₁₂ may lead to a wide range of neurological disorders. Due to the strong correlation with the intensity of neuropathic pain, the assessment of levels of vitamin B₁₂ and cobalamin deficiency markers, e.g., homocysteine and methylmalonic acid, may be useful for diagnostic purposes and serve as a marker of neuropathy in various diseases.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgements

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. R. Furgala is MSc student of Physiotherapy at University of Rzeszow, Poland.

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