Buccal and Sublingual Administration of Micronutrients

BACKGROUND

Nutrients are the substances found in food which drive biological activity and are essential for the human body. They are categorized as: **macronutrients** (proteins, fats, and carbohydrates), and **micronutrients** (vitamins and minerals).

Global micronutrient supplements market is valued at $27.15 billion in 2022 [45], with significant growth expected. The vast majority of supplements are formulated for oral administration and are usually offered as pills, capsules, or chewables (i.e., gummies) for the digestive system.

Buccal (buccal = related to cheek or mouth [31]; in this context, buccal means "to be held in the mouth" in order to be absorbed through buccal mucosa; not to be confused with oral administration, where the supplement is swallowed) and **sublingual** (which means "to be held under the tongue") administration may provide better bioavailability of some micronutrients, and a more rapid onset of action compared to standard (oral) administration. This is largely due to the fact that the micronutrient does not pass through the digestive system and thereby avoids first pass metabolism.

The anatomy of the oral cavity highlights the various routes a substance can enter the body with the sublingual and buccal regions being the main focus areas (Figure 1, taken from [30]). The **sublingual region** includes the ventral side of the tongue and the floor of the mouth, whereas **buccal region** includes interior sides of cheeks, inner lips and gingivae (gums).

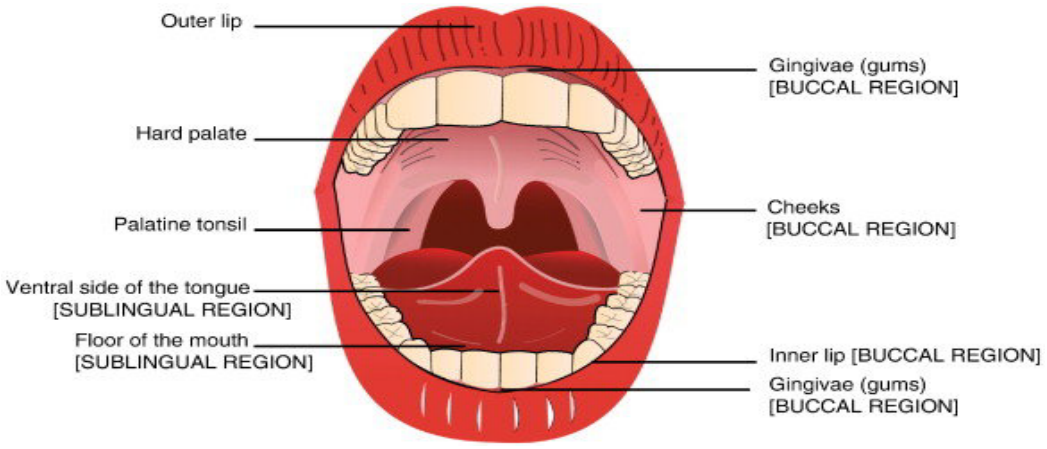

Figure 1: Anatomy of the oral cavity with sublingual region (noted on the left) and buccal region (noted on the right)

Certain agents that increase substance delivery through the skin, including surfactants, bile salts, and fatty acids, have been shown to exert a similar effect on the buccal mucosa [36-38]. This class of compounds is called penetration/permeation **enhancers** and they are not covered in this report.

The main objective of the report is to provide an overview of scientific evidence on the efficacy of buccal and/or sublingual administration of chosen micronutrients. The focus is on 5 micronutrients: **Vitamin A, Vitamin B1, Vitamin B12, Vitamin C,** and **Vitamin D**.

The review of referenced scientific publications consisted of queries in Google Scholar, PubMed, clinicaltrials.gov and additional proprietary publication databases. The keywords for search included the micronutrient name in combination with specific terms: "buccal", "sublingual", "spray", "supplement", "bioavailability", "toothpaste," and "absorption." This report covers all scientific publications which were found after an extensive and detailed search.

Micronutrient	Number of Studies Reviewed
Vitamin A	2
Vitamin B1	1
Vitamin B12	11
Vitamin C	1
Vitamin D	11
TOTAL	26

1) Vitamin A

Vitamin A is a fat-soluble vitamin. More precisely, it is a group of organic compounds that includes retinol, retinal (also known as retinaldehyde), retinoic acid, and several provitamin A carotenoids (most notably beta-carotene). Vitamin A has multiple functions in the body: it is essential for embryo development and growth, for maintenance of the immune system, and for vision [28].

Vitamin A deficiency is rare in developed countries but may occur. This might be the reason why very limited evidence exists on buccal/sublingual administration of vitamin A. Conditions that interfere with normal digestion can lead to vitamin A malabsorption such as celiac disease, Crohn's disease, cirrhosis, alcoholism, and cystic fibrosis [29].

On the other hand, Vitamin A deficiency remains a prevalent problem in developing countries secondary to chronic malnutrition [2]. The World Health Organization estimates that 250,000–500,000 children become blind every year secondary to this deficiency, and half are estimated to die within 12 months of vision loss.

In one clinical trial, researchers studied the effect of vitamin A supplement in the form of retinyl palmitate (RP) taken buccally via toothpaste, and then they measured RP and retinol (ROH) in the buccal mucosal cells samples [1]. They found that there was a significant increase of RP and ROH in buccal mucosal cells after participants brushed their teeth for 3 minutes every morning for 56 days. Scientists also measured serum RP and ROH but found no significant difference between the placebo and active arms, which was somewhat expected given the low dose of RP contained in the toothpaste.

There also exists a case report on an older individual with quite pronounced vitamin A deficiency to the point that her vision was negatively impacted [2]. Taking palmitate sublingual drops improved her vision after only 10 days, and significantly (17 times) increased vitamin A level. It is difficult to draw larger conclusions on a single case, but these findings might be a good starting point for larger studies to be conducted in the future.

2) Vitamin B1 (thiamine)

Vitamin B1 (one of eight B vitamins) is a water-soluble vitamin which cannot be produced by the body. It helps the body's cells change carbohydrates into energy, plays a role in muscle contraction and conduction of nerve signals, and is important for the growth and function of various cells [32].

In an older study, and the only study available on this vitamin, researchers assessed the absorption of vitamin B1 via buccal route using a solution and found that the buccal mucosa was quite permeable [3]. The absorption rates did not change when they changed the concentrations of supplement, nor were they altered in any way by adding valine or tyrosine.

3) Vitamin B12 (cobalamin)

Vitamin B12 is a water-soluble vitamin involved in metabolism. It is used as a cofactor in DNA synthesis. It is important for the normal functioning of the nervous system via its role in the synthesis of myelin, and in the circulatory system in the maturation of red blood cells in the bone marrow. In food, vitamin B12 comes from animal-based sources. Its manufactured forms are cyanocobalamin and methylcobalamin [34].

The buccal and sublingual absorption of vitamin B12 is well studied [4-14].

In a study with a toothpaste enriched by the vitamin B12 with vegan participants, it was demonstrated that the vitamin B12 penetrates well into the blood [4]. The same conclusion is made in another study with toothpaste, with elderly people as participants [14]. Both studies concluded that toothpaste is an effective vitamin B12 supplement.

In a very large observational study with more than 4,000 participants with vitamin B12 deficiency in Israel, it was shown that the sublingual tablets are efficient, and even more superior to the B12 supplements administered via

the intramuscular route (i.e., injections) [5]. The authors therefore advocated that sublingual tablets should be used as the first option for patients with B12 deficiency. This was particularly encouraging to learn given the inconvenience associated with intramuscular injections and the often-experienced pain.

Three recent studies conducted in Turkey and including children with vitamin B12 deficiency also agree that the sublingual route (spray and tablets) is effective for treatment of B12 deficiency [6-8]. In addition, one of these studies showed that the efficacy of the sublingual route is comparable to the intramuscular route [7], and another showed that they are both comparable to the oral route [8].

An interesting comparison of five vitamin B12 delivery routes is made in an Australian study [9]. Absorption profiles over a 6-hours period were tracked and the nanoparticle formulation in the form of an oral-buccal spray showed the best absorption. The dissolvable (chewable) tablet showed the same result, but it administered a five

times higher dose of the supplement. Those two produced a significantly better result than liposome oral spray formulation, followed by sublingual emulsion formulation. Finally, the standard (oral) tablet formulation produced the lowest increase in serum vitamin level.

Another study conducted in Italy followed two groups of subjects with B12 deficiency [10]. The first group consumed sublingual tablets of vitamin B12 supplement once per day, and the second group consumed the same supplement, but with a much higher dose and only once per week. After 90-day supplementation, both groups were able to restore adequate serum concentrations of vitamin B12.

One more study also looked at subjects with vitamin B12 deficiency, and compared sublingual vitamin B12 tablets, oral vitamin B12 tablets, and oral tablets of a vitamin B complex [11]. In all three groups, the serum vitamin B12 concentrations rose to the normal range within 4 weeks of treatment. The best results were achieved with sublingual tablets, whereas the most inferior were the oral tablets.

There were two more studies demonstrating that sublingual vitamin B12 is an effective, safe, and convenient treatment, which provides rapid restoration of serum cobalamin concentrations and should be considered as an alternative method of administration [12-13]. In addition, methylcobalamin can be an alternative to the commonly used cyanocobalamin.

4) Vitamin C (ascorbic acid)

Vitamin C is a micronutrient necessary for the growth, development, and repair of all body tissues. It is involved in many body functions, including formation of collagen, absorption of iron, the proper functioning of the immune system, wound healing, and the maintenance of cartilage, bones, and teeth [33].

In the only published study on the vitamin C buccal absorption, dating from 1979, a vitamin C solution is used, and absorption is assessed from the spitted sample [15]. It was found that vitamin C was absorbed across the mucosa of the mouth. In addition, D-glucose, 3-O-methyl-D-glucose, and calcium ions increased the absorption.

5) Vitamin D

Vitamin D is a prohormone, more accurately a group of fat-soluble secosteroids, responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and many other biological effects. In humans, the most important compounds in this group are vitamin D3 (also known as cholecalciferol) and vitamin D2 (ergocalciferol). Vitamin D deficiency is the most common medical condition worldwide [35].

The buccal/sublingual absorption of vitamin D is well studied [16-26]. In all of these studies, buccal or sublingual spray is used for delivery, except for one study which used sublingual drops [17].

One study demonstrated that buccal spray supplement produced a significantly better result as compared to the soft gelatin oral capsule [16]. Compared to this study, five other studies have not demonstrated superiority of the buccal delivery methods, but instead showed that the buccal and oral delivery are equally effective [19, 20, 21, 22, 25]. On the other hand, buccal spray was more acceptable by the subjects, especially for the pediatric

population, and therefore was the preferred option. It is worth mentioning that the increase of serum vitamin D levels were higher in individuals with lower initial levels, making a case for effective vitamin D delivery for subjects who have the greater need for it.

Finally, four studies performed on healthy subjects or the subjects who are resistant to oral vitamin D supplementation simply confirmed the efficacy of the sublingual vitamin D supplementation [17, 18, 23, 24]. The same conclusion was made in a study in patients with Irritable Bowel Syndrome (IBS) [26], which in addition demonstrated that the presence of probiotics in the supplement did not change the final result.

Conclusions

Current literature review suggests that there exists a significant body of evidence to support buccal and/or sublingual administration of micronutrients. Producers of products which offer supplements via these routes should be encouraged to generate further clinical studies and proofs.

ABOUT DR. ANDRIJANA RADIVOJEVIC

Andrijana Radivojevic, PhD is an experienced quantitative scientist with an international career in large pharmaceutical and biotechnology companies. Her prior position at Novartis established Dr. Radivojevic as a leading pharmacometrics expert. She has contributed to programs in all phases of drug development, spanning various therapeutic areas, and overseeing the quantitative strategy for the entire portfolio of indications.

Dr. Radivojevic has been active in pursuing her life-long interest in helping others grow professionally and personally. As a certified Executive Coach, she has worked with many scientists, medical doctors, engineers, programmers, entrepreneurs, and pharmaceutical professionals of all levels. Dr. Radivojevic has supported her clients in achieving their goals for leadership development, career advancement, impact, and other topics of their interest. As a result of coaching engagement, her clients are using their full potential and their breakthroughs while driving advances in science and technology.

OVERVIEW OF SCIENTIFIC PAPERS

1. Sobeck “Uptake of vitamin A in buccal mucosal cells after topical application of retinyl palmitate: a randomised, placebo-controlled and double-blind trial"

https://pubmed.ncbi.nlm.nih.gov/12844377/

Authors, institutions and journal

- U. Sobeck, A. Fischer and H. Biesalsk
- University of Hohenheim, Department of Biological Chemistry and Nutrition, Stuttgart, Germany
- British Journal of Nutrition, 2003
- Sponsored by GABA International, Switzerland - producer of vitamin A enriched toothpaste

Background and methods

Vitamin A and its compounds are essential micronutrients. Retinyl palmitate (RP) and its metabolites (retinal, retinol (ROH) and the most active metabolite, retinoic acid) play an important role in spermatogenesis, hearing, smelling, control of growth and epithelial differentiation, and in the visual cycle (retinal).

In the human body, dietary retinoids are taken up by the intestinal mucosa in the form of ROH. ROH is then re-esterified to RP, and released via the lymphatic system in the blood. It is further absorbed by the liver, and bound as ROH to the cellular ROH-binding protein or stored as RP in the stellate cells. When vitamin A is required by peripheral tissues it is re-mobilised by the liver. First, vitamin A is re-mobilised by hydrolysis, then it is bound to the ROH binding protein, released as a ROH-binding protein–transthyretin complex into the blood circulation, and is finally taken up by the peripheral tissue, depending on its need for vitamin A.

In this study, the uptake of topically applied RP in buccal mucosal cells is evaluated.. In addition, blood samples were taken from the volunteers to investigate changes in plasma RP and ROH concentrations.

An RP-containing toothpaste (1 mg/g, Aronal forte; GABA International, Therwil, Switzerland) or a placebo toothpaste are used in the morning during the trial. A normal toothpaste is used in the evening by all volunteers. The duration of teeth cleaning was fixed to 3 minutes.

The duration of the study was 84 days. During days 0–56, the volunteers cleaned their teeth as explained. During the wash-out phase, days 56–84, the volunteers cleaned their teeth with the placebo toothpaste in the morning, and with the normal toothpaste in the evening. Buccal mucosal cell samples were taken by the participants themselves during this phase on days 0, 3, 7, 10, 14, 17, 21, 28 and 56 with a surgical, soft toothbrush. Blood samples were taken on days 0 and 56 to investigate changes of plasma RP concentration and plasma ROH concentration.

Results and conclusions

A significant uptake of RP in buccal mucosal cells after 7 days and a significant increase of ROH after 17 days was demonstrated. There were no significant differences observed in the placebo and treated group for RP and ROH in the blood. This was expected as only the low dose (5000 UI) of RP was given. Plasma ROH is homeostatically regulated, and as a consequence, ROH never increases, even when high doses are given. It is possible that there is a very small increase of plasma RP as a cause of unintentional swallowing of the toothpaste directly after application. However, RP in plasma (chylomicrons) only increases significantly following an intake of 10 000 IU.

Cited by 16 papers

https://scholar.google.com/scholar?cites=3768577260909027000&as_sdt=2005&sciodt=0,5&hl=en

2. Singer "Treatment of vitamin A deficiency retinopathy with sublingual vitamin A palmitate"

https://pubmed.ncbi.nlm.nih.gov/26980447/

Authors, institutions and journal

- J. Singer, B. Bakall, G. Gordon, R. Reddy
- University of Arizona College of Medicine, Phoenix, AZ, USA
- Doc Ophthalmol, 2016

Background and methods

Vitamin A is a vital fat-soluble compound required for normal visual function. It is necessary for epithelial maintenance of the conjunctiva and cornea, and nourishment of the retinal pigment epithelium and has a requisite biochemical role in phototransduction.

Vitamin A deficiency (VAD) remains a prevalent problem in developing countries secondary to chronic malnutrition. The World Health Organization estimates that 250,000–500,000 children become blind every year secondary to VAD, and half are estimated to die within 12 months of vision loss. In developed countries, VAD is quite rare with most cases attributable to gastrointestinal malabsorption. The liver typically contains a 2-year reservoir of vitamin A in the form of retinyl palmitate [4]. Consequently, VAD and its incumbent ocular manifestations often take years to develop, but it may result in retinopathy, a disease of the retina.

The case of a 69-year-old woman with malabsorption-associated VAD confirmed with serology, and with history of progressive visual dimming, decreased central vision, and nyctalopia was assessed. She was subsequently treated with sublingual vitamin A palmitate drops, dosed 25,000 IU daily. The electrophysiologic findings including ERG, mfERG, and dark adaptometry are measured in addition to kinetic perimetry, before and after treatment.

Baseline serology was initially obtained, confirming severely depleted vitamin A levels at 3 mcg/dL (normal: 38–98 mcg/dL).

Results and conclusions

The patient noted improved vision within 10 days of starting therapy. She related complete resolution of nyctalopia and described general improvement in visual quality.

Repeat serology performed after 3 weeks of sublingual drops revealed improved vitamin A levels to 50 mcg/dL (17x increase). All the ophthalmology parameters significantly improved.

Cited by 11 papers

https://scholar.google.com/scholar?cites=17163094022908148939&as_sdt=2005&sciodt=0,5&hl=en

3. Evered "Thiamine Absorption Across Human Buccal Mucosa in vivo"

https://pubmed.ncbi.nlm.nih.gov/6834992/

Authors, institutions and journal

- D. Evered, C. Mallett
- Department of Biochemistry, Chelsea College, University of London, London, UK
- Life Sciences, 1983

Background and methods

The mucosa of the human mouth is proven to be permeable to several vitamins. Also, the absorption characteristics are broadly similar to those with rat small intestine, which occurs by an active process at low concentrations; transport at higher concentrations is largely by passive diffusion.

The purpose of this study was to investigate the kinetics of thiamine absorption from the human mouth *in vivo*. The possible influence of valine and tyrosine isomers was also tested. Subjects were 6 caucasians between 25 and 40 years of age, apparently healthy, with no dentures.

Buccal absorption was studied by circulating a pre-incubated buffered solution of thiamine in the mouth for five minutes. The solution, of known initial concentration, was ejected and followed by a five-second wash with fresh buffer solution. The pooled sample and washings were diluted, centrifuged, and assayed for thiamine using a spectrophotometric method. A minimum of six buccal experiments were performed to permit statistical analysis.

Results and conclusions

As the main result, buccal mucosa was permeable to thiamine. Absorption rates showed saturation with respect to initial concentration, in the range 50 to 1000 µM.

For the initial concentrations of thiamine 100, 500 and 1000 µM, mean uptake during five minutes was 0.99, 2.42, and 5.70 µmoles, respectively.

In addition, neither the L-isomers nor the D-isomers of valine and tyrosine (1 mM) altered statistically the rate of thiamine absorption from the mouth over a range of different concentrations of thiamine.

Cited by 44 papers

https://scholar.google.com/scholar?cites=13862083742585933300&as_sdt=2005&sciodt=0,5&hl=en

4. Siebert "Vitamin B12–fortified toothpaste improves vitamin status in vegans: a 12-wk randomized placebo-controlled study"

https://pubmed.ncbi.nlm.nih.gov/28052884/

Authors, institutions and journal

- A. Siebert, R. Obeid, S. Weder, H. Awwad, A. Sputtek, J. Geisel, M. Keller
- Institute of Alternative and Sustainable Nutrition, Biebertal, Giessen, Germany; Aarhus Institute of Advanced Studies, Aarhus University, Aarhus, Denmark; Department of Clinical Chemistry and Laboratory Medicine, Saarland University Hospital, Homburg, Saarland, Germany; Center for Laboratory Medicine and Microbiology, Essen, Germany
- Am J Clin Nutr, 2017

Study details

The study is supported in part by a grant from Logocos Naturkosmetik AG. It was registered at clinicaltrials.gov with ID NCT02679833:

https://clinicaltrials.gov/ct2/show/NCT02679833?id=NCT02679833&draw=2&rank=1

Background and methods

Vitamin B12 deficiency is common in individuals with low intake of animal-based foods. Vegans do not consume any animal products and are, therefore, a classic risk group for vitamin B12 deficiency.

In this study, participating vegans used a special toothpaste with B12 vitamin: it contained cyanocobalamin (a manufactured version of vitamin B12) in the concentration of 100 µg/g. Thus, the average amount of cyanocobalamin that was delivered into the oral cavity was 130 or 290 mg/d for the 2 brushing sessions with the use of an electrical or manual toothbrush, respectively. The markers of the B12 vitamin were measured at the beginning and at the end of the study period, in order to determine whether, and in which quantity, the vitamin presented in the toothpaste penetrated into the blood. The mechanisms of vitamin B12 absorption via the mucosal barrier were not previously known.

There were four measured B12 markers: serum concentrations of vitamin B12, holotranscobalamin, total homocysteine (tHcy), and methylmalonic acid (MMA). For the first and second marker, the concentration is directly proportional to that of the vitamin B12 in the blood; for the third and fourth markers, it is inversely proportional (i.e., their concentration is higher when there is a vitamin deficiency).

The study was 12-week long, double-blinded, randomized, and placebo-controlled. Only vegans, male and female, ages between 18 and 50, participated: 76 of them received either a placebo toothpaste (34 of them who form the placebo arm) or vitamin B12 toothpaste (42 of them who form the B12 arm). Out of those, 66 participants completed the study. Participants were instructed to use the toothpaste 2 times per day, for 2 minutes at a time. Some of the participants were already regularly taking vitamin B12 supplements, and were instructed to continue with normal use during the study period.

Results and conclusions

At the end of the study, concentrations of vitamin B12 and holotranscobalamin were higher, concentrations of MMA were lower, and concentrations of tHcy tended to be lower in the vitamin B12 arm than in the placebo arm, after adjustment for baseline concentrations. This confirms that the vitamin has penetrated into blood. In addition, the participants who have not taken B12 supplements have achieved higher change.

More precisely, in the placebo arm, the mean vitamin B12 level changed from 149 to 134 pmol/L (i.e. decreased for 15 pmol/L, or 10.1%); in the B12 arm, the level changed from 197 to 279 pmol/L (i.e. increased for 82 pmol/L, or 41.6%).

Cited by 27 papers

https://scholar.google.com/scholar?cites=3145630075498278417&as_sdt=2005&sciodt=0,5&hl=en

5. Bensky "Comparison of sublingual vs. intramuscular administration of vitamin B12 for the treatment of patients with vitamin B12 deficiency"

https://pubmed.ncbi.nlm.nih.gov/30632091/

Authors, institutions and journal

- M. Bensky, I. Ayalon-Dangur, R. Ayalon-Dangur, E. Naamany, A. Gafter-Gvili, G. Koren, S. Shiber
- Maccabi Healthcare Services, Tel-Aviv, Israel; Rabin Medical Center, Petach Tikva, Israel; Faculty of Engineering Sciences, Ben-Gurion University of the Negev, Beersheba, Israel; Sackler Faculty of Medicine, Tel Aviv University, Israel; Institute of Hematology, Rabin Medical Center, Petach Tikva, Israel; The Maccabi-Kahn Institute of Research and Innovation, Tel Aviv, Israel; The Department of Emergency Medicine, Rabin Medical Center, Petach Tikva, Israel
- Drug Delivery and Translational Research, 2019

Background and methods

The study focuses on two supplementation methods to treat vitamin B12 deficiency: sublingual (SL) and intramuscular (IM). Traditionally, IM has been the preferred method with 10% of the injected dose absorbed; however, it has inherent disadvantages, such as pain, higher cost when provided by a health professional, bleeding, and inconvenience. The SL method has several advantages including convenience, safety, potentially good adherence, and reduced cost.

Large studies comparing the efficacy of SL vs IM supplementation methods are lacking. The aim of this study was to compare the efficacy of SL vs IM in restoring B12 levels in the case of deficiency.

This is a retrospective analysis of data from the pharmacy records of Maccabi Health Service. Data were recorded for all patients older than 18 years, who were prescribed B12 supplementation during the period 2014–2017. Overall, there were 4281 patients treated with supplements. Of them, 3451 (81%) were treated with SL tablets (high-dose sublingual tablet containing 1 mg of cyanocobalamin), and 830 (19%) with IM injections (high-dose ampule containing 1 mg of cyanocobalamin).

Results and conclusions

The main outcome of supplementation therapy was the rise in levels of serum vitamin B12 after treatment. The mean difference between serum B12 levels before and after administration of supplements was significantly higher in the SL subjects vs IM subjects (252 vs 218 ng/L).

In addition, a subgroup of patients is analyzed, with a baseline of serum vitamin B12 < 300 ng/L (which is considered the deficiency limit): of those with SL supplementation, 87% elevated their serum levels to values higher than 300 ng/L, compared to 77% of those with IM supplementation.

This is the largest study documenting that therapy using the SL route is sufficient and even superior to the IM route. The SL tablets overcome the challenges of IM injections and should be the first option for patients with B12 deficiency.

Cited by 26 papers

https://scholar.google.com/scholar?cites=16202927415977105345&as_sdt=2005&sciodt=0,5&hl=en

6. Koksal “Sublingual spray treatment of vitamin B12 deficiency in children”

https://www.ejgm.co.uk/download/sublingual-spray-treatment-of-vitamin-b12-deficiency-in-children-12047.pdf

Authors, institutions and journal

- A. Koksal, T. Koksal, A. Camurdan
- Ambulatory Pediatric Clinic, Ankara, Turkey; Department of Social Pediatrics, Faculty of Medicine, Gazi University, Ankara, Turkey
- Electronic Journal of General Medicine, 2022

Background and methods

Intramuscular injection therapy is the gold standard in the treatment of vitamin B12 deficiency. There are also oral, nasal, and sublingual spray treatment methods. In this study, it is aimed to show the efficacy of sublingual spray treatment of vitamin B12 deficiency in children.

Forty-five pediatric patients (25 boys, 20 girls), aged 9-36 months (mean age 15 months), with serum cobalamin concentrations <200 pg/mL (which is considered deficiency), were treated with sublingual vitamin B12 (methylcobalamin) spray. All patients were treated for four months by giving 500 µg oral spray daily for the first week, every other day for the next one week, two days a week for the next two weeks and then once a week for three months. Vitamin B12 levels were checked after four months.

Results and conclusions

Post-treatment vitamin B12 values were significantly higher than pre-treatment values. Vitamin B12 serum levels increased from 161.58 pg/mL to 427.44 pg/mL. After the treatment, the vitamin B12 level of all patients was found to be >200 pg/mL, except for only two of them. Vitamin B12 levels raised to normal in 96% of the patients with a sublingual spray treatment. Absorption occurs through numerous capillaries under the tongue. No treatment-induced side effects were detected in the patients.

Data from this study indicate that sublingual application of vitamin B12 (methylcobalamin) spray (500 µg per dose/puff) for four months is effective for treatment of children with vitamin B12 deficiency. Sublingual route is easier and more practical to use, and can be preferred for children with vitamin B12 deficiency instead of parenteral and oral routes.

Cited by 0 papers

7. Tugba "Comparison of Sublingual and Intramuscular Administration of Vitamin B12 for the Treatment of Vitamin B12 Deficiency in Children"

https://pubmed.ncbi.nlm.nih.gov/33053572/

Authors, institutions and journal

- A. Tugba-Kartal, Z. Cagla-Mutlu
- Division of Pediatric Neurology, Faculty of Medicine, Ankara University, Ankara; Department of Pediatrics, Kutahya Parkhayat Hospital, Kutahya, Turkey
- Revista de Investigacion Clinica, 2020

Background and methods

In most countries, contrary to its disadvantages, such as pain, relatively higher cost, and poor adherence to treatment, intramuscular (IM) route is still the primary treatment method for Vitamin B12 deficiency. In recent years, because of these difficulties, new treatment methods are being sought for.

The estimated prevalence of vitamin B12 deficiency in the general population varies between 1.5% and 15%. The most common cause of vitamin B12 deficiency in children is inadequate dietary intake.

The study aimed to compare sublingual (SL) and IM routes of B12 administration, during 4 weeks, in children with B12 deficiency, and in addition to compare the efficacy of methylcobalamin and cyanocobalamin therapy in these children.

This retrospective study comprised 129 patients with B12 deficiency (serum B12 level <200 pg/mL), aged 5-18 years (mean age: 12 years). Based on the formulations of B12, the patients are divided into three treatment groups as: SL cyanocobalamin, SL methylcobalamin and IM cyanocobalamin. The data are obtained from the electronic medical record system and patient files.

The SL cyanocobalamin therapy consisted of: a 1000 µg SL tablet once daily for 7 days, then every other day for 3 weeks. The SL methylcobalamin therapy consisted of: a 1000 µg SL spray puff for 7 days, then every other day for 3 weeks. The IM cyanocobalamin therapy consisted of: a 1000 µg ampule every other day for 1 week, then weekly for 3 weeks.

Results and conclusions

After vitamin B12 therapy, serum B12 levels increased significantly in all patients. There was also a statistically significant difference between the treatment groups.

In the SL cyanocobalamin group, the serum B12 levels rose from mean value 137.2 to 483.4 pg/mL (difference 346.2 pg/mL, or 252%). In the SL methylcobalamin group, the levels rose from 146.7 to 565.5 pg/mL (difference 418.8 pg/mL, or 285%). In the IM cyanocobalamin group, the levels rose from 147.5 to 602.0 pg/mL (difference 454.5 pg/mL, or 308%).

In addition, in the SL cyanocobalamin group, the percentage of patients with anemia (Hb < 11 g/dL) dropped from 53% to 37%; in the SL methylcobalamin group it dropped from 64% to 41%; in the IM cyanocobalamin group it dropped from 60% to 32%.

SL cyanocobalamin and SL methylcobalamin were found to be effective (the latter more than the former) for children with B12 deficiency in correcting serum B12 level, and comparable to IM cyanocobalamin.

Cited by 3 papers

https://scholar.google.com/scholar?cites=13585585222223873556&as_sdt=2005&sciodt=0,5&hl=en

8. Kilic "Sublingual methylcobalamin treatment is as effective as intramuscular and peroral cyanocobalamin in children age 0–3 years"

https://pubmed.ncbi.nlm.nih.gov/34871525/

Authors, institutions and journal

- B. Kilic, S. Kilic, E. Eroglu, E. Gul, F. Burcu, B. Apak
- Department of Pediatrics, Baskent University Faculty of Medicine, Ankara, Turkey; Department of Biostatistics, Baskent University Faculty of Medicine, Ankara, Turkey; Department of Pediatric Hematology, Baskent University Faculty of Medicine, Ankara, Turkey
- Hematology, 2021

Background and methods

Vitamin B12 deficiency is a cause of growth and developmental retardation in children. The goal is to compare the efficacy of oral, sublingual, and intramuscular vitamin B12 treatments in children aged 0–3 years.

The study included 158 patients with vitamin B12 deficiency (defined as serum vitamin B12 level <300 ng/L), aged 0–3 years, retrospectively. According to the vitamin B12 treatment therapy, the patients were divided into three groups: oral cyanocobalamin (group 1), sublingual methylcobalamin (group 2), and intramuscular cyanocobalamin (group 3).

Group 1 received one 1000 µg ampule of oral cyanocobalamin: every day for the first week, every other day for next 2 weeks, twice a week for next 2 weeks, followed by once a week for next three months. Group 2 received one 1000 µg spray puff of sublingual methylcobalamin with the same protocol as the Group 1. Group 3 received 100 µg (1/10) of 1000 µg ampule cyanocobalamin intramuscularly: every day for the first week, every other day for 2 weeks, twice a week for 2 weeks, followed by once a week for three months.

Results and conclusions

The mean values of vitamin B12 levels significantly increased to >300 ng/L in all three groups. In group 1, the mean value of serum B12 level increased from 201.1 to 449.2 ng/L (123%), in group 2 from 187.0 to 427.1 ng/L (128%), and in group 3 from 176.1 to 526.1 ng/L (199%).

Note that there is an apparent mistake in this paper as the numerical values from Table 1 and Figure 1 do not correspond to those in the text.

Therefore, all three proposed therapies have given satisfactory results in improving vitamin B12 levels in children aged 0–3 years. Sublingual methylcobalamin is as effective as oral and intramuscular cyanocobalamin. In addition, the level of anemia marker Hb has not changed significantly in either of the three groups.

Cited by 0 papers

9. Vitetta "Route and Type of Formulation Administered Influences the Absorption and Disposition of Vitamin B12 Levels in Serum"

https://pubmed.ncbi.nlm.nih.gov/29361736/

Authors, institutions and journal

- L. Vitetta, J. Zhou, R. Manuel, S. Dal Forno, S. Hall, D. Rutolo
- Sydney Medical School, University of Sydney, Australia; Medlab Clinical, Sydney, Australia
- Journal of Functional Biomaterials, 2018

Study details

The clinical trial was registered with the Australian and New Zealand Clinical Trial Registry (ACTRN12616001326482).

Background and methods

The article summarizes the findings from an Australian comparative study in adults administered vitamin B12 supplements through five different delivery routes. A total of 16 healthy subjects (9 males and 7 females) voluntarily partook in a comparative clinical study across a six-month period, completing 474 person-hours of cumulative contribution.

The aim of this clinical study was to compare the absorption profiles over a 6-hours period of five different vitamin B12 formulations: 1) a nanoparticle formulation (average particle size of 20 nm) of methylcobalamin B12 in the form of an oral-buccal spray (two actuations of the pump delivering a 1000 µg dose); 2) an emulsion formulation of cyanocobalamin B12 that is absorbed through the sublingual mucosa (two actuations of the pump delivering a 1000 µg dose); 3) a standard tablet formulation of cyanocobalamin B12 that is absorbed through the gastrointestinal tract (a 1000 µg dose); 4) a dissolvable (chewable) tablet of methylcobalamin B12 that is absorbed through the sublingual mucosa via passive diffusion (a 5000 µg dose, i.e. 5 times higher content than the four others formulations); 5) a liposome oral spray formulation of methylcobalamin B12, providing B12 in vesicles constructed of a phospholipid bi-layer (particle sizes of 100 nm), with nano-sized liposome preparation posited to assist with the absorption of B12 across mucosal membranes (two actuations of the pump delivering a 1000 µg dose).

Results and conclusions

The value of serum vitamin B12 level (all units in pmoles/L) is measured at baseline, after 1 hour, after 3 hours and after 6 hours after the supplement administration. For the formulation 1, after 6 hours of administration, the level increased from 383 to 491 (28%), for the formulation 2 from 450 to 493 (10%), for the formulation 3 from 419 to 441 (5%), for the formulation 4 from 429 to 545 (27%), and for the formulation 5 from 385 to 438 (14%). No adverse events were reported to any of the formulations tested.

Therefore, the nanoparticle formulation (1) showed the best absorption. The dissolvable tablet (4) showed the same result, but it administered a five times higher dose of supplement. Those two produced a significantly better

result than liposome formulation (5) followed by emulsion formulation (2). The standard tablet formulation (3) produced a low raise in serum vitamin level.

This study has demonstrated that an active metabolite embedded in a functional biomaterial (nanoparticles) may constitute a drug delivery method that can best access the circulatory system.

Cited by 18 papers

https://scholar.google.com/scholar?cites=6979812503503779525&as_sdt=2005&sciodt=0,5&hl=en

10. Bo "Effect of two different sublingual dosages of vitamin B12 on cobalamin nutritional status in vegans and vegetarians with a marginal deficiency: A randomized controlled trial"

https://pubmed.ncbi.nlm.nih.gov/29499976/

Authors, institutions and journal

- C. Del Bo, P. Riso, C. Gardana, A. Brusamolino, A. Battezzati, S. Ciappellano
- Department of Food, Environmental and Nutritional Sciences, Università degli Studi di Milano, Milan, Italy
- Clinical Nutrition, 2019

Study details

The study was registered at ISRCTN with registration number ISRCTN75099618. The study was supported by the Phoenix Srl.

https://www.isrctn.com/ISRCTN75099618

Background and methods

Vegetarians and vegans are more vulnerable to vitamin B12 deficiency, with severe risks of megaloblastic anemia, cognitive decline, neuropathy, and depression. The most common method of supplementation consists of taking one weekly dosage of 2000 µg. However, single large oral doses of vitamin B12 are poorly absorbed. This paper evaluates the ability of two different sublingual doses of vitamin B12 (350 µg/week vs 2000 µg/week) in improving cyanocobalamin (vitamin B12) nutritional status in vegans and vegetarians with a marginal vitamin B12 deficiency (<220 pmol/L).

A 12-week randomized, double-blind, controlled, parallel trial was performed. Forty subjects with marginal vitamin B12 deficiency were enrolled and randomly divided into two groups of twenty subjects each: test group LD (low dose, administered once a day), and control group HD (high dose, administered once a week). More precisely, the LD group consumed 7 sublingual tablets each providing 50 µg/day (totaling 350 µg/week) of vitamin B12, while the HD group consumed 1 sublingual tablet (2000 µg) for the entire week.

Blood samples were collected at baseline and after 15, 30, 60, and 90 days. The improvement of serum levels of vitamin B12 was considered the primary endpoint. The other variables under study were as follows: holotranscobalamin, methylmalonic acid, succinic acid, methionine, homocysteine, vitamin B6, folic acid, and complete blood count [those will not be mentioned further as irrelevant].

Results and conclusions

Serum concentration of vitamin B12 increased after 90-day supplementation, in both groups, compared to baseline. Both supplements were able to restore adequate serum concentrations of vitamin B12 to above 240 pmol/L. After 15 days from the start of the intake of the supplements, the mean increase in B12 serum level was 51.7% in the LD group vs 74.2% in the HD group.

The authors support the use of a sublingual dosage of 50 mg/day (350 mg/week) of cobalamin, instead of 2000 mg/week (provided as a single dose), to reach a state of nutritional adequacy of vitamin B12 in this target population.

Cited by 34 papers

https://scholar.google.com/scholar?cites=4964629770767395996&as_sdt=2005&sciodt=0,5&hl=en

11. Sharabi "Replacement therapy for vitamin B12 deficiency: comparison between the sublingual and oral route"

https://pubmed.ncbi.nlm.nih.gov/14616423/

Authors, institutions and journal

- A. Sharabi, E. Cohen, J. Sulkes, M. Garty
- Recanati Center for Medicine and Research and Clinical Pharmacology Unit, and Epidemiology Unit, Rabin Medical Center, Beilinson Campus and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
- Br J Clin Pharmacol, 2003

Background and methods

Cobalamin (vitamin B12) deficiency is caused by pernicious anemia, food–cobalamin malabsorption, vegetarianism, and other deficiency states. It has a reported prevalence of 3–29%. The study aim was to compare the efficacy of sublingual and oral administration of a smaller dose of 500 µg daily of cobalamin, in subjects with cobalamin deficiency without anemia.

Thirty subjects with low serum concentrations of cobalamin (<138 pmol/l) participated in the study. Subjects were randomly allocated to receive: one tablet daily of 500 µg cobalamin sublingually (sublingual B12 group), or one tablet daily of 500 µg cobalamin orally (oral B12 group), or two tablets daily of a vitamin B complex (oral B complex group). One B complex tablet contains cobalamin (250 µg, therefore two tablets provide 500 µg), thiamine, and pyridoxine.

The study duration was 8 weeks. Complete blood count and serum cobalamin measurements were obtained before the study, and at the end of weeks 1, 2, 3, 4 and 8 of treatment.

Results and conclusions

In all three groups, cobalamin concentrations rose to the normal range within 4 weeks of treatment, and were maintained after 8 weeks. Most of the increase was achieved by the end of the first week of treatment. The proposed daily dose of 500 µg was therefore effective in correcting cobalamin deficiency in all the three groups.

Serum cobalamin concentrations (mean values) before the treatment were: 94, 108, and 98 pmol/l in the sublingual B12, oral B12 and oral B-complex groups, respectively. After 4 weeks, concentrations rose to: 288 (increase by 206% from the baseline), 286 (increase by 165%), and 293 (increase by 199%) pmol/l, respectively. After 8 weeks, concentrations were: 279 (increase by 197% from the baseline), 241 (increase by 123%), 266 (increase by 171%) pmol/l, respectively.

In summary, a dose of 500 mg of cobalamin given either sublingually or orally, is apparently effective in correcting cobalamin deficiency in subjects with early stage disease.

Cited by 103 papers

https://scholar.google.com/scholar?cites=15621392768043824 31&as_sdt=2005&sciodt=0,5&hl=en

12. Delpre "Sublingual therapy for cobalamin deficiency as an alternative to oral and parenteral cobalamin supplementation"

https://pubmed.ncbi.nlm.nih.gov/10475189/

Authors, institutions and journal

- G. Delpre, P. Stark, Y. Niv
- Department of Gastroenterology, Rabin Medical Center, Beilinson Campus, Tel Aviv, Israel
- The Lancet, 1999

Background and methods

The traditional treatment of cobalamin (vitamin B12) deficiency, including pernicious anemia, food-cobalamin malabsorption in the elderly, vegetarianism, and other deficiency states, is by intramuscular injections. However, injections can be painful, are difficult in patients who have a tendency to bleed, are difficult to provide for elderly or disabled patients, and are costly if given by health professionals.

On the other hand, oral cobalamin-replacement therapy has proved reliable and effective, but is rarely prescribed. Additionally, oral therapy is not efficient in patients with diarrhea, vomiting, or who are unable to take oral medication.

In this prospective open-labelled study, 18 patients with cobalamin deficiency of various causes were treated with sublingual cobalamin preparation, and the efficacy of treatment was assessed. Cobalamin deficiency is defined as serum cobalamin concentration less than 200 pg/mL (normal concentration 200–900 pg/mL).

Patients were given sublingual nuggets of 1000 µg cobalamin, to be held under the tongue until completely dissolved. Cobalamin is isolated from yeast fermentation medium, which provides a product that is technically yeast free. Two sublingual nuggets (i.e. total daily dose of 2000 µg) were given for the period of 7–12 days, 30 min before breakfast.

Serum cobalamin concentrations were measured before therapy and 2 days after completion of the treatment.

Results and conclusions

The mean serum cobalamin concentration before treatment was 127.9 pg/mL and after treatment was 515.7 pg/mL (increase of 303%). An increase in cobalamin concentration as much as four-fold compared with pretreatment concentration was seen in most patients. No patient had side-effects. All participants found the method of administration convenient and preferred it to intramuscular injections.

Therefore, sublingual cobalamin is an effective, safe, and convenient treatment, which provides rapid restoration of serum cobalamin concentrations and should be considered as an alternative method of administration.

Cited by 62 papers

https://scholar.google.com/scholar?cites=13342587970498395760&as_sdt=2005&sciodt=0,5&hl=en

13x. Varkal "Efficiency of the sublingual route in treating B12 deficiency in infants"

https://econtent.hogrefe.com/doi/epdf/10.1024/0300-9831/a000724

Authors, institutions and journal

- M. Varkal, M. Karabocuoglu
- Department of Pediatrics, Faculty of Medicine, Istanbul University, Istanbul, Turkey; Department of Pediatrics, Memorial Atasehir Hospital, Istanbul, Turkey
- International Journal for Vitamin and Nutrition Research, 2021

Background and methods

Vitamin B12 deficiency is common in children. In breastfed infants, the main reason is maternal B12 deficiency. Parenteral administration is commonly prescribed. However, patient compliance is not satisfactory due to repeated painful parenteral applications. It is also known that the oral route is efficient in high doses. In recent years, the sublingual route has been tried. This route stands out due to its easy applicability and low cost. However, there are few efficacy studies in infants for the sublingual route.

The study included 49 infants aged 6–12 months. All infants with marginal or deficient B12 levels (<300 pg/mL) were incidentally detected and treated with sublingual methylcobalamin. Each dose was 1000 µg and administered once a day in the first week, every other day in the second week, twice a week in the third week, and once a week in the fourth week. Serum vitamin B12 levels were measured before and after the treatment. Paired Sample T-Test was used to compare variables.

Results and conclusions

All infants had normal physical development and had no hematological or neurological issues. It was learned from the parents that the infants tolerated treatment well, and no side effects related to the treatment, such as vomiting or rash, were observed. Before and after the treatment, the mean vitamin B12 levels were 199 pg/mL and 684 pg/ml, respectively (increase of 244%). The difference between the means was statistically significant.

According to the study, it seems possible to treat vitamin B12 deficiency via a sublingual route in infants. In addition, methylcobalamin can be an alternative to the commonly used cyanocobalamin.

Cited by 1 paper

https://scholar.google.com/scholar?cites=7804260250145988273&as_sdt=2005&sciodt=0,5&hl=en

14x. Zant "Vitamin B12-fortified toothpaste improves vitamin status in elderly people: a randomized, double-blind, placebo-controlled study"

https://link.springer.com/article/10.1007/s40520-019-01125-6

Authors, institutions and journal

- A. Zant, H. Awwad, J. Geisel, M. Keller, R. Obeid
- Department of Clinical Chemistry and Laboratory Medicine, Saarland University Hospital,, Homburg, Saar, Germany
- Aging Clinical and Experimental Research, 2019

Study details

The study was registered at clinicaltrials.gov with ID NCT02679833:

https://clinicaltrials.gov/ct2/show/NCT02679833?id=NCT02679833&draw=2&rank=1

Background and methods

Elderly people are at risk for vitamin B12 deficiency. The study goal was to assess the ability of vitamin B12-enriched toothpaste vs. placebo to increase vitamin B12 status in elderly subjects.

A randomized double-blind placebo-controlled intervention is conducted in 103 elderly subjects. Serum concentrations of vitamin B12 , holotranscobalamin (holoTC), methylmalonic acid (MMA), and plasma total homocysteine (tHcy) were measured at baseline and after 3 months. The toothpaste was enriched with 100 µg cyanocobalamin/g.

Results and conclusions

After the intervention, concentrations of vitamin B12 were higher (mean = 368 vs. 295 pmol/L) in the vitamin B12 group compared with the placebo group. The changes of serum vitamin B12 (54 vs. 3 pmol/L) were significantly different between the intervention groups. Mean percentage increase of serum vitamin B12 (+ 23% corresponds to + 54 pmol/L) in the vitamin B12 toothpaste group suggests that the intervention had provided an additional daily intake of approximately + 7 µg oral B12.

To conclude, the toothpaste has increased vitamin B12 status and can thus be used for preventing vitamin B12 depletion in elderly people. Common diseases and drugs did not predict the change of blood markers in the vitamin group. No side effects were observed.

Cited by 3 papers

https://scholar.google.com/scholar?cites=5393513277227813458&as_sdt=2005&sciodt=0,5&hl=en

15. Sadoogh "Absorption of vitamin C from the human buccal cavity"

https://pubmed.ncbi.nlm.nih.gov/486391/

Authors, institutions and journal

- F. Sadoogh-Abasian, D. F. Evered
- Chelsea College, University of London
- Br. J. Nutr, 1979

Background and methods

The purpose of the present study was to investigate the buccal absorption *in vivo* of L-ascorbic acid (vitamin C) and compare it with the results obtained from the small intestine.

Results and conclusions

Ascorbic acid was absorbed across the mucosa of the human mouth. Omission of sodium ions from the medium decreased the absorption of ascorbic acid. The presence of D-glucose, or 3-O-methyl-D-glucose, increased the absorption of ascorbic acid; D-fructose had little effect and D-mannitol had no effect. Calcium ions increased ascorbic acid absorption. Buccal mucosa was also permeable to dehydroascorbic acid and D-isoascorbic acid.

Cited by 37 papers

https://scholar.google.com/scholar?cites=14617117851328822086&as_sdt=2005&sciodt=0,5&hl=en

Note: Those 37 papers are concerned by the buccal delivery of various drugs (not even one paper is devoted to the vitamin C), and by the question how to enhance the bioavailability by this way of administration.

16. Satia "A randomized two way cross over study for comparison of absorption of vitamin D3 buccal spray and soft gelatin capsule formulation in healthy subjects and in patients with intestinal malabsorption"

https://pubmed.ncbi.nlm.nih.gov/26514332/

Authors, institutions and journal

- M. Satia, A. Mukim, K. Tibrewala, M. Bhavsar
- Ethicare Clinical Trial Services, Ahmedabad, India; Mukim Medical And Nursing Homes, Ahmedabad, India; Tibrewala's Clinic, Ahmedabad, India; Bhavsar's Clinic, Ahmedabad, India
- Nutrition journal, 2015

Background and methods

The objective was to compare the absorption of vitamin D3 through the oral route by comparing a 1000 IU soft gelatin capsule and a 500 IU buccal spray (delivering 1000 IU in two spray shots) in healthy subjects and in patients with malabsorption disease.

An open label, randomized, two-periods, two-way crossover study was conducted, in healthy subjects (n=20) and in patients with malabsorption syndrome (n=20). The study participants were equally divided and received either of the treatments: buccal spray (n=7), soft gelatin capsule (n=7), and control (n=6), in Period I for 30 days. After a washout of another 30 days, the treatments were changed in crossover fashion in Period II: in such a manner, participants who had received the buccal spray in period I received the soft gelatin capsule in period II, and vice versa (the control group remained the same).

Fasting blood samples were collected to measure 25-hydroxyvitamin D [25(OH)D] (a vitamin D marker) levels in all participants at day 0 (screening visit - baseline), at day 30 (completion of Period I), at day 60 (end of wash out and start of Period II) and at day 90 (completion of Period II). Statistical analysis was performed using differences of mean and percentage change from baseline of 25(OH)D levels..

Results and conclusions

In healthy subjects in the buccal spray group, at the end of the 30-days trial, the mean increase in serum 25(OH)D concentration was from 18.91 (baseline) to 26.91 ng/mL (42.3%). In patients with malabsorption disease in the buccal spray group, at the end of the 30-days trial, the mean increase in serum 25(OH)D concentration was from 10.01 (baseline) to 20.47 ng/mL (104.5%).

In healthy subjects in the soft gelatine capsule group, the mean increase was from 18.69 to 22.75 ng/mL, 21.7%). In patients with malabsorption disease in the soft gelatine capsule group, the mean increase was from 11.01 (baseline) to 14.97 ng/mL (35.7%).

The control groups for healthy subjects as well as patients with malabsorption syndrome showed no significant change in concentration.

It can be concluded that the buccal spray produced a significantly higher mean serum 25(OH)D concentration as compared to the soft gelatin capsule, in both healthy subjects as well as in patients with malabsorption syndrome over a period of 30 days administration. The mean increase was much higher in the patients group as compared to the healthy subjects group.

Treatments were well tolerated by both subject groups.

Cited by 26 papers

https://scholar.google.com/scholar?cites=13090461309872966758&as_sdt=2005&sciodt=0,5&hl=en

17. Faisal "Sublingual vitamin D3 effective in a patient resistant to conventional vitamin D supplementation"

https://pubmed.ncbi.nlm.nih.gov/33244499/

Authors, institutions and journal

- S. Faisal, F. Mirza
- Primary Care Internal Medicine Residency Program, UConn Health, Farmington, Connecticut, and Division of Endocrinology and Metabolism, Department of Medicine, UConn Health, Farmington, Connecticut, USA
- AACE Clinical Case Reports, 2020

Background and methods

Vitamin D deficiency is prevalent world-wide and is usually treated with oral supplementation. However, bioavailability of supplemental vitamin D may differ among individuals due to variable absorption or altered metabolism. For example, it is influenced by several different factors after ingestion, including gastric pH, gastric enzymes including pepsin and trypsin, and duodenal enzymes. It is supposed that medications administered via the sublingual route are more easily absorbed through the sublingual blood vessels, bypassing the first-pass hepatic metabolism.

In this case report, a 66-year old woman with a history of osteoporosis presented for evaluation of low 25-hydroxyvitamin D (25[OH]D) level (the 25-hydroxyvitamin D is the active metabolite of vitamin D, and is used to monitor blood D levels). She had no known prior history of gastric or intestinal surgeries or malabsorptive conditions. She had previously been treated with oral vitamin D3 at 2,000 IU daily with poor response. She was then treated with oral vitamin D2 at 50,000 IU weekly, with persistently low 25(OH)D level at 14 ng/mL after 8 weeks of treatment. Therefore, this experiment is aimed to assess if she will absorb more vitamin D sublingually.

Results and conclusions

Due to demonstration of mentioned poor oral absorption, the woman was at first prescribed vitamin D2 at 50,000 IU weekly sublingually for 8 weeks. After this period, her 25(OH)D levels had improved to 23 ng/mL, which is still relatively low even after this high-dose intervention. Indeed, the Endocrine Society defines vitamin D deficiency as 25(OH)D levels <20 ng/mL, insufficiency between 21 to 29 ng/ mL, and optimal as >30 ng/mL (levels <12 ng/mL are considered severe deficiency).

So the therapy is then changed to over-the-counter vitamin D3 drops sublingually (1,000 IU/drop) at 4,000 IU twice daily. As a result, 25(OH)D level improved gradually to 28 ng/mL after 12 weeks on this regimen and was at 37 ng/mL after 1 year. The patient's 25(OH)D level was checked mainly

using immunoassays.

To conclude, sublingual vitamin D3 is proven to be (D2 less so), in this case, an effective alternative mode of vitamin D supplementation in patients who demonstrate poor oral vitamin D absorption.

Cited by 0 papers

18. Todd "Vitamin D3 supplementation using an oral spray solution resolves deficiency but has no effect on VO2 max in Gaelic footballers: results from a randomized, double-blind, placebo-controlled trial"

https://pubmed.ncbi.nlm.nih.gov/27015912/

Authors, institutions and journal

- J. Todd, E. McSorley, L. Pourshahidi, S. Madigan, E. Laird, M. Healy, P. Magee
- Northern Ireland Center for Food and Health, University of Ulster, Coleraine, Northern Ireland, UK; Irish Institute of Sport, Abbotstown, Dublin, Ireland, UK; Institute of Molecular Medicine, Trinity College, Dublin, Ireland, UK; Department of Medicine, Trinity Center for Health Science St. James's Hospital, Dublin, Ireland, UK
- Eur J Nutr, 2016

Study details

The study was registered at clinicaltrials.gov with ID NCT02278172:

https://clinicaltrials.gov/ct2/show/NCT02278172?id=NCT02278172&draw=2&rank=1

Background and methods

Vitamin D inadequacy is a global health concern in athletes as well as the general population. This study aims to verify if the vitamin D supplementation, using a buccal spray, increases the concentration of a total serum 25-hydroxyvitamin D (a marker of vitamin D in blood),

In addition, the study aims to verify if the supplementation improves parameters of physical abilities: VO2 max (maximal oxygen consumption), vertical jump height, left and right handgrip strength, forced vital capacity (FVC), and forced expiratory volume at 1 s (FEV1). In fact, concerning the physical abilities, in some observational studies total 25(OH)D concentration has been positively associated with measures of aerobic fitness (a major limitation of those studies is inability to determine causality).

This parallel group, double-blind, randomized, placebo-controlled trial in healthy male and female Gaelic footballers (n = 42) investigated the effect of vitamin D3 supplementation (cholecalciferol) of 3000 IU = 75 µg daily for 12 weeks, via an buccal spray solution, on the vitamin D marker measured in blood, and on mentioned physical abilities parameters.

Results and conclusions

Supplementation significantly increased total 25-hydroxyvitamin D concentrations compared to the placebo group: the mean increases from baseline were 36.31 (from baseline 47.37 to 83.68) compared to 6.11 nmol/L (from baseline baseline 43.10 to 49.22).

At baseline, 50% and 22 % of footballers presented with vitamin D insufficiency (31–49 nmol/L) and deficiency (<30 nmol/L), respectively. The high prevalence of vitamin D inadequacy observed in this cohort of Gaelic footballers supports the need for vitamin D supplementation during wintertime. The supplementation resolved vitamin D deficiency in all footballers. There were no adverse health effects to supplementation.

On the other hand, total 25-hydroxyvitamin D concentration did not significantly correlate with any measure of physical performance, i.e. the use of supplements did not improve physical fitness. It was demonstrated that vitamin D supplementation over 12 weeks had no significant effect on VO2 max, vertical jump height, left and right handgrip strength, forced vital capacity or forced expiratory volume at 1 s, after adjusting for confounders.

Cited by 45 papers

https://scholar.google.com/scholar?cites=12889520871423813777&as_sdt=2005&sciodt=0,5&hl=en

19. Nalbantoglu "Investigating the Efficiency of Vitamin D Administration with Buccal Spray in the Treatment of Vitamin D Deficiency in Children and Adolescents"

https://pubmed.ncbi.nlm.nih.gov/34109778/

Authors, institutions and journal

- O. Nalbantoglu, S. Acar, G. Arslan, O. Koprulu, B. Ozkan
- University of Health Sciences Turkey, Dr. Behcet Uz Child Diseases and Pediatric Surgery Training and Research Hospital, Clinic of Pediatric Endocrinology, İzmir, Turkey
- J Clin Res Pediatr Endocrinol, 2021

Background and methods

The aim of this study was to evaluate the efficiency of buccal spray supplementation of vitamin D compared to regular oral drops therapy, and to single oral high dose (Stoss) therapy, in the treatment of vitamin D deficiency in the young population.

90 healthy children and adolescents (3-18 years) with vitamin D deficiency (serum level of 25(OH)D <12 ng/mL) were randomized to receive vitamin D3 buccal spray (2000 IU, n=30, group 1) for 6 weeks, oral drops (2000 IU, n=30, group 2) for 6 weeks, and a single oral high dose (300 000 IU) vitamin D3 (n=30, group 3). Serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone and 25(OH)D levels of the patients were measured at baseline and after the treatment on the 42nd day.

Results and conclusions

All three groups had a significant increase in serum 25(OH)D concentrations. In group 1, baseline mean 25(OH)D was 8.0 ng/mL, which rose to 22.1 ng/mL after treatment, with a mean increase of 15.6 ng/mL. Similarly in group 2, baseline, post-treatment and mean increase in 25(OH)D concentrations were 7.9 ng/mL, 24.4 ng/mL and 17.3 ng/mL, respectively. For group 3 these values were 7.6 ng/mL, 40.3 ng/mL and 34.3 ng/mL, respectively.

Therefore, vitamin D3 supplementations with buccal spray and oral drops are equally effective in terms of raising vitamin D concentrations in short-term treatment of vitamin D deficiency.

Cited by 0 papers

20. Todd "Vitamin D3 supplementation in healthy adults: a comparison between capsule and oral spray solution as a method of delivery in a wintertime, randomized, open-label, cross-over study"

https://pubmed.ncbi.nlm.nih.gov/27724992/

Authors, institutions and journal

- J. Todd, E. McSorley, L. Pourshahidi, S. Madigan, E. Laird, M. Healy, P. Magee
- Northern Ireland Center for Food and Health, University of Ulster, Coleraine, UK; Irish Institute of Sport, Sports Campus Ireland, Dublin, Ireland; School of Biochemistry and Immunology, Trinity College, Dublin, Ireland; Department of Biochemistry, Central Pathology Laboratory, St. James's Hospital, Dublin, Ireland
- British Journal of Nutrition, 2016

Study details

The study was registered at clinicaltrials.gov with ID NCT02608164:

https://clinicaltrials.gov/ct2/show/NCT02608164?id=NCT02608164&draw=2&rank=1

Background and methods

This study aimed to compare the efficacy of vitamin D3 liquid capsules and oral spray solution in increasing total 25-hydroxyvitamin D (25(OH)D) concentrations in wintertime. In this randomized, open-label, two-period, cross-over trial, healthy adults (n=22) received 3000 IU (75 µg) vitamin D3 daily, for a 4 weeks period, in either capsule or oral spray form. Following a 10-week washout phase, participants received the opposite treatment for a final 4 weeks period.

Results and conclusions

Anthropometrics and fasted blood samples were obtained before and after supplementation, with samples analyzed for total 25(OH)D, creatinine, intact parathyroid hormone, and adjusted calcium concentrations. At baseline, vitamin D sufficiency (total 25(OH)D >50 nmol/l), insufficiency (31–49 nmol/l) and clinical deficiency (<30 nmol/l) were evident in 59%, 23% and 18% of the participants, respectively.

Mean values of the total 25(OH)D concentration before vs after supplementation are: with capsules 60.0 vs 90.4 nmol/l (increase of 30.4 nmol/l, i.e. 51% – *larger increase than what was observed by Satia et al.*), and with oral spray solution 59.6 vs 85.8 nmol/l (increase 26.2 nmol/l, i.e. 44% – *the same as observed by Satia et al.*). The statistical analysis revealed no significant difference in the change from baseline between oral spray and capsule supplementation methods.

Therefore, oral spray vitamin D3 is an equally effective alternative to capsule supplementation in healthy adults. Nevertheless, the ability of oral spray vitamin D3 to bypass the intestinal absorption route may well prove superior for those with gastrointestinal malabsorption syndromes and for individuals with difficulty swallowing such as the elderly, young children and babies.

Cited by 12 papers

https://scholar.google.com/scholar?cites=10971175245783677580&as_sdt=2005&sciodt=0,5&hl=en

21. Penagini "Short-Term Vitamin D3 Supplementation in Children with Neurodisabilities: Comparison of Two Delivery Methods"

https://pubmed.ncbi.nlm.nih.gov/28898870/

Authors, institutions and journal

- F. Penagini, B. Borsania, K. Maruca, V. Giosia, S. Bova, M. Mastrangelo, G. Zuccotti, S. Mora
- Department of Pediatrics, University of Milan, "V. Buzzi" Children's Hospital, Milan, Italy; Laboratory of Pediatric Endocrinology, Division of Genetics and Cell Biology, IRCCS San Raffaele Scientific Institute, Milan, Italy; Pediatric Neurology Unit, "V. Buzzi" Children's Hospital, Milan, Italy
- Horm. Res. Paediatr, 2017

Background and methods

Vitamin D deficiency is common in children with neurodisabilities. Oral vitamin D3 may not be absorbed appropriately, due to dysphagia and tube feeding. The aim of this study was to compare the efficacy of vitamin D3 buccal spray with that of oral drops.

The buccal spray contains micro-sized droplets of vitamin D3 that are supposed to be rapidly and completely absorbed by the oral mucosa, bypassing problems linked to dysphagia, malabsorption, unpredictable GI transit, and PEG feeding.

24 children with neurodisabilities (5–17 years) and vitamin D deficiency (25(OH)D ≤ 20 ng/mL) were randomized to receive vitamin D3 buccal spray 800 IU/daily (n = 12) or oral drops 750 IU/daily (n = 12) for 3 months during winter.

We evaluated the effect of this short-time supplementation on: serum concentration of 25(OH)D [only those results will be presented here as relevant], parathyroid hormone (PTH), and two markers of bone metabolism.

Results and conclusions

Both groups had a significant increase in 25(OH)D. After 3 months of supplementation, the 25(OH)D concentration increased from 15.5 ng/mL to 34.5 ng/mL (increase by 123%) in the group receiving oral drops, and from 11.5 ng/mL to 26.5 ng/mL (increase by 130%) in the buccal spray group.

The satisfaction with the formulation was, however, significantly higher in the patients using the spray compared to those using oral drops: 54% of participants scored 2 and 46% scored 3 in the oral drops group vs. 8% scored 2 and 92% scored 3 in the buccal spray group (0 = not satisfied at all, 1 = quite dissatisfied, 2 = quite satisfied, 3 = completely satisfied). Palatability issues were reported only in the oral drops group.

Vitamin D3 supplementation with buccal spray and oral drops are equally effective in short-term treatment of vitamin D deficiency in children with neurodisabilities. Buccal spray may be more acceptable by the patients.

Cited by 5 papers

https://scholar.google.com/scholar?cites=3439870283652003811&as_sdt=2005&sciodt=0,5&hl=en

22x. Williams "Rate of change of circulating 25-hydroxyvitamin D following sublingual and capsular vitamin D preparations"

https://www.nature.com/articles/s41430-019-0503-0

Authors, institutions and journal

- C. Williams, E. Williams, B. Corfe
- Department of Oncology & Metabolism, University of Sheffield, Sheffield, UK
- European Journal of Clinical Nutrition, 2019

Background and methods

Vitamin D is critical for skeletal health, and is increasingly associated with other pathologies encompassing gastrointestinal, immunological and psychological effects. A significant proportion of the population exhibits suboptimal levels of vitamin D. Supplementation is therefore advocated. There has been considerable interest in the potential use of sublingual sprays for delivery of nutrient supplements.

A randomized, placebo-controlled, three-arm parallel design study was conducted in healthy volunteers (n = 75) to compare the rate of change of vitamin D status in response to vitamin D3 (3000 IU/day) supplementation in capsule and sublingual spray preparations over a 6-week period. Blood 25(OH)D concentrations were measured on days 0, 3, 7, 14, 21 and 42.

Results and conclusions

Baseline measurements show 25(OH)D deficiency (<30 nmol/l), insufficiency (31–46 nmol/l) and sufficiency (> 50 mmol/l) in 15, 45 and 40% of the participants, respectively. At the study end, there was a significant elevation in blood concentrations of 25(OH)D in both of the treatment arms compared with control. The capsule and spray were equally efficacious.

The rate of change ranged from 0.69 to 3.93 (capsule: increase of 470%) and 0.64 to 3.34 (spray: increase of 422%) nmol/L day with average change in blood 25(OH)D levels of 2 nmol/l/day. The rates of change are higher in individuals with lower levels of 25(OH)D.

To conclude, a sublingual vitamin D spray is an effective mode of delivery for supplementation in a healthy population.

Cited by 7 papers

https://scholar.google.com/scholar?cites=5968027681587376126&as_sdt=2005&sciodt=0,5&hl=en

23. Batchelor "The effectiveness of buccal Vitamin D replacement in patients requiring home parenteral nutrition"

https://www.sciencedirect.com/science/article/abs/pii/S2405457721000632

Authors, institutions and journal

- S. Batchelor, L. Gemmell, C. Kirk, C. Mountford, N. Thompson
- Department of Gastroenterology, Freeman Hospital, Newcastle upon Tyne, UK
- Clinical Nutrition ESPEN, 2021

Background and methods

Patients with intestinal failure requiring home parenteral nutrition are at risk of vitamin D and other micronutrient deficiencies. Conventional enteral replacement of Vitamin D may not be sufficient for this patient group. This study examines whether buccal Vitamin D provides an alternative, effective route for supplementing Vitamin D in patients with intestinal failure.

A retrospective review of patients who received buccal Vitamin D replacement was carried out. The buccal preparation prescribed to these patients was the 'Better You Dlux 3000 Vitamin D spray' which contains 3000 IU of vitamin D3 (cholecalciferol).

Serum Vitamin D levels were recorded prior to buccal replacement, and then at a minimum interval of 3 months after commencement. A cost comparison of a 6 month course of this preparation was also made with an equivalent duration of replacement using oral cholecalciferol capsules. 17 patients were identified.

Results and conclusions

The mean level of Vitamin D prior to replacement was 28.4 nmol/l with 65% of patients classed as Vitamin D deficient (<25 nmol/l). Following buccal Vitamin D replacement, no patients were classed as Vitamin D deficient, with all levels ≥25 nmol/l and a mean of 62.3 nmol/l (increase of 119%).

Using costings from our hospital pharmacy, a 6 month course of this buccal Vitamin D preparation was 38% less expensive than 6 months of replacement with oral cholecalciferol capsules.

This study therefore shows that in patients with intestinal failure on home parenteral nutrition, buccal Vitamin D is both a use and cost-effective method of replacement.

Cited by 0 papers

24x. Thomson "Use of Buccal Vitamin D Supplementation in Patients with Short Bowel Syndrome"

https://gut.bmj.com/content/65/Suppl_1/A16.2.abstract

Authors, institutions and journal

- G. Thomson, C. Mountford, N. Thompson
- Newcastle Upon Tyne Hospitals, Newcastle Upon Tyne, UK
- Gut, 2016

Background and methods

Vitamin D deficiency is a common consequence of short bowel syndrome and can detrimentally affect bone and muscle health. Oral vitamin D supplements can be absorbed variably and parenteral supplementation does not always result in improved serum levels. The research aimed to see if buccal vitamin D supplementation represents a useful alternative.

Patients with short bowel syndrome who had not responded to high doses of oral vitamin D supplementation and were prescribed buccal vitamin D spray were identified through the regional nutrition service (n = 13).

Participants were prescribed between 3000 and 9000 IU/day. Serum 25(OH) vitamin D was used to measure vitamin D status. Baseline levels were obtained prior to when buccal vitamin D was prescribed. This was compared with the level obtained at their next clinic appointment, at least one month later.

For analysis, a paired t-test was undertaken in two groups; A, including (n = 13), and B, excluding (n = 8), patients using other vitamin D supplements concurrently. Of those in group B, 75% had previously been prescribed oral vitamin D supplements without achieving vitamin D sufficiency.

Results and conclusions

In Group A, the mean baseline 25(OH)D was 22.3 ng/ml, and buccal vitamin D supplementation increased it to an average of 61.4 ng/ml (i175%). This increase proved to be statistically significant, and suggests that buccal vitamin D either alone or as an adjunct to oral supplements produces a significant rise in vitamin D level from that of deficiency to sufficiency.

In Group B, the mean baseline 25(OH)D was 21.9 ng/ml, and using buccal vitamin D spray alone, the mean 25(OH)D was increased to 53 ng/m (142%). This suggests that buccal vitamin D monotherapy may be sufficient to achieve adequate vitamin D levels in those patients who have not responded to oral supplements.

This study provides preliminary evidence, from a small number of patients, that buccal vitamin D spray may be an effective adjunct to oral vitamin D supplementation, or be an effective monotherapy in short bowel patients who do not respond adequately to oral supplements.

Cited by 0 papers

25x. Sausa "A comparison study of sublingual spray versus peroral capsules and oil in vitamin d supplementation"

https://www.endocrine-abstracts.org/ea/0081/ea0081ep138

Authors, institutions and journal

- S. Sausa, M. Aleksejeva, I. Trapina, V. Pirags
- University of Latvia, Faculty of Medicine, Riga, Latvia; Pauls Stradins Clinical University Hospital, Internal Medicine, Riga, Latvia; University of Latvia, Genomics and Bioinformatics, Institute of Biology, Riga, Latvia

- Endocrine Abstracts, 2022

Background and methods

Vitamin D is a vital hormone for calcium metabolism, bone and muscle health, and immune responses. Its deficiency affects the entire Latvian population. The goal of this study was to compare the effectiveness of three different forms of vitamin D supplements.

In a prospective, open-label, randomized study, data from 98 vitamin D deficient volunteers over one month at initiation of substitution with 4000 IU (100 µg) colecalciferol was analyzed. The efficacy of the peroral oil (oil group), lanolin-derived microemulsion sublingual spray (spray group) and peroral capsules dissolved in sunflower oil (capsules group) was evaluated by comparing patient data with age, BMI and renal function.

Results and conclusions

Among 98 volunteers with total 25(OH)D vitamin levels < 30 ng/ml, mean 18.30 ng/ml, and BMI < 35 kg/m2, mean age 39 years, 60% were female. After one month of intervention, the increase in vitamin D in all groups was 13.21 ng/ml (72%). The increase (all units in ng/ml) was 14.98 (82%), 11.06 (60%) and 9.97 (54%) in the oil group, capsules group and spray group, respectively. There was at least one respondent with negative vitamin D dynamics in each group.

In the capsule group, the changes in vitamin D were statistically significantly inversely related to the respondent's age and BMI – the younger the person, the more pronounced the increase in vitamin D; similarly, the lower the BMI, the higher the increase in vitamin D. In the spray group, a statistically significant correlation was found between the increase in vitamin D and higher glomerular filtration rate (GFR).

Therefore, an increase in vitamin D levels was observed in all groups after one month of supplementation, and the formulation did not statistically significantly affect the overall outcome.

Cited by 0 papers

26. Tazzyman "Vitamin D associates with improved quality of life in participants with irritable bowel syndrome: outcomes from a pilot trial"

https://pubmed.ncbi.nlm.nih.gov/26719813/

Authors, institutions and journal

- S. Tazzyman, N. Richards, A. Trueman, A. Evans, V. Grant, I. Garaiova, S. Plummer, E. Williams, B. Corfe
- Academic Unit of Surgical Oncology, Department of Oncology, University of Sheffield, Sheffield , UK; Research Department, Cultech Ltd, Baglan Industrial Park, Port Talbot, UK; Human Nutrition Unit, Department of Oncology, University of Sheffield, Sheffield, UK
- BMJ Open Gastroenterol, 2015

Background and methods

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder which profoundly affects quality of life (with symptoms as diarrhea, constipation, abdominal pain), with a prevalence of 10–15% in the industrialized world. It is poorly understood, and is generally regarded as a multifactorial disorder involving host and environmental factors, including diet. Symptom treatment meets with limited success and may not be effective for long-term management of IBS.

A case study of an IBS patient taking high dose (3000 IU daily) vitamin D is reported. The participant reported remission of IBS symptoms following supplementation. On the basis of this, the hypothesis was that patients with IBS (vitamin D insufficient or not), would report improvement in symptoms following vitamin D supplementation. The research further sought to test whether vitamin D supplementation in combination with a probiotic preparation would act synergistically.

This was a 12-week double-blind, placebo-controlled, stratified study. By the end of the study 51 participants were recruited. Participants were stratified by baseline vitamin D status as follows: 'Vitamin D deficient' (25OHD < 20 ng/mL) and 'Vitamin D replete' (25OHD > 20 ng/mL).

Participants were randomized to receive: either double placebo (n=18, Placebo arm), or vitamin D supplementation and probiotic placebo (n=17, Vitamin D arm) or both probiotic and vitamin D supplementation (n=16, Vitamin D + Probiotic arm).

To assess vitamin D status, participants provided a blood sample from which baseline and exit 25OHD was measured in serum. In addition, baseline IBS symptom questionnaires were completed: the participants assessed their abdominal pain, bloating, bowel habits and quality of life over each 2-week period [those results will not be presented as irrelevant].

Vitamin D3 and the corresponding placebo were provided as 15 mL liquid sublingual sprays. Both contained identical buffers, with placebo lacking the active vitamin D3. Each spray of vitamin D3 gave a single dose daily, containing 3000 IU vitamin D3.

Results and conclusions

At the baseline, in the Placebo, Vitamin D, and Vitamin D + Probiotic arms, the percentage of vitamin D replete patients was 18.5%, 22.2% and 25.0%, respectively [the numbers are somewhat confusing in the paper, so the value from the tables are taken, rather from the text]. Mean serum 25OHD was 15, 14 and 16 ng/mL in the three arms, respectively.

At the exit, in the Placebo, Vitamin D, and Vitamin D + Probiotic arms, the percentage of vitamin D replete patients was 60.0%, 92.3% and 87.5%, respectively. Mean serum 25OHD was 25, 37 and 37 ng/mL in the three arms, respectively, which means that the increase was 67%, 164% and 131%, respectively. There were no adverse events.

To conclude, supplementation significantly improved vitamin D level versus placebo. IBS symptoms were not significantly improved in this pilot. The presence of probiotics in the supplement did not change the final result.

Cited by 41 papers

https://scholar.google.com/scholar?cites=10334389578063543656&as_sdt=2005&sciodt=0,5&hl=en

BONUS PUBLICATIONS

B1. Bubshait "Topical vitamin D3: A randomized controlled trial"

https://pubmed.ncbi.nlm.nih.gov/30144887/

Authors, institutions and journal

- D. Bubshait, D. Al-Dakheel, F. Alanii
- Department of Orthopedic Surgery, College of Medicine, Imam Abdul Rahman Bin Faisal University, Dammam, King Fahd Hospital of the University, Al Khobar, Saudi Arabia
- Clinical Nutrition ESPEN, 2018

Study details

The study was registered at clinicaltrials.gov with ID NCT02735200:

https://clinicaltrials.gov/ct2/show/NCT02735200?id=NCT02735200&draw=2&rank=1

Background and methods

The intent of the study was to test the effect of Top-D, a topical Vitamin D preparation, in delivering vitamin D. Five hundred and fifty healthy patients, with vitamin D insufficiency and deficiency were recruited. A vitamin D3 level of 30 ng/mL is accepted as normal, 21-29 ng/mL as insufficiency, and under 20 ng/mL as deficiency. Complete blood analysis, serum calcium, phosphorus, Parathormone and 25 Hydroxy-vitamin D3 (25OHD) was carried out before enrollment of the patients. Patients were then divided randomly into two groups: 350 in the study group, and 200 in the control group. Patients in the study group were given Top-D (Vitamin D3 gel made from proniosomal technology) to apply daily on the skin. Top-D 1 g contained 5000 IU of vitamin D3. The control group was given 1 g of Aloe vera gel to be applied every day. After 4 months serum 25OHD was tested again.

Results and conclusions

345 patients in the study group and 192 in the control group completed the study. The mean age of the patients in both the groups was 42 years (18 to 80 years). The pretreatment 25OHD levels in the study group were 11.03 ± 4.57 ng/l, compared to 10.36 ± 4.09 in the control group. The posttreatment levels were 37.17 ± 6.04 ng/ml, compared to 10.51 ± 3.5 ng/ml. The results of this study indicate that transdermal route of vitamin D is potentially safe

and can give desired results to raise the vitamin D levels. The size of the skin pores are approximately the diameter of 50 µm, whereas the average particle size of proniosomal Top-D gel is 3.84 ± 0.35 µm, hence the absorption of vitamin D3 through the pores was without difficulty.

Cited by 11 papers

https://scholar.google.com/scholar?cites=4910436645127239003&as_sdt=2005&sciodt=0,5&hl=en

B2. Alsaqr "Investigating Transdermal Delivery of Vitamin D3"

https://pubmed.ncbi.nlm.nih.gov/25609377/

Authors, institutions and journal

- A. Alsaqr, M. Rasoully, F. Musteata
- Department of Pharmaceutical Sciences, Albany College of Pharmacy and Health Sciences, Albany, New York, USA
- AAPS PharmSciTech, 2015

Background and methods

Transdermal delivery of therapeutic amounts of vitamin D3 is proposed to overcome its variable oral bioavailability, especially for people who suffer from fat malabsorption. The main challenge for the transdermal delivery route is to overcome the barrier properties of skin, especially for very lipophilic compounds such as vitamin D3.

In this study, the effect of different penetration enhancers, such as oleic acid, dodecylamine, ethanol, and oleic acid in propylene glycol were evaluated *in vitro* for their effectiveness in delivering vitamin D3 through: polyamide filter, polydimethylsiloxane (PDMS) membrane, and porcine skin. A diffusion cell was used to study the transdermal permeability of vitamin D3.

Ointment formulations of vitamin D3 were prepared containing the most widely used penetration enhancers: oleic acid and dodecylamine. Petroleum jelly (white Vaseline) was used as an ointment base, because it is compatible with many drugs, and increases drug permeation because of its occlusive properties.

Three formulations with vitamin D3 were prepared: one as control and two with penetration enhancers. Formulation 1 (F1) consists of vitamin D3 ointment without any penetration enhancers and is used as control. Formulation 2 (F2) contains oleic acid as penetration enhancer, while formulation 3 (F3) contains dodecylamine as penetration enhancer.

Results and conclusions

The cumulative amounts of vitamin D3 permeated through the polyamide filter in 24 h were (mean values): 4.0×10^4, 5.2×10^3, and 6.6×10^4 ng/cm2 for F1, F2, and F3 ointments, respectively. The amounts permeated through the PDMS membrane in 24 h from the F1, F2, and F3 ointments were: 1.3×10^3 ng/cm^2, 3.3×10^3 ng/cm^2, and 6.4×10^3 ng/cm^2, respectively.

The cumulative amounts of vitamin D3 penetrated through the skin over 24 h from F1, F2, and F3 were 170, 0, and 360 ng/cm^2, respectively. For F2, no detectable increase in the concentration of vitamin D3 was observed. Since these amounts are too low for delivering the daily dose of vitamin, pretreatment of skin with other penetration enhancers was investigated. Indeed, skin pretreatment with 50% ethanol resulted in higher transdermal delivery of vitamin D3 in contrast to experiments that did not include pretreatment.

As a conclusion, the ointment containing oleic acid as chemical penetration enhancer did not improve delivery compared to control. On the other hand, the formulation containing dodecylamine as a penetration enhancer did improve the transdermal delivery of vitamin D3. However, statistical significance and an amount high enough for nutritional supplementation purposes were reached only when the skin was pretreated with 50% ethanol. In these conditions, the ointment delivered an amount of 760 ng vitamin D3 per cm^2 of skin. The research therefore shows promise that transdermal delivery could be an effective administration route for vitamin D3 when ethanol and dodecylamine are used as penetration enhancers.

Cited by 34 papers

https://scholar.google.com/scholar?cites=13824818861988583746&as_sdt=2005&sciodt=0,5&hl=en

Nutrient	Description	Reference	Values
Vitamin A	A fat-soluble vitamin; it is a group of organic compounds that includes retinol, retinal (also known as retinaldehyde), retinoic acid, and several provitamin A carotenoids (most notably beta-carotene); it has multiple functions: it is essential for embryo development and growth, for maintenance of the immune system, and for vision	Source	**normal:** serum retinol level above 0.70 µmol/L **subclinical deficiency:** serum retinol level 0.35-0.70 µmol/L **severe deficiency:** serum retinol level under 0.35 µmol/L
Vitamin B1 (thiamine)	A water-soluble vitamin which cannot be produced by the body; it helps the body cells change carbohydrates into energy; it also plays a role in muscle contraction and conduction of nerve signals; it plays a vital role in the growth and function of various cells	Source	**normal:** blood thiamine level 50 – 220 nmol/L **marginal deficiency:** blood thiamine level 5 – 50 nmol/L **overt deficiency:** blood thiamine level < 5 nmol/L
Vitamin B12 (cobalamin)	A water-soluble vitamin (one of eight B vitamins) involved in metabolism; it is used as a cofactor in DNA synthesis; it is important for the normal functioning of the nervous system via its role in the synthesis of myelin, and in the circulatory system in the maturation of red blood cells in the bone marrow; it is the only vitamin that must be sourced from animal-derived foods or supplements; its manufactured forms are	Source	**normal**: plasma vitamin B12 levels 160-950 pg/mL (118-701 pmol/L)

	cyanocobalamin and methylcobalamin.		
Vitamin C (ascorbic acid)	Nutrient necessary for the growth, development and repair of all body tissues; it is involved in many body functions, including formation of collagen, absorption of iron, the proper functioning of the immune system, wound healing, and the maintenance of cartilage, bones, and teeth	Source	**normal**: plasma vitamin C levels 0.4-1.7 mg/dL **insufficiency**: plasma vitamin C levels 0.2-0.4 mg/dL **deficiency**: plasma vitamin C levels <0.2 mg/dL
Calcium	Mineral most often associated with healthy bones and teeth, although it also plays an important role in blood clotting, helping muscles to contract, and regulating normal heart rhythms and nerve functions	Source	**normal:** serum level from 8.5 to 10.2 mg/dL (2.13 to 2.55 millimol/L).
Vitamin D	Prohormone, more accurately a group of fat-soluble secosteroids, responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and many other biological effects; in humans, the most important compounds in this group are vitamin D3 (also known as cholecalciferol) and vitamin D2 (ergocalciferol)	Source	**normal**: serum hydroxyvitamin D levels 75-100 nmol/L (30-40 ng/ml) **insufficiency**: serum hydroxyvitamin D levels 50-75 nmol/L (20-30 ng/ml) **deficiency**: serum hydroxyvitamin D levels <50nmol/L (20 ng/ml)
Iron	Mineral that the body uses it to make hemoglobin, a protein in red blood cells that carries oxygen from the lungs to all parts of the body, and myoglobin, a protein that provides oxygen to muscles; the body also needs iron to make some hormones; the lack of iron is	Source	**normal:** serum iron level Iron: 60 to 170 micrograms per deciliter (mcg/dL), or 10.74 to 30.43 micromoles per liter (micromol/L)

	the most common nutritional deficiency worldwide; Iron from food comes in two forms: heme and non-heme; iron is stored in the body as ferritin		
Vitamin E	A group of eight fat-soluble antioxidant compounds that include four tocopherols (alpha, beta, gamma, delta) and four tocotrienols (alpha, beta, gamma, delta); among them, alpha-tocopherol is essential and has the highest biological activity; vitamin E deficiency, which is rare and usually due to an underlying problem with digesting dietary fat rather than from a diet low in vitamin E, can cause neurological dysfunction	Source	**normal**: plasma alpha-tocopherol level 5 to 20 µg/mL (11.6 to 46.4 µmol/L)
Magnesium	Mineral that plays an important role in assisting more than 300 enzymes to carry out various chemical reactions in the body such as building proteins and strong bones, and regulating blood sugar, blood pressure, and muscle and nerve functions; it also acts as an electrical conductor that contracts muscles and makes the heart beat steadily.	Source	**normal:** serum magnesium level 1.7 to 2.2 mg/dL (0.85 to 1.10 mmol/L).
Zinc	Essential nutrient required for numerous processes in the body, including: gene expression, enzymatic reactions, immune function, protein synthesis, DNA synthesis, wound healing, growth and development.	Source	**normal**: serum zinc levels 0.66-1.10 µg/mL

GLOSSARY

Absorption

The process of movement of a drug into the bloodstream after administration

ADME

Abbreviation in pharmacokinetics and pharmacology for "absorption, distribution, metabolism, and excretion", which describes the disposition of a pharmaceutical compound within an organism

Baseline values

Values gathered at the beginning of a study, which are used as a reference point to determine a subject's response to the experimental treatment

Bioavailability

A subcategory of absorption defined as the fraction (%) of an administered drug that reaches the bloodstream; when a medication is administered intravenously, its bioavailability is 100%; when a medication is administered orally, its bioavailability is lower than 100% due to intestinal endothelium absorption and first-pass metabolism

Buccal

Related to the route of administration of the substance in the mouth through buccal mucosa

Controlled study

Study that includes a comparison (control) group; the comparison group receives a placebo, another treatment, or no treatment

Clinical Pharmacology

Discipline that teaches, does research, frames policy, gives information and advice about the actions and proper uses of medicines in humans and implements that knowledge in clinical practice

Clinical trial

Clinical study (two terms are equal and widely used)

Crossover study

Study in which all participants receive the same two or more treatments, but the order in which they receive them depends on the group to which they are randomly assigned (for example, one group is randomly assigned to receive

drug A followed by drug B; the other group receives drug B followed by drug A; there is usually a rest period between treatments)

Distribution

The process of transfer of a drug from one location to another within the body, most often via the bloodstream

Double-blinded study

Study in which neither the researchers nor the subjects know which treatment a specific subject is receiving; this helps prevent bias or expectations from influencing the results of the study

Elimination

Process of how the drug expels from the organism, which happens in the liver and kidneys

Metabolism

The process of how the drug is metabolized (chemically altered) in the liver of the human body

Mucosa

The moist, inner lining of some organs and body cavities (such as the mouth)

Nutrients

Substances found in food which drive biological activity, and are essential for the human body; they are categorized as macronutrients (proteins, fats and carbohydrates) and micronutrients (vitamins and minerals)

Open-label study

Study in which both the researchers and the subjects are aware of the drug or treatment being given

Oral

The process by which drugs are delivered by mouth through the alimentary tract

Palatal membrane

The lining of the mouth on the hard (located at the front of the roof of the mouth) and soft (muscular part at the back of the roof of the mouth) palates

Parenteral

The process by which the drug is injected directly into the body, bypassing the skin and mucous membranes

Pharmacology

Science of how drugs act on biological systems and how the body responds to the drug; the study of pharmacology encompasses the sources, chemical properties, biological effects and therapeutic uses of drugs

Pharmacokinetics (PK)

Branch of pharmacology dedicated to determining the fate of substances administered to a living organism, from the moment at which it is administered up to the moment at which it is completely eliminated from the body; simply, it is the study of how an organism affects a drug

Pharmacodynamics (PD)

Branch of pharmacology dedicated to studying the biochemical and physiologic effects of drugs; simply, it is the study of how a drug affects a organism

Plasma

Fluid and solute component of blood, defined as blood with all cells removed

Randomized study

Study in which the subjects are divided randomly (by chance) into separate groups that compare different treatments or drugs

Sampling

Gathering of matter from the body to aid in the process of a medical diagnosis and/or evaluation of an indication for treatment, further medical tests or other procedures

Serum

Fluid and solute component of blood, defined as blood with all cells and clotting factors removed

Sublingual

Administered under the tongue

Supraphysiological

Greater than normally present in the body

Topical

Administered to body surfaces, such as the skin or mucous membranes; it is different from transdermal: transdermal products penetrate epidermis and dermis and enter the blood circulation, while topical products generally do not reach layers below the epidermis

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