

Local anti-inflammatory effect of vitamin D in acute and chronic gouty arthritis

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RESEARCH

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ABSTRACT

Background

Vitamin D has immunomodulatory, anti-inflammatory properties and important role in bone metabolism. Effects of vitamin D supplementation in musculoskeletal diseases are well known, but it is unknown if local application of vitamin D can have an anti-inflammatory potential.

Aims

The aim of this study was to investigate local influence of vitamin D on inflammation, pain, redness and swelling of the affected joint in acute and chronic gouty arthritis. 40 patients with acute gouty arthritis and 40 patients with chronic gouty arthritis were included in study.

Methods

We did topical application of cholecalciferol in a dose of 180,000 IU daily through seven days on the affected joint for one hour. Local changes of the affected joint such as swelling and redness were observed. Also, serum samples were taken on a 1st, 3rd and 7th day of application in order to measure levels of vitamin D, urates, calcium and C reactive protein.

Results

We found that local application of vitamin D increased its serum levels in both groups of patients while urates level, swelling, redness and pain was reduced. Effect of vitamin D on pain, redness and inflammation was stronger in a group with acute inflammation.

Conclusion

Local application of vitamin D may be linked to the reduction of acute and chronic inflammation in gouty arthritis. Relationship between vitamin D and urates in inflammatory process should be investigated further.

Key Words

Vitamin D, gout, arthritis, inflammation, topical

What this study adds:

1. What is known about this subject?

There is a growing number of studies investigating potential anti-inflammatory effects of vitamin D.

2. What new information is offered in this study?

Our study showed that topical application of vitamin D in acute and chronic gouty arthritis may be linked to the reduction of inflammation.

3. What are the implications for research, policy, or practice?

Vitamin D topical application can be used as additional therapy in acute and chronic gouty arthritis.

Background

Vitamin D is crucial for our health through its important role in bone metabolism and immunity. It exists in two forms as D2 (ergocalciferol) and D3 (cholecalciferol) and is made in the skin by sunlight exposure or consumed in food. When vitamin D3 enters the circulation it is delivered primarily to the liver where 25(OH)D is produced. 25(OH)D then travels to the kidney, where it is further hydroxylated to 1,25-dihydroxy-vitamin D (1,25(OH)₂-vitamin D or calcitriol), the

physiologically active form of vitamin D.¹

Recently, there are many studies suggesting how vitamin D deficiency is associated with growing incidence of cancer, cardiovascular diseases, diabetes mellitus, neurodegenerative diseases, depression and impaired cognitive function.^{2,3}

There is a growing interest about effects of vitamin D on inflammatory cells and processes. In vitro, vitamin D has been shown in promoting monocyte differentiation to macrophages, preventing them from releasing inflammatory cytokines and reducing their ability in presenting antigens to lymphocytes. Also, it suppresses the proliferation of T cells and monocytes and downregulates production of proinflammatory cytokines, including C reactive protein (CRP), tumour necrosis factor α (TNF α), interleukin 6 (IL-6), interleukin 1(IL-1), interleukin 8 (IL-8), while upregulating anti-inflammatory cytokines production such as interleukin 10 (IL-10).⁴ *In vivo* studies using animal models have shown that supplementation with 1,25(OH)D prevented the development of inflammatory arthritis.⁵ Higher vitamin D levels were associated with lower inflammatory markers levels including CRP, IL-6 and TNF α in healthy populations,⁶ and in those with proinflammatory conditions, such as diabetes, arteriosclerosis and inflammatory polyarthritis.⁷

It is known that high uric acid levels induce urate crystallization in many organs causing gout, urolithiasis, and acute and chronic nephropathy, but also diabetes mellitus, hypertension, metabolic syndrome and endothelial dysfunction which can lead to cardiovascular disease.⁸ Gouty arthritis is one of the most common forms of adult arthritis. It is condition caused by urate crystal deposits in joints. Crystals trigger an inflammatory response causing pain, warmth, swelling and redness of the affected joints. If this process is continuous over time it can lead to chronic tophaceous gout resulting in bone erosion, joint destruction and functional disability.⁹

Recent studies have investigated possible association between vitamin D and uric acid. Both vitamin D deficiency and hyperuricemia are related to the risk of occurrence of chronic diseases like cardiovascular disease and diabetes mellitus.¹⁰ There is an animal study showing how increased circulating uric acid was found to suppress 1 α -hydroxylase leading to lower 1,25(OH)₂D and increased PTH in rats.¹¹ Human studies are showing how administration of allopurinol reduces serum uric acid levels and increases 1,25(OH)₂D with a reduction in PTH.^{12,13} It is possible that PTH may influence uric acid metabolism directly or through

other mediators like vitamin D as one of them but this associations should be investigated further.¹⁰

This prospective study was done to investigate effects of vitamin D in acute and chronic gouty arthritis following its topical application and to further explore relationships between vitamin D, uric acid, calcium and C reactive protein in inflammatory processes.

Method

Study design: This was a seven days, open-label, prospective clinical study conducted in the Department of Internal Medicine in General hospital "Dr. Josip Bencevic", Slavonski Brod.

Patient selection: 40 patients with acute gouty arthritis were included in study, 20 male and 20 female. All patients had at least one episode of acute gouty arthritis before and at the time when study was conducted they also had acute gouty arthritis confirmed by clinical examination and laboratory results. There was a control group, 20 male and 20 female, with chronic gouty arthritis without signs of acute inflammation at the time of the study. Both groups had similar characteristics according to age and sex. All the patients gave verbal and written informed consent before enrolment. At the time of the study patients with acute inflammation received standard treatment for acute gouty arthritis – NSAID and paracetamol and with topical application of vitamin D while patients with chronic gouty arthritis received allopurinol therapy and topical application of vitamin D.

Exclusion criteria were age under 18 years or over 79 years, pregnancy, breastfeeding, severe cardiac, renal or hepatic disease, cancer, rheumatoid, infectious or psoriatic arthritis, previous joint surgery or arthroscopy within six months, uncontrolled systemic diseases including HIV infection or any immunosuppressive therapy, hypersensitivity to vitamin D or history of significant trauma of the joint. Patients with a history of current vitamin D supplementation, calcium treatment, hypercalcaemia, current treatment for osteoporosis, bisphosphonates use in the past two years, known primary hyperparathyroidism or an investigational drug usage within the last six months were also excluded from the study. A detailed history was taken, family history, duration of disease, and history of precipitating or initiating factors.

Treatment schedule: In both groups of patients we did topical application of vitamin D (cholecalciferol) in a dose of 180,000 IU daily for seven days to the affected joint for one

hour every day. We used oily suspension of vitamin D which we impregnated into the non-adherent dressing and then dressing was applied to the affected joint.

Blood collection and serum measurements: The collected venous blood sample and serum were separated and stored at -70°C until examination. Serum 25(OH)D levels were measured using the ADVIA Centaur and ADVIA Centaur XP systems (Siemens Healthcare Diagnostics). There has been a long debate on the cut-off points for vitamin D status. The Institute of Medicine considers inadequate if 25(OH)D levels are <50nmol/L or <20ng/mL.¹⁴ Serum calcium was measured by the *O*-cresolphthalein method. Levels of CRP were measured by the turbidimetric method using commercial kits (Cobas Integra CRPLX). Serum uric acid levels were measured on stored baseline samples via the Clinical Analyser utilizing a uricase-based commercial kit.

Clinical assessment: We measured local changes of the affected joint, such as swelling, redness and pain and during the time of the study. Serum samples were taken on the first, third and seventh day of the treatment in order to measure vitamin D, uric acid, calcium and C reactive protein (CRP) levels. We observed effect of the treatment on the affected joint like swelling by measuring joint circumference using a measuring tape in centimetres. Pain was measured according to 10cm long Visual Analogue Scale and redness was observed visually on a scale from 1 to 5. Value of 1 means there is no redness of the affected joint, 2 is mild redness, 3 is moderate redness, 4 severe and 5 very severe redness. Same treatment was applied in control group of patients with chronic gouty arthritis without the signs of acute inflammation at the time of the study.

Statistical analysis: Normally distributed data were presented as mean±standard deviation, and non-normally distributed data were presented as median (interquartile range [IQR]). Shapiro-Wilk test was used to measure the distribution. The Mann-Whitney *U* test was used for comparison of quantitative variables. Data were analysed using Friedman analysis of variance. All statistical tests were two-tailed, and the significance level was set at $P < 0.05$. The statistical analyses were performed using MedCalc Statistical Software version 14.12.0 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2014).

Results

Results are shown in Table 1. There were no significant differences between the two patients group in age and serum calcium levels. In group with acute gouty arthritis

serum levels of vitamin D3 were significantly higher while urates, CRP levels, joint circumference, redness and pain were significantly lower during and after treatment. In a group with chronic gouty arthritis vitamin D3 serum levels were increased significantly, while urate levels, joint circumference, redness and pain were significantly lower during and after treatment. There was no significant difference in serum CRP levels in this group.

In group with acute gouty arthritis urate levels, CRP levels, joint circumference and redness are significantly higher than in chronic gouty arthritis group through treatment. On 7th day of the treatment redness was the same between the two groups. Vitamin D3 levels were not significantly different between the two groups in all three measures through treatment. On the 3rd day of the treatment no difference in pain was observed.

Discussion

The interest in vitamin D has increased rapidly with the finding of its diverse biological effects over the past few years. There is a growing number of publications showing that vitamin D is essential for many physiological functions through its immunomodulatory properties, skeletal and extraskeletal functions mentioned previously.

Gouty arthritis is an inflammatory condition triggered by the deposition of monosodium urate crystals into the joint space. This can cause an inflammatory cascade activation resulting in the secretion of proinflammatory cytokines and neutrophils into the joint causing functional impairments and decreased quality of life.¹⁵

There are many studies investigating vitamin D3 topical application with promising results in psoriasis, vitiligo and corneal epithelial wound healing for example.¹⁶⁻¹⁸ This is a first study investigating effects of vitamin D3 topical application in gouty arthritis.

The results of this study showed that according to Institute of Medicine reference values both groups of patients had sufficient vitamin D values.¹⁴ Also, our study showed that vitamin D3 serum levels are increasing with every measuring during topical application. This is comparable to study of Sadat-Ali et al. where transdermal delivery of vitamin D was explored. This study showed that supplementation of vitamin D3 by topical route is sufficient in healthy participants and can be delivered safely through the dermal route. Moreover, they suggest that this kind of treatment could be exploited in treating vitamin D

deficiency with increased compliance among patients comparing to oral and injection forms of vitamin D.¹⁹

Our results also showed that during and after the treatment there were significantly lower levels of urates and clinical signs of inflammation in both group of patients, while CRP levels were significantly lower after treatment only in acute group of patients. This could suggest possible association between CRP and vitamin D status in acute inflammatory processes.

This results are comparable to study of Cannel et al. showing that vitamin D tends to lower markers of inflammation in highly inflammatory conditions.²⁰ Also, there is Study of Amer et al. showing that there is inverse relation between this parameters: vitamin 25(OH)D levels $\geq 21\text{ng/ml}$ are associated with an increase in serum CRP. This study suggests that vitamin D supplementation to reduce inflammation could be beneficial only if there is vitamin D deficiency.²¹

There are a couple of limitations of this study that should be discussed. We did not measure other inflammatory markers and cell levels such as sedimentation, leukocytes, neutrophils, lymphocytes and inflammatory cytokines.

Also, two compared groups received standard acute and chronic gouty arthritis treatment with topical vitamin D application. Other medications such as NSAID also affected inflammatory process.

However, our results are clinically significant showing topical effect of vitamin D and its transdermal absorption in both groups. This is confirmed through clinical examination and biochemical parameters measuring.

Conclusion

This study confirms anti-inflammatory potentials of vitamin D3.

It remains unclear what is the possible association between vitamin D3 and urates in gouty arthritis. Also, our study showed that there is an association between vitamin D3 and CRP in acute inflammation, but mechanisms following this should be investigated further.

Furthermore, our study has promising results for topical application of vitamin D3 in gouty arthritis. This could be a potential base for topical usage of vitamin D3 in other forms of arthritis, but other forms of inflammatory diseases also.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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Table 1: Differences between two patients group

	Median (interquartile range)				P [†]
	Chronic gouty arthritis group	P*	Acute gouty arthritis group	P*	
Age	56 (53.5-59.75)		56.5 (54-61.5)		0.79
Ca levels (mmol/L)	2.33 (2.21-2.39)		2.31 (2.18-2.44)		0.83
Vitamin D3 1st day(ng/ml)	37 (30.13-41.45)	0.001	32.65 (22.95-40.98)	0.002	0.53
Vitamin D3 3rd day(ng/ml)	40.3 (34.45-46.1)		36.4 (30.68-48.63)		0.60
Vitamin D3 7th day (ng/ml)	43.3 (39.7-48.18)		44.7 (40.65-57.4)		0.37
Urates 1st day (µmol/L)	221 (192-293.75)	0.03	425 (355.75-503.75)	0.01	0.001
Urates 3rd day(µmol/L)	200 (176.5-255.25)		400 (356.25-472)		0.001
Urates 7th day(µmol/L)	213.5 (184.5-253.75)		328 (301.75-442.75)		0.001
CRP 1st day (mg/L)	3.35 (2.13-4.08)	0.16	11.85 (8.23-14.75)	0.001	0.001
CRP 3rd day(mg/L)	3 (2.13-3.4)		7.05 (5.03-9.5)		0.001
CRP 7th day(mg/L)	2.85 (2.28-3.08)		5.8 (4.3-8.38)		0.001
Joint circumference 1st day (cm)	16.85 (14.53-18.25)	0.01	23.1 (21.5-24.8)	<0.001	0.001
Joint circumference 3rd day (cm)	16.35 (13.68-17.75)		22.1 (20.93-23.48)		0.001
Joint circumference 7th day (cm)	16.15 (13.65-17.95)		20.9 (19.65-22.25)		0.001
Redness 1st day	2.5 (2-3)	0.001	5 (5-5)	<0.001	<0.001
Redness 3rd day	2 (1-2)		3.5 (3-4)		0.001
Redness 7th day	1.5 (1-2)		1 (1-2)		0.63
Pain 1st day (VAS)	7.5 (7-8.75)	0.001	10 (9.25-10)	<0.001	0.001
Pain 3rd day(VAS)	7 (7-8)		7.5 (7-8)		0.62
Pain 7th day (VAS)	4 (3.25-5)		2.5 (1-3)		0.006