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Musculoskeletal Pain and Vitamin D Deficiency in Children: A Pilot Follow-up Study of Vitamin D Therapy in Musculoskeletal/Orthopedic Conditions

Muskuloskeletální bolest a deficit vitaminu D u dětí: pilotní studie sledování terapie vitaminem D u muskuloskeletálních ortopedických onemocnění

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ABSTRACT

PURPOSE OF THE STUDY

The prevalence of vitamin D deficiency in pediatric populations is high. In the present study we analyzed associations between vitamin D therapy and pain, mobility, fatigue, and daily functioning in children with musculoskeletal/orthopedic conditions suffering from chronic and recurrent pain, but also diagnosed with vitamin D deficiency.

MATERIAL AND METHODS

Children with different musculoskeletal/orthopedic conditions and vitamin D deficiency were prescribed to receive vitamin D over 6 months. Thirty-five children (18 males; age 10.48 ± 3.87 years) completed a 6-month follow-up. Self- and parent/proxy rating scales were used to evaluate pain, movement, fatigue, and daily functioning.

RESULTS

At a six-month follow-up assessment involving child- and parent-reported scores, worst pain intensity significantly decreased ($p \leq 0.03$) after vitamin D therapy, as well as functioning problems related to pain ($p \leq 0.01$). The children reported better movement and balance with less fatigue. The parents reported better functioning in everyday activities of their children.

CONCLUSION

This pilot study showed that vitamin D therapy possibly reduces pain intensity and improves mobility and daily functioning in children with musculoskeletal/orthopedic disorders, chronic recurrent pain, and vitamin D deficiency. Further follow-up and randomized studies are required in order to assess the validity of clinical recommendations.

Key words: vitamin D, pain, musculoskeletal disorders, children, adolescents.

INTRODUCTION

Chronic pain is a significant pediatric problem. It can be challenging to diagnose its underlying cause and to treat it; children may experience different physical and psychological sequelae, while their families may report emotional and social consequences. Regarding the consequences of pain and associated disability, huge costs for the healthcare provider could be involved (3, 7).

Musculoskeletal pain is one of the most frequent pediatric pain syndromes estimated to affect 4–40% of children with various disorders (7, 18, 19, 32). Chronic and recurrent musculoskeletal pain is also often present in pediatric orthopedic population (3, 7, 18). The pain may have various underlying causes; it can start at any age and may involve any part of the musculoskeletal system, intensifying or radiating to other areas (32). These children frequently present muscular spasms, abnormal posture and gait associated with a reluctance to mobilize, and general discomfort and amplification of pain (7). Additionally, musculoskeletal pain could have direct effects on other systems, leading to various symptoms, such as hypervigilance and hypersensitivity, thermodysregulation or autonomic dysfunction leading to further negative impacts on musculoskeletal disequilibrium, overall growth and development (7).

A recent review showed that vitamin D exerts various anatomic, hormonal, neurological, and immunological

influences on pain manifestation, thereby playing a role in the etiology and maintenance of chronic pain (for detailed review see ref. 29). The role of vitamin D deficiency in musculoskeletal pain is also implicated (1, 10, 21, 23, 26), possibly attenuating this type of pain (10, 14, 28). Some studies have reported that children receiving vitamin D experience fewer pain-days per week and show improved physical activity (25, 30).

As known, vitamin D exerts a wide range of effects on the skeletal muscles, such as muscular strength or function, as well as bone density (2, 9, 13), the pathophysiological mechanism of how vitamin D deficiency relates to musculoskeletal pain still remains unclear. For example, it has been suggested that there is a possible link between vitamin D and mostly pain, where vitamin D influences pain processing and muscular hypersensitivity (12). Vitamin D deficiency may alter central pain processing explained by higher levels of pro-inflammatory and procoagulation biomarkers (12, 17), which is indicative of endothelial activation and vascular reactivity caused by inflammation and oxidative stress, as seen in vitamin D deficiency and some types of pain-like headaches (24). It has been also implicated that low vitamin D levels may enhance central sensitivity, namely increased mechanical pain sensitivity and severity of somatic symptoms as shown in patients with chronic pain (37). Animal models have shown that vitamin D deficiency contributes to muscle hypersensitivity through direct effects on sensory nociceptor neurons in skeletal muscles (31). Additionally, it is speculated that pain suppression by the central nervous system, through top-down inhibition of musculoskeletal pain, is dysfunctional if there is a low vitamin D level (27). Beside these possible explanations, pain in vitamin D deficiency is also postulated to originate when there is insufficient calcium phosphate to mineralize the expanding collagen matrix of bone, which results in the rubbery matrix that does not provide sufficient support, but instead it hydrates and expands causing an outward pressure under the periosteal covering, which is richly innervated with sensory pain fibers (22, 27).

The prevalence of vitamin D deficiency in pediatric orthopedic populations could be high (4, 6), as it is musculoskeletal pain (7, 18). However, whether vitamin D therapy improves musculoskeletal pain in this population is unclear. We organized a pilot follow-up naturalistic study to analyze possible associations between vitamin D therapy and changes in pain occurrence and its severity, with changes in mobility and daily functioning in children with musculoskeletal disorders/orthopedic conditions suffering from chronic recurrent pain and who are diagnosed with vitamin D deficiency. Of special interest is to consider changes in the levels of pain and daily functioning as measured by patient-reported outcome (PRO) data. Including the PRO measure in clinical evaluations is important, because it provides information on how children perceive the impacts of their health condition and its treatment on everyday well-being and functioning.

MATERIAL AND METHODS

Participants and procedures

The current study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and it was approved by the Ethics Committee of the Institute for Orthopedic Surgery "Banjica", Belgrade, Serbia.

Children with chronic recurrent musculoskeletal pain in musculoskeletal/orthopedic conditions and who have vitamin D deficiency were eligible for the present study. The general study inclusion criteria were age 5–16 years, presence of musculoskeletal/orthopedic disorders, chronic and recurrent musculoskeletal pain, untreated vitamin D deficiency and ability to read/comprehend Serbian. The musculoskeletal/orthopedic condition refers to any condition involving the musculoskeletal system that might be subjected to orthopedic surgery with the use of both surgical and nonsurgical means to treat trauma, injuries, degenerative diseases, infections, tumors, congenital and other disorders. Vitamin D deficiency was diagnosed if serum 25-hydroxyvitamin D concentrations were ≤ 50 nmol/l (11). For the in-vitro determination of total 25-hydroxyvitamin, D Elecsys® "Vitamin D Total" Electro-chemiluminescence binding assay (ECLIA) by Cobas, Roche was used.

All children with the musculoskeletal/orthopedic condition referred for chronic musculoskeletal pain assessment and treatment at the Institute for Orthopedic Surgery "Banjica" were screened for vitamin D deficiency. During the period September 2012–March 2014, 37 consecutive patients diagnosed with vitamin D deficiency were included in this study. Each subject was prescribed a daily therapeutic vitamin D dose, which ranged from 1000 to 2000 IU, according to his/her body mass. The dose was administered for 6 months. Considering that this is a naturalistic study, all subjects were allowed to take analgesics if needed during the study period, but none of the subjects were prescribed regular treatment with analgesics at the start of the study. All participants were assessed during regular clinic visits after an informed consent was obtained prior to the study and assessments were organized at baseline and six months follow-up. However, all subjects were contacted monthly by their physicians in order to check for compliance and presence of possible side effects of the therapy.

Based on the probability of type I error of 0.05, power (1-beta) of 0.8, and medium effect size of 0.50 calculated in a statistical software G*Power version 3.1.2. (8), minimal sample size is 27 for pair t-test analyses.

Considering that there are no available generic PRO measures for children with orthopedic disorders, the Pediatric Quality of Life Inventory™ (PedsQL) Measurement Model was used (33). This measurement model integrates various generic and/or disease-specific PRO questionnaires for children with chronic disorders, available as self- and proxy-rating versions (34). Impor-

tantly, generic scales integrated in the PedsQL questionnaires are scored independently, which allows to be used separately in PRO assessments.

For the present study, we selected the following scales and questionnaires.

Presence of pain and its intensity was assessed by the PedsQL Pediatric Pain Questionnaire (PPQ), (35). The PPQ has two items that assess intensity of present and worst past pain by using age-appropriate visual analogue scale (VAS) response format scored on 0–100 points. The higher the PPQ VAS score, the higher the pain intensity.

The assessments of everyday functioning included the following: problems with pain in functioning were assessed by the Pain and Hurt generic scale (4 items), which is included in some PedsQL questionnaires, such as arthritis or cancer module (35, 36). Problems with moving body parts, walking, and balance were assessed by the Movement and Balance scale (5 items), the scale also included in the PedsQL questionnaires (35). Problems with feeling tired, weak or low energy were assessed with the Fatigue scale, which has 4 items (35, 36). Finally, participation in and problems with regular activities were assessed using the Daily activities scale (16 items). This scale is combined of similar scales that are included in various PedsQL modules (35, 36), and it assesses difficulties and problems in daily functioning such as with using tools, dressing, toileting, using computer and school activities. All used scales have a 5-point response format (0 = never a problem to 4 = almost always a problem) and they are reverse-scored and linearly transformed to a 0–100 scale. The summary score is computed as the sum of items in the scale divided by all answered items. A higher score indicates the lower level of problems and better functioning. Children aged 8–18 years self-completed all questionnaires, while parents completed parent-proxy versions.

Statistical plan

Mean (M) and standard deviation (SD) values were calculated for all scores. The pair t-test was used determine significance in differences between the scores at baseline and follow-up. The magnitude of differences was calculated as an effect size (ES); (mean follow-up scores, mean baseline scores)/pooled SD. According to Cohen's d thresholds (34), the ES was categorized as follows: trivial (0–0.19), small (0.20–0.49), medium (0.50–0.79) and large effects (≥ 0.80). All p values below 0.05 were considered significant.

RESULTS

Thirty-five children completed the full six months of follow-up; 18 (51.4%) males and 17 (48.6%) females aged 10.48 (± 3.87) years. One child was lost to follow-up and one child did not regularly receive therapy. There were 24 children aged 8–18 years who completed self-reports (in two children PPQ VAS were incomplete) and 32 parents who completed parent/proxy-report sets of questionnaires. Three parents provided incomplete data for their children. A developmental/congenital musculoskeletal disorder was present in 10 (28.6%) children, Perthes disease in 4 (11.4%), a bone tumor in 3 (8.6%), cerebral palsy in 6 (17.1%), while 9 (25.7%) children had a long-bone fracture, while 3 (8.6%) had recurrent joint dislocations treated surgically over 3–6 months. The sites of chronic pain were arms/shoulders in 2 (5.7%), legs/feet in 21 (60%), pelvis in 5 (14.3%), and other sites in 5 (14.5%) children. At the end of the study, 8 children reported using analgesics at least once a month, while one used one to two times per week, however none received regular analgesic treatment.

There was a significant increase in serum 25-hydroxy-vitamin D concentrations for the whole group from baseline (29.72 ± 11.55 nmol/l) to follow-up (51.19 ± 24.60 nmol/l), ($p < 0.001$). All laboratory values (i.e., electrolytes, hematological parameters, lipids, acid base status, and gastrointestinal function) at the beginning and the end of the study were within the reference range and no adverse effects of vitamin D therapy were reported by the subjects.

Table 1 and Table 2 present scale scores at baseline and follow-up.

The PPQ VAS child- and parent-report scores for present pain intensity decreased over the follow-up period, but without statistically significant change. However, the PPQ VAS scores for worst pain intensity showed a statistically significant decrease both when self- and parent-rated ($p \leq 0.03$). The Pain and Hurt scale scores significantly increased ($p \leq 0.01$).

The Movement and Balance and Fatigue scale self-report scores showed a statistically significant increase over the follow-up period ($p \leq 0.05$). This was not the case with the parent-reported scores of the two scales. On the contrary, only the parent-rated scores of the Daily activities showed a statistically significant increase ($p \leq 0.01$).

Table 1. Scales scores – self-report (mean – M and standard deviation – SD)

Scale score	Baseline, M (SD)	Follow-up, M (SD)	Pair t-test (p), d*
PPQ VAS – present, n = 23	21.30 (23.17)	19.34 (33.06)	0.87 (0.38), /
PPQ VAS – worst, n = 22	43.63 (22.38)	27.27 (25.57)	3.42 (< 0.01), 1.49
Pain and Hurt, n = 24	80.47 (21.67)	89.06 (14.88)	-3.57 (< 0.01), 1.48
Movement and Balance, n = 24	92.08 (13.74)	96.25 (8.62)	-2.25 (< 0.01), 0.93
Fatigue, n = 24	72.92 (17.64)	78.39 (16.78)	-2.88 (< 0.01), 1.2
Daily activities, n = 24	92.01 (21.57)	94.79 (19.87)	-1.37 (1.81), /

Note: Pediatric Pain Questionnaire – Visual analog scale (PPQ VAS); *Cohen's d effect size

Table 2. Scale scores – parent/proxy-report (mean – M and standard deviation – SD)

Scale score	Baseline, M (SD)	Follow-up, M (SD)	Pair t-test (p), d*
PPQ VAS – present, n = 32	17.18 (25.01)	12.34 (20.11)	1.29 (0.20), /
PPQ VAS – worst, n = 32	27.50 (30.55)	20.62 (29.39)	2.30 (0.03), 0.83
Pain and Hurt, n = 32	84.96 (21.70)	90.82 (14.37)	-2.69 (0.01), 0.97
Movement and balance, n = 32	88.87 (18.04)	90.69 (16.06)	-1.63 (0.11), /
Fatigue, n = 32	72.07 (24.43)	76.95 (22.69)	-1.60 (0.12), /
Daily activities, n = 32	90.93 (18.97)	93.31 (17.72)	-2.98 (< 0.01), 1.07

Note: Pediatric Pain Questionnaire – Visual analog scale (PPQ VAS); *Cohen's d effect size

DISCUSSION

In this pilot study we evaluated vitamin D therapy as related to pain, fatigue, mobility, and overall daily functioning in children with different musculoskeletal/orthopedic conditions suffering from chronic pain and vitamin D deficiency. We observed a large clinically significant increase in serum 25-hydroxyvitamin D concentrations that was treated with regular vitamin D therapy and followed by significant changes in the PRO measure scores used in the study.

Data from children and their parents showed that there was no significant decrease in the present pain intensity in the studied subjects. However, there was a large, clinically significant decrease in the worst past pain intensity and increase in everyday functioning directly related to pain, as measured by the Pain and Hurt scale at the follow-up assessment. Considering that we included children suffering of chronic recurrent pain, it is possible that at the time of assessments there were low levels of pain intensity, which is why no significant decrease in the present pain intensity was found. The worst past pain intensity decreased, while everyday functioning related to pain improved during the treatment period, which could be an effect of improved vitamin D deficiency. This finding is in accordance with some previous reports suggesting that vitamin D therapy attenuates musculoskeletal pain in children and adults (10, 14, 20, 25, 28, 30), throughout various anatomic, hormonal, neurological, and/or immunological pathways (29).

During the follow-up period the children reported clinically significant improvements in movement and fatigue, while their parents observed improvements in regular daily activates of the children, such as using tools, dressing, toileting, using computer and school activities. Although not definitely known, improvements in movement and fatigue with better daily function could be an effect of lowered pain intensity (7) or better condition of the musculoskeletal system due to increased serum 25-hydroxyvitamin D concentrations, whereas vitamin D possibly improves muscle strength or function and regulates bone density (2, 9, 15, 37). Considering PRO assessments, our finding is in accordance with a study on adults which showed that standardized vitamin D supplementation in chronic pain could be effective in improving pain levels, sleep and some aspects of quality of life (16).

An additional observation is important to consider; although there was a significant increase in serum 25-hydroxyvitamin D concentrations in the whole group from baseline to follow-up, a substantial number of subjects still had low serum levels of 25-hydroxyvitamin D. This can be possibly explained by notion that a 6-month treatment with suggested vitamin D dosage for children is not a sufficient period to reach appropriate levels of serum 25-hydroxyvitamin D in children with musculoskeletal disorders and orthopedic conditions, so that higher doses might be required. Another possibility could be poor compliance, although all subjects were contacted monthly by their physicians in order to check for compliance and presence of the possible side effects of the therapy. However, in the light of the main study findings, it is possible that with the increased serum levels of 25-hydroxyvitamin D, irrespective of whether the child still has vitamin D deficiency or not, there are changes in perceiving pain intensity, with improvements in movement and fatigue, which could be the direct effect of postulated decreased hypersensitivity to pain or improved muscle condition (27).

There are several strengths of the present study. First, the follow-up period was six months, which is actually suggested for optimal treatment time when it is expected that change in serum 25-hydroxyvitamin D concentrations could occur. Second, we used self-and parent/proxy ratings for all scales in order to better capture perceptions of pain and functioning. Third, loss to follow-up was negligible, considering that all subjects were regularly contacted over the study period. However, several study limitations should be also acknowledged. First, we included a different group of different musculoskeletal disorders and orthopedic conditions, thus heterogeneity could significantly affect PRO findings. Second, a randomized clinical trial could only give true estimations in regard to how vitamin D therapy reduces pain and improves mobility and daily functioning taking into account the causal relationship. Third, this study did not consider how specific factors, especially treatment options and seasonal influence affect PRO over time. Finally, there could be a selection bias, as the study was organized at one site only and also the group was heterogeneous in regard to included conditions, while there are still other musculoskeletal disorders and orthopedic conditions that could be included.

CONCLUSION

This pilot study has shown that vitamin D therapy can reduce pain intensity and improve mobility and

daily functioning in children with musculoskeletal disorders and orthopedic conditions, suffering from chronic recurrent pain and also diagnosed with vitamin D deficiency. However, further follow-up and randomized studies are needed prior to giving valid clinical recommendations. It would be of particular importance to evaluate the association of vitamin D and pain in patients allocated to different groups according to the diagnoses, moderating and mediating the effects of rehabilitation treatments, seasonal impacts (spring and winter) and other clinical factors.

Conflict of interest: *the authors declare that there are no conflicts of interest.*

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