25-Hydroxyvitamin D Deficiency in Pediatric Epistaxis

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Abstract	Patients and Methods	 ³⁰ 28 ²⁵ Before Treatment With & After Treatment 	35 30 31 At the Study Start By the Study End
Objectives: Recognize a possible relation between 25-hydroxyvitamin D deficiency and recurrent idiopathic epistaxis in pediatric cases. Methods: Noticing that a four years old female patient known to have idiopathic recurrent epistaxis showed cessation of epistaxis attacks after treatment of 25-hydroxyvitamin D deficiency that was discovered while investigating an irrelevant complaint of skeletal pain, a two years prospective study was conducted in two tertiary referral centers and included cases under the age of fifteen years of both genders presented with recurrent epistaxis not responding to usual treatment and diagnosed as idiopathic type after exclusion of all possible systematic and local etiologies. The total number of included cases was forty-nine. Serum levels of 25-hydroxyvitamin D were measured for all cases. Cases with insufficiency or deficiency were treated and their serum 25-hydroxyvitamin D levels were maintained according to the Institute of Medicine and the Endocrine Society guidelines. All cases were followed-up for both epistaxis recurrence and serum levels of 25-hydroxyvitamin D insufficiency (seventeen cases, 35%) or deficiency (thirteen cases, 27%) with more incidence in females (sixteen cases, (77%) showed marked improvement of the enistaxis within the average of four	Study Population: The total number of included cases in this study was forty-nine. Females were twenty-seven (55%) and males were twenty-two (45%). The age range was from two years old to fifteen years old (median 6.7). All were of the Caucasian race except two males, one was of the Negroid race and the other was of the Mongoloid race. Two cases were sisters and another two were a brother and his sister. One male teenager was absolutely vegan. None was known to be on any medications or suffering from chronic disorder. The two teenager sisters had history of two courses of vitamin D replacement for previously diagnosed 25[OH]D deficiency. <i>Follow-up:</i> All cases were followed-up for at least one year after the end of the main replacement vitamin D course regarding both their epistaxis recurrence and prognosis and their 25[OH]D serum levels. Follow-up protocol included regular monthly phone calls, regular clinic visits every three months and laboratory estimation of cases 25[OH]D serum levels after two months and six months. Case were also instructed for immediate reporting and or appearing in the emergency department or outpatient clinic in case of any epistaxis depending on its significance. There was a special consideration for 25[OH]D serum levels during winter time while the study following-up period. STATISTICAL ANALYSIS: Contingency table and chi-square statistic test was performed to find the significance level by comparing the improved and non-improved epistaxis cases due to the correction of the 25[OH]D serum levels between the cases with sufficient and insufficient 25[OH]D	The second equation of the second equation	The study cases at the beginning and the study case at the beginning at the study case
weake of treatment with no more than one attack over the follow up period		Case 14	Case 17

weeks of treatment with no more than one attack over the follow-up period. **Conclusions:** Vitamin D deficiency might be a contributing factor in some of epistaxis cases previously were recognized as idiopathic.

Introduction

This study was triggered by a case of a four years old female who was suffering from recurrent attacks of epistaxis and her epistaxis was diagnosed as idiopathic after many investigations. The frequency of her epistaxis attacks had increased over the last six months and five of her attacks needed cauterization with silver nitrate in the emergency department by an Otolaryngologist to stop the bleeding. She started gradually to complain of persistent, nonspecific musculoskeletal pain. Her pediatrician wanted to exclude any anemia due to the recurrent epistaxis and re-investigated her. Her laboratory investigations showed no anemia or other deficiencies except for 25-hydroxyvitamin D (25[OH]D) sever deficiency. Her 25[OH]D blood level was 13 nmol/liter (5.2 ng/mL), so her pediatrician started an aggressive, high-dose prescription vitamin D replacement for her to avoid any adverse effect on her musculoskeletal system or other body systems from the low 25[OH]D levels. She needed six months of vitamin D replacement for her 25[OH]D blood level to be elevated to 65 nmol/liter (26 ng/mL). Meanwhile during her vitamin D replacement period, her family noticed improvement of her epistaxis. She only had two minor attacks of epistaxis during her first month of treatment and none of them needed any intervention or visiting the emergency department. During her routine follow-up Otolaryngology outpatient clinic visits, her nasal mucosa was normal without any crusting, bleeding points or tortuous engorged blood vessels. Her condition was followed-up for two years and she did not develop any further attacks of epistaxis. In addition, her 25[OH]D blood level was kept sufficient by a maintenance dose.

Several studies have linked low 25[OH]D blood levels to various pathological conditions and manifestations. So, the prognosis of this case could be an indicator for a possible relation between 25[OH]D deficiency and some cases of unexplained or so called idiopathic epistaxis. This study was undertaken to recognize any relation between 25-hydroxyvitamin D deficiency and epistaxis in pediatric cases and to review what could be the possible theories might explain this relation if any could be demonstrated.

Patients and Methods

Study design: This study was a prospective study and conducted over a two years period and the last case was followed for one year after initial treatment, so the study extended from October 2012 and until September 2016, in two tertiary referral centers after all the needed approvals were obtained. It included cases of both genders under the age of fifteen years presented with recurrent epistaxis not responding to usual treatment and diagnosed as idiopathic type after exclusion of all possible systematic and local etiologies. Clinical Protocol: The protocol was based mainly on three steps, initial assessment + / resuscitation, dealing locally with the epistaxis and diagnosis of its etiology for the long-term management of the case. The cases with recurrent epistaxis would be evaluated and investigated by full and detailed history taking, local examination, endoscopic evaluation and imaging studies if necessary, then evaluated by pediatrician and laboratory investigations to exclude any systematic etiology (mainly blood disease, coagulopathy and organ failure). For all cases that were included in this study serum concentration of 25[OH]D was assessed for vitamin D status in fasting morning venous blood samples (after an eight hour overnight fast) and was analyzed on a Cobas e601 immunoassay analyzer (Roche Diagnostics, USA) using the manufacturer's Kit after explaining and consenting the legal guardian for including the child in the study. Also, serum calcium (Ca), phosphorus (P), magnesium (Mg), alkaline phosphatase (ALP), inorganic phosphate (Pi), glucose levels, ferritin, insulin, calculated insulin resistance and PTH were evaluated and measured when needed and indicated. In addition, 1,25[OH]₂D was measured in cases with suspicious acquired and inherited disorders of vitamin D metabolism including pseudo-vitamin D deficiency or vitamin D resistance. Body mass index (BMI) was calculated to adjust doses and due to the relation between obesity and 25[OH]D insufficiency. The same methods of assay were used throughout the study in the same laboratory. The current study adopted the institutional reference normal and abnormal serum 25[OH]D concentrations which also the same as classified by the Endocrine Society guidelines.³¹ The sufficient serum level of 25[OH]D is classified as > 75 nmol/L (30 ng/mL), the insufficiency is classified as concentrations between 50 – 75 nmol/L (20 - 30 ng/mL), the deficiency is classified as < 50 nmol/L (20 ng/mL) and the critically high level is classified as > 250 nmol/L (100) ng/mL) Management Protocol: The study implemented a fixed protocol to achieve replacement and maintain the target vitamin concentrations for all the cases which followed the guidelines of the IOM and the Endocrine Society.⁴⁰ According to the laboratory finding, all the study cases were classified according to their serum 25[OH]D levels into, cases with sufficient levels, cases with insufficient levels and cases with deficient levels. Infants and children cases with insufficient and deficient levels were replaced by 2000 IU of vitamin D daily for six - eight weeks or 50,000 IU of vitamin D once a week for eight weeks and their vitamin D was maintained by 600 to 800 IU of vitamin daily for at least two years. For adolescents cases with insufficient and deficient levels were replaced by 50,000 IU of vitamin D once a week for eight weeks and their vitamin D was maintained by 50,000 IU of vitamin D once every 2 weeks for at least two years. Replacement courses were repeated as directed by the cases follow-up laboratory results. Study cases with sufficient 25[OH]D serum levels were divided randomly into two groups, first group received the same above maintenance vitamin D dose according to cases age group and the second group did not receive any vitamin D supplementations. They were randomized by the even numbered cases according to their turn upon presentation received vitamin D maintenance dose and the odd numbered cases did not receive

Results

This study included forty-nine recurrent idiopathic epistaxis cases with twenty-seven females (55%) and twenty-two males (45%). Thirty cases out of the forty-nine (61%) had abnormally low serum 25[OH]D levels with seventeen cases had serum 25[OH]D insufficiency (35%) and thirteen cases had serum 25[OH]D deficiency (27%). Among the thirty cases with the abnormally low serum 25[OH]D levels, sixteen were females (53%) and fourteen were males (47%). The age range of the whole study group was from two years old to fifteen years old (median 6.7). Epistaxis incidence had two peaks, among male infants (39% of cases) and female adolescents (37% of cases). The 25[OH]D deficiency had only one peak, among the female adolescents (42% of cases) (Figure 1). Body mass indices (BMI) for the cases were not significant as they were between the fifth percentile to less than the eighty-fifth percentile range which means non-obese non-underweight, except for 2 cases who were obese. None was found to have any chronic conditions might affect the 25[OH]D serum level. None of the forty-nine total study cases or the thirty cases with 25[OH]D deficiency had symptoms or signs for 25[OH]D deficiency apart from some fatigue and chronic pain in general in fourteen cases (29% of the total study cases and 47% of the study 25[OH]D deficiency cases). Nonsignificant fluctuations of Ca, P, Mg, ALP, Pi, glucose levels, ferritin, insulin and PTH were detected in some cases. Seasonal variations were evident in the study cases with two peaks of 25[OH]D insufficiency, cold months and extremely hot months.

Table one and **two** shows the frequency of the recurrence of the epistaxis attacks in all the study cases over the six months period before including any case in the study and the need for any intervention. Bilateral incidence of epistaxis was recorded in twenty-eight cases (57%).

Obvious regression and improvement in the epistaxis course could be noticed in twenty-three cases The chi-square statistic is 7.1795. The p-value is .007374. This result out of the thirty cases who had abnormally low serum 25[OH]D levels (77%) with the vitamin D replacements (Figures 2 - 4). In two cases of them (9%) epistaxis did not recur at all with the start of the vitamin D replacement therapy, while one attack occurred without the need for any intervention during the first week of the vitamin D replacement therapy in three cases (13%), one attack occurred without the need for any intervention during the first two weeks in seven cases (30%), one attack occurred without the need for any intervention during the first four weeks in two cases (9%) and one attack occurred with the need for intervention in five cases (22%) (Figure 5). No bleeding occurred after four weeks of the vitamin D replacement therapy and any case with more than one attack of bleeding during the replacement stage or maintenance and follow-up was classified as failure of treatment. Seven cases out of the thirty cases who had abnormally low serum 25[OH]D levels (23%) did not show improvement of their epistaxis with the vitamin D replacement and maintenance therapy

Nine cases of the nineteen cases with sufficient 25[OH]D serum levels randomly received vitamin D maintenance doses according to their ages. Five of them showed improvement of their epistaxis (55%) with no attacks at all in two cases (22%), one attack occurred without the need for any intervention during the first three weeks in one case (11%) and one attack occurred with the need for intervention during the first four weeks in two cases (22%) (Figure 6). While ten cases of the nineteen cases with sufficient 25[OH]D serum levels randomly did not receive any vitamin D supplementations during the study period. Three of them (30%) showed improvement of their epistaxis with no attacks at all in one case (33%) and one attack occurred without the need for any intervention during the follow-up period (66%) The present work showed significant improvement of the recurrent idiopathic epistaxis attacks in both cases groups, with sufficient and insufficient 25[OH]D serum levels, due to improvement of their 25[OH]D serum levels in comparison to cases with recurrent idiopathic epistaxis and otherwise sufficient 25[OH]D serum levels (Table 3 & 4).



Discussion

is significant at p < .05.

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The recurrent idiopathic epistaxis occurs mainly from a bleeding vessel from the rich vascular anastomosis of large thin walled vessels occurs within the mucosa over the cartilaginous anterior nasal septum.^{51,54} In general, the main and characteristic pathological changes in the body resulting from 25[OH]D insufficiency or deficiency are related to bone and cartilage

Lacey and Huffer in 1982 investigated the skeletal morphologic changes due to hypocalcemia and hypophosphatemia resulting from three weeks vitamin D deficiency in avian species. They found accumulation of proliferating and maturing cartilage in hypocalcemic chicks which was accompanied by increased length and increased variation in length of perforating epiphyseal vessels and a change in the distribution but not the total number of DNA-synthesizing chondrocytes ber unit width of growth plate, while in hypophosphatemic chicks there were accumulation of hypertrophic cartilage

the chondroclast's, the cells responsible for removing unhealthy cartilage and responsible for In addition, resorption of the mineralized cartilage were found in deficiency to be replaced by distinctly different



Figure 1: Distribution of 25[OH]D deficiency cases among the total study cases according to their gender (No. 49).

Table 1: Frequency of recurrent epistaxis attacks for the whole study cases before treatment (No. 49).

Before Treatment

5 Attacks

With & After Treatment



morphological appearances of clast-like cells which were incapable of degrading the poorly mineralized and un healthy cartilage efficiently, i.e. impaired cartilage healing and regeneration process.

Rickets is mainly due to vitamin D deficiency, however, it is now widely recognized that there is an intermediate state, vitamin D "insufficiency," when levels of vitamin D are not frankly depleted but are associated with increased levels of PTH (secondary hyperparathyroidism) due to low serum Ca which enhancing osteoclastic activity and lead to the skeletal changes.^{57,58} That is why skeletal radiographs in vitamin D insufficiency are likely to be normal.⁵⁷ This means that, it is evident now that the body response to 25[OH]D insufficiency differ than its response to deficiency and its response to both insufficiency and deficiency occur by various degrees. 65,66,67 The nasal septum and nasal septal cartilage are considered to be a dominant growth center which continuously grow so it will easily affect by any hypocalcemia or hyperphosphatemia.69



Many of the other pathological changes that occur in the body different systems due to vitamin D deficiency might be responsible to the incidence of epistaxis. In addition, vitamin D itself influencing many vital functions in the body which become affected with its deficiency and predispose to the epistaxis. Lower levels of 25[OH]D have been associated with endothelial dysfunction which predispose to the development of atherosclerosis in non-hypertensive.⁷² Even normal levels of 25[OH]D are required for the body to be able to control the systolic blood pressure and keeping it from elevation above normal.⁷³ Vitamin D is a potent immunomodulator capable of dampening inflammatory signals in several cell types involved in the asthmatic response and same in allergic response, so its deficiency exaggerate the body response by certain types of inflammation.⁷⁴ It functions also as a steroid hormone (or more accurate a secosteroid hormone) through binding to its specific intranuclear receptor, the vitamin D receptor (VDR) which leads to activation of a variety of genes associated with calcium homeostasis and cellular functions of the immune system.^{75,76} Estrogen, which is known to its protective effect in epistaxis through its effect on the nasal mucosal integrity and thickness and also through its vascular protective effects, vitamin D resistant individuals may also be at risk for low levels of estrogen through the affection of 1α-OHase and through the affection of vitamin D receptors throughout the body which it acts on it as a prohormone.^{77,78} Vitamin D is a fat-soluble vitamin and if its deficiency is due to malabsorption, all other fat soluble vitamins (A, E and K) absorption and storage in the body will be affected with subsequent affection of their functions including vitamin K.79

Conclusions

The data available from the current study are supportive for the role of lower serum vitamin D levels as a contributing factor in some of the recurrent epistaxis cases previously were recognized as idiopathic. Further longer and involving more cases, multi medical centers, locations and specialties, observational studies are needed to confirm these findings and establish the mechanisms underlying

vitamin D maintenance dose.	Table 2: Number of epistaxis attacks for each case ne intervention for the whole study cases before treatment (I	eded Figure 2: Comparison between the frequency of epistaxis attacks these observations and attacks for the study cases with 25[OH]D deficiency before and after treatment and during follow-up period (No. 30).	a randomized prospective clinical trial will be needed to determine if vitamin prevent the incidence of this kind of epistaxis.
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