ORIGINAL ARTICLE

Relation of blood pressure values in thirteen-years old adolescents to the mode of vitamin D prophylaxis during their infancy

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Abstract

OBJECTIVE: The broad spectrum of extraosseal functions of vitamin D has recently been investigated. Although majority of recent studies have documented its hypotensive effect, some older studies warrant the risk of development the juvenile hypertension namely after pulse-fortified D vitamin supplementation during infancy. The aim of this study was to compare of the blood pressure in 13 year old groups of adolescents to the mode of D vitamin supplementation during their infancy.

METHODS: Study group represent 1138 thirteen year old adolescents in complex health care of 21 primary care pediatricians (PCPs). This group was divided into three subgroups according their mode of D vitamin supplementation in infancy. 100 children were given the continuous daily supplementation of AD vitamin 200–400 IU /day – " regular subgroup 0", 933 children were given by bolus doses of D vitamin forte 450 000 IU every three months during first year of life – "fortified subgroup 2", and 105 children given by bolus doses of D vitamin during winter, and continuous daily AD drops during summer – " mixed subgroup 1". D vitamin supplementation was done approximately 13 years before blood pressure study.

RESULTS: The mean systolic blood pressure was 110 mmHg, and mean diastolic one was 70 mmHg in all subgroups, regardless the mode of vitamin D supplementation. There were no statistic differences among subgroups, between girls/boys, blood pressure levels were in normal limit. Although calculated daily doses of D2 vitamin during infancy exceeded RDA (200–400 IU) four to ten time, no difference in morbidity was found, concerning various chronic diseases (allergy, cardiovascular, renal, etc.). These results are in full accordance to recent knowledge of higher requirement and safety limit during vitamin D application.

CONCLUSION: The mode of D vitamin prophylaxis during infancy (pulse or daily application) has no influence to blood pressure level in early adolescence. No adverse effects have been found despite that the calculated daily dose was exceeded from three to ten times the recommended daily allowance.

INTRODUCTION

Vitamin D deficiency is one of the most common nutritional deficiencies in all age groups worldwide, and it has shown a dramatic increase its prevalence in recent years (Holick 2007; Kumar *et al.* 2009). This increase is attributable to lifestyle changes, e.g. different feeding patterns, sun protection, urbanization, etc. (Baz-Hecht & Golfine 2010; Abdullah *et al.* 2002). Vitamin D deficiency has a direct impact on the health status of the population (Gannage-Yared et.al. 2000a). For decades vitamin D has been known as the regulator of calcium and bone metabolism. Its deficiency is principal for the development of rickets in childhood and osteoporosis in adult. Recent investigations have revealed receptors for vitamin D in a wide range of tissues with corresponding biological extraosseal functions (Gannage-Yared *et al.* 2000b; Norman 2008). D vitamin suppress the renin production in junxtaglomerular apparatus (Yuan et.al. 2007), modifies endothelial tissue response (Sugden *et al.* 2008), and suppress proinflammatory cytokine production (Schleithoff *et al.* 2006) with the direct antihypertensive and vasoprotective effect (Witham *et al.* 2009). Low 25-hydroxyvitamin D blood level is an independent risk factor of cardiovascular disease (Wang *et al.* 2008). Moreover, vitamin D deficiency is associated with an increased risk of obesity and both types of diabetes mellitus (Littorin *et al.* 2006), potentiating cardiovascular risk. Hence, vitamin D supplementation is relevant not only in infancy and childhood, but in all age groups, including the elderly. There has been some controversy about the optimal supplementation of vitamin D. For many years a daily oral dose of vitamin D ranging from 200 to 800 IU was recommended for infants. Many recent studies on 25-hydroxyvitamin D blood levels have found that the dosage has not always been fully sufficient (Vieth *et al.* 2001a,b). In addition, there is controversy about vitamin D safety and toxicity (Hayes 2008). Supplementation of vitamin D in infancy has been used in preventive programme for decades. Generally, two modes of vitamin D supplementation have been used – continuous daily application of oral drops, or fish oil in daily recommended dose of 400–800 IU of vitamin D_2, or D_3, and/or so-called pulse-fortified supplementation containing from 300 000 to 450 000 IU every three months during the first year of life, according Harnapp (1938). The rationale for this "pulse-fortified" supplementation was to avoid D vitamin deficiency in children of uncooperative parents, particularly from low social minority group. However, during the time the widespread use of this supplementation mode predominated in Europe, namely in second half of the 20th century. Despite this, reports concerning overdoses and toxicity have seldom been published (Debré & Brissard 1949, Wolf & Solar 1969). In Czechoslovakia the pulse fortified vitamin D supplementation was used fore more than five decades. During this time there was found that the shift to a daily application was immediately followed by an increased incidence of rickets (Central Slovakia 1978–79 – unpublished data). On the other side, there were some cases of nephrocalcinosis and hypercalcinemia, mainly after overdosed fortified vitamin D prophylaxis (Misselwitz *et al.* 1990). The main argument against fortified prophylaxis was put forward in an article by Lagomarsini *et al.* (1996) claiming that children receiving this mode of prophylaxis reported significantly higher blood pressure compared to children with a regular daily prophylaxis. Moreover, there has not yet been any study concerning the effect of fortified vitamin D prophylaxis in infancy to blood pressure in adolescence and adulthood (Janda & Bláhová 1998). The aim of this study is to compare systolic and diastolic blood pressure in 13-year-old teenagers of both sexes in relation to the mode of vitamin D prophylaxis in infancy (daily, or pulse-fortified mode).

MATERIAL AND METHOD

The investigated study group comprised 1138 thirteen-year-old children (teenagers attending the 7th class at a primary school) in the primary care of 21 paediatricians (PCP). During a regular preventive health check-up, their blood pressure was measured using a standard mercury tonometer. In all cases, the information about the mode of vitamin D prophylaxis in infancy was extracted from the children's health chart. The study group was divided into three subgroups: children in the "fortified subgroup 2" had received 450 000 IU of vitamin D_2 (Infadin forte SPOFA) in one capsule in the 2nd week, and at the 3rd, 7th, and 12th month of age, comprising a total dose from 1 200 000 to 1 650 000 IU per year. In the "regular subgroup 0" receiving daily vitamin D supplementation, two to four drops of the combined AD vitamin (SPOFA AD vitamin drops, containing 45 000 IU of vitamin A and 10 000 IU of vitamin D_2 in 1 ml) were administered in a spoon with milk during a week; no dose was administered at the weekend (Blažek *et al.* 1964). The "mixed subgroup 1" was given a combination of vitamin D forte, two to three doses (mainly in winter) with regular drop prophylaxis (spring, autumn). This study was conducted in 1999, when the children were thirteen, which means they had received vitamin D prophylaxis in 1986–1987. At that time no infant formula fortified with vitamin D was available. Study subgroups are presented in Table 1. The "regular" (0) subgroup comprised 100 (8.8%) of the children, the "fortified" subgroup (2) 933 (81.9%) of the children, and the "mixed" subgroup (1) 105 (9.2%) of the children. Gender prevalence reflected the normal distribution of the population. The frequency of chronic diseases in all group was registered. Using statistical analysis we evaluated the values of systolic and diastolic blood pressure in boys and girls in the above-mentioned three subgroups separately. In each subgroup, the median value and percentiles were established and the statistical differences were tested using the nonparametric, unpaired Wilcoxon test.

RESULTS

Results are presented in Table 3. The median of systolic pressure was 110 mmHg in both sexes. Only in boys from the "regular" group it was insignificantly higher (113 mmHg). There were no statistically significant differences of the median of diastolic pressure in all subgroups, and both sexes (70 mmHg). Tables 2–3, Figures 1–4 present the median and range blood pressure values. Blood pressure values were in the normal physiological range for this age group and no individual case of juvenile hypertension has been found. The frequency of various chronic disorders does not exceeds the frequency in normal population (Table 4).

DISCUSSION

There are only a few reports dealing with the association of the hypertension and vitamin D overdose (Misselwitz *et al.* 1990; Lagomarsino *et al.* 1996; Janda & Bláhová 1998). Authors of presented study have found no article describing the impact of the mode of preventive vitamin D supplementation in infancy on blood pressure level in late childhood or adolescence. In contrast of this, there are many articles founding the protective effect of vitamin D on hypertension in all age groups (Heaney 2008a,b). The mechanism of vitamin D activation in relation to atherosclerosis, arterial stiffening and hypertension is discussed, and therefore the safety and efficacy of vitamin D supplementation is still open to question Our study has not shown any significant difference in blood pressure among the tested subgroups of young adolescents, and has not

Tab. 1.

Group	regular	mixed	fortified	sum	%
boys	50	55	450	555	48.8
girls	50	50	483	583	51.2
sum	100	105	933	1138	100

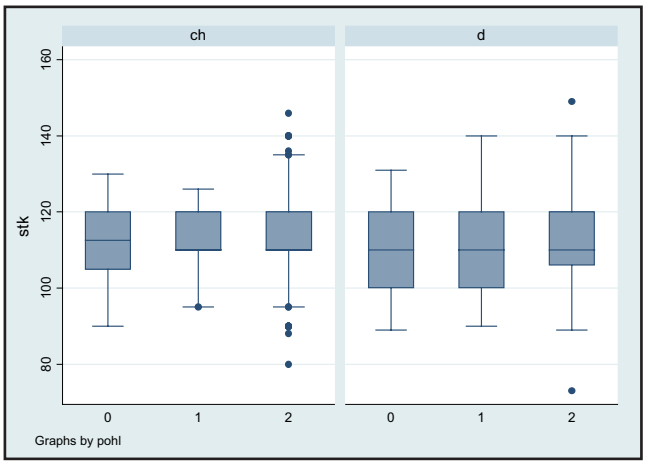

Fig. 1. Mean systolic blood pressure after sex.
0 – regular, 1 – mixed, 2 – fortified; Abbr: ch = boys, d = girls.

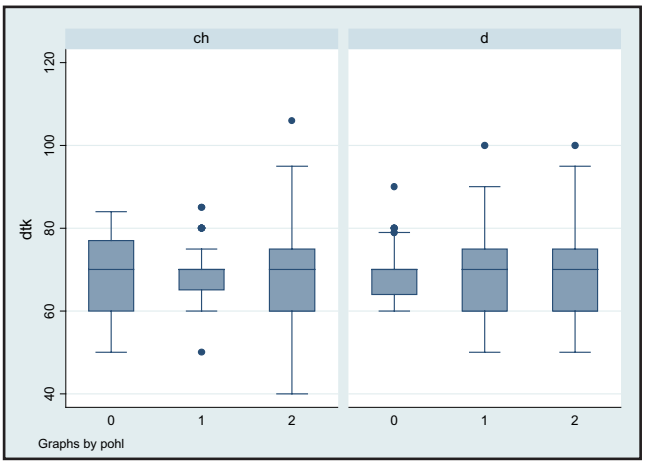

Fig. 2. Mean diastolic blood presssure after sex.
0 – regular, 1 – mixed, 2 – fortified; Abbr.: ch = boys d = girls.

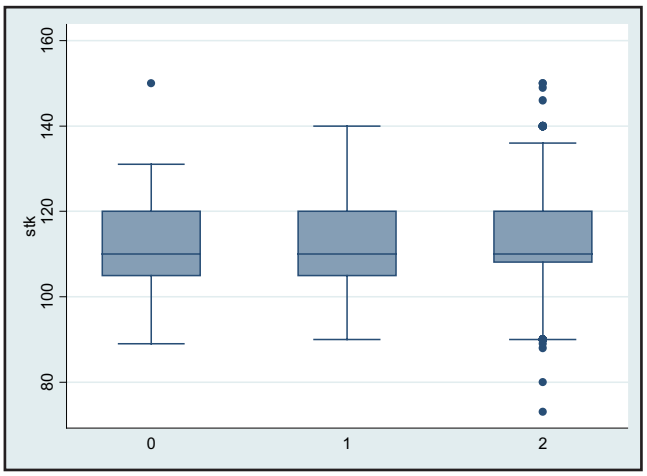

Fig. 3. Systolic blood presssure and mode of D vitamin supplementation. 0 – regular, 1 – mixed, 2 – fortified.

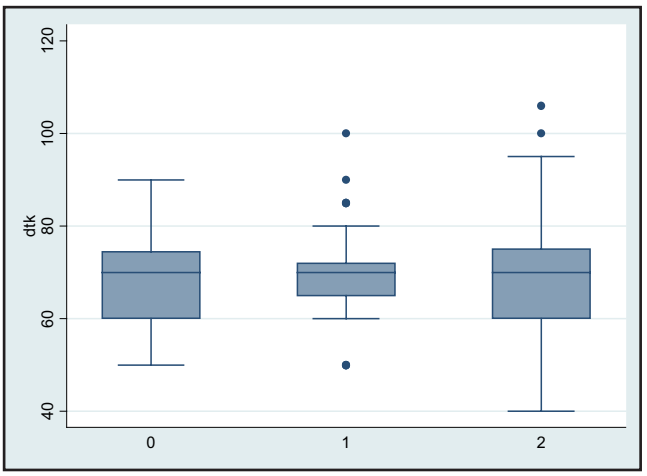

Fig. 4. Diastolic blood presssure and mode of D vitamin supplementation. 0 – regular, 1 – mixed 2 – fortified.

Tab. 2. Blood pressure – boys.

	N	1P	5P	Median	95P	99P
Syst. BP						
0	50	90	94	113	128	150
1	55	95	100	110	120	126
2	450	90	100	110	130	140
Diast. BP						
0	50	50	60	70	80	84
1	55	50	60	70	80	85
2	450	55	60	70	80	90

Tab. 3. Blood pressure – girls.

	N	1P	5P	Median	95P	99P
Syst. BP						
0	50	89	95	110	125	131
1	50	90	98	110	130	140
2	483	90	100	110	130	140
Diast. BP						
0	50	60	60	70	80	90
1	50	50	60	70	85	100
2	483	50	55	70	80	90

Tab. 4.

Disease	number	%
Allergy	41	3.6
Obesity	34	2.98
Scoliosis	12	1.05
Epilepsy	4	0.35
CP	5	0.43
Coeliakia	2	0.17
Nephritis	1	0.08
TCP	1	0.08
JIA	1	0.08
Nanismus	2	0.17
XO	1	0.08
Struma	8	0.7
VCC	2	0.17
Sum	114	10

CP - cerebral palsy
TCP - thromocytopenia
JIA - juvenile rheumatic arthritis
XO - monosomy X
VCC - vitium cordis congenitum

confirmed the hypertensive effect of the fortified pulse mode of D vitamin dosage. Presented mode of supplementation and cumulative doses of vitamin D in studied subgroups of infants reflects the system of vitamin D prophylaxis which has been used in Czechoslovakia for many years (Blažek *et al.* 1964). In total, 82% of infants received the fortified mode of supplementation every child was given three to four doses of 450 000 IU during this first year of life, that means the total dose of vitamin D_2 was from 1 200 000 to 1 600 000 IU (divided into daily doses it was from 3 300 to 4 400 IU, which exceeds RDA by at least ten times). In the regular daily supplementation mode using AD vitamin drops, 53% of children were given two, 8% of children three, and 39% of children four drops (i.e. 400, 600, 800 IU/day). Using AD drops the children received, apart from vitamin D, also vitamin A in a daily dose from 3 600 to 7 200 IU, which exceeds RDA by two to four times (1 200–2 000 IU). The system of children's preventive care (including vitamin D prophylaxis) in Czechoslovakia has been mandatory for many decades (since 1950s, in fact) and was provided by primary care paediatricians (PCP). We can extrapolate from this, that almost the whole of the Czechoslovak population was overdosed with vitamin D, approximately 8% of them with vitamin A as well. However, we have not found any long-term adverse sequelae on blood pressure, or health status, in any of our study subgroups. The limitations of our study are obvious. It is a retrospective comparative analysis oriented towards blood pressure. Therefore the global health status of children was not evaluated in detail. Further studies should follow in order to evaluate other possible effects e.g. bone density, incidence of diabetes mellitus, and other parameters. Nevertheless, the absence of any obvious late adverse effect of vitamin D and vitamin A overdose support the recent investigation into safety level of higher dosage reaching up to 10 000 IU/day .

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