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No Major Metabolic Alterations Accompany the Hypotensive Effect of Active Vitamin D

Results from three double-blind, placebo-controlled studies

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ABSTRACT

A hypotensive effect of active vitamin D treatment (alphacalcidol 1 mg daily) has previously been reported in three double-blind, placebo-controlled studies over 4-6 months in subjects with mild primary hyperparathyroidism (HPT), intermittent hypercalcemia and essential hypertension.

The commonly used antihypertensive drugs, thiazides and betablockers, both induce impairments in both glucose and lipid metabolism and the thiazides are known to cause an elevation of serum urate. The effects of vitamin D treatment on these metabolic variables were recorded in these studies.

Alphacalcidol did not induce any changes in fasting glucose HbA1c or insulin, serum triglycerides, cholesterol or serum urate in any of the treated groups. Neither was HDL cholesterol affected, except for a rise seen in the HPT subjects.

It is therefore concluded that no major metabolic alterations in glucose or lipid metabolism or serum urate accompany the hypotensive effect of vitamin D.

INTRODUCTION

Hypertension is a well-known cardiovascular risk factor. Despite of this fact, prospective clinical trials with antihypertensive drugs in mild to moderate hypertension have failed to demonstrate any reduction of the incidence of myocardial infarction. One explanation to this disappointing result is that hypertension is a disorder often characterized by impairment of cardiovascular risk factors, such as hyperlipidemia and impaired glucose tolerance (1, 4, 9) and under these circumstances a blood pressure reduction may not be so effective as when other risk factors are not present. Furthermore, the drugs that have been used in these trials, thiazides and betablockers, themselves further impair the glucose and lipid metabolism (2, 10, 11). The thiazides are also known to elevate the levels of serum urate. Other drugs with a hypotensive effect should therefore be investigated with regard to their metabolic effects.

Vitamin D supplementation has been found to lower blood pressure in subjects with impaired glucose tolerance (5), mild primary hyperparathyroidism (HPT) (6),

intermittent hypercalcemia (3) and in low-renin hypertension (7) in double-blind, placebo-controlled studies. The hypotensive effects of vitamin D in patients with IGT has previously been reported to be found independent of any effects on glucose or lipid metabolism (8). The present study investigates if the reduction of blood pressure induced by vitamin D in the other disease states was associated with any effects on glucose, lipid metabolism or serum urate.

MATERIAL AND METHODS

In Gävle, Sweden, a health screening survey was conducted in 1969 and followed up in 1971. Among over 18.000 adult participants a hypercalcemic group was defined in retrospect as showing serum calcium >2.60 mmol/l at both occasions. One hundred seventy-two such persons were found. This group was reexamined twice in 1983. Of the 95 examined subjects, 47 were still hypercalcemic and 48 were found to be normocalcemic at the reexamination.

The group being hypercalcemic at all four investigations performed over 14 years was found to have higher PTH levels, lower levels of serum phosphate and similar levels of serum creatinine as an age and sex matched normocalcemic control group. This hypercalcemic group was therefore considered to represent subjects with mild primary hyperparathyroidism. The mean age was 65 years (6 men and 27 women) and the mean serum calcium was 2.66 ± 0.09 mmol/l (6).

The group being normocalcemic at the reexamination in 1983 is denoted intermittent hypercalcemia (IntHC) and consisted of 26 subjects (6 men and 20 women, mean age 63) with a serum calcium at 2.51 ± 0.08 mmol/l (3).

Patients with a well documented mild hypertension (DBP 95-110 mm Hg) without any antihypertensive treatment were recruited from general practitioners. Forty-two hypertensive subjects (30 men and 12 women, mean age 51) were available for this study (7).

In the group of HPT and IntHC subjects, 1 mg alphacalcidol (1(OH)vitamin D_3) per day was given in a double-blind, placebo-controlled fashion for 6 months. Fasting glucose, fasting insulin, serum urate, serum and HDL-triglycerides and cholesterol were measured before and at 6 months of therapy. In the HPT group a significant reduction in diastolic blood pressure (-6.7 mm Hg, DBP) was induced by treatment (6) while a reduction in DBP of 9.2 mm Hg was seen in the IntHc group (3).

1.0 mg alphacalcidol per day was also given to the hypertensive subjects in a double-blind, placebo-controlled study over 4 months. Fasting glucose, fasting insulin, serum urate, serum and HDL-triglycerides and cholesterol concentrations were measured before initiation of therapy and after 4 months of treatment. A reduction in DBP (5 mm Hg) in the low-renin hypertensives was induced by treatment in this study (7).

In all three studies the groups were matched for age and sex. There were two drop-

outs in the HPT group, one in the IntHC group and three in the hypertensive group.

All these studies were approved by the Ethics Committee of the University of Uppsala and all subjects gave their informed consent.

Glucose was measured by an oxidase method and insulin by a commercial kit (Pharmacia, Uppsala, Sweden). Serum lipids were determined with enzymatic methods (Boehringer, Mannheim, West Germany). HbA1c was determined by fast performance limit chromatography. Serum urate was measured in the multianalyser SMAC (Technicon Inc, USA) used in hospital practice.

All data were computerized and the statistical programme package SAS (SAS Inc, USA) was used for statistical evaluation of the data. Paired t-test was used for determining treatment results within groups and unpaired t-test between groups. The method of least squares was used for correlation analyses. Two-tailed significance limits were used. $p<0.05$ was regarded as significant.

Table 1
Effect of treatment on glucose and lipid metabolism and serum urate in the group with mild HPT, n=33.

	Treatment group		Placebo group		Treatment-	Placebo	
Time	0 months	6 months	0 months	6 months	effect	effect	ment vs placebo
Serum glucose (mmol/l)	4.9 ± 0.56	4.7 ± 0.59	5.0 ± 0.52	4.9 ± 1.0	ns	ns	ns
Fasting insulin (mU/l)	9.0 ± 6.7	7.3 ± 3.8	10 ± 7.1	7.7 ± 3.7	ns	ns	ns
Serumtriglycerides (mmol/l)	2.1 ± 1.6	2.1 ± 2.0	1.9 ± 1.2	2.2 ± 1.6	ns	ns	ns
Serumcholesterol (mmol/l)	6.8 ± 1.0	6.7 ± 1.1	7.1 ± 1.5	6.6 ± 1.6	ns	p<0.01	ns
HDL triglycerides (mmol/l)	0.20 ± 0.092	0.23 ± 0.087	0.16 ± 0.083	0.23 ± 0.070	ns	p<0.01	ns
HDL cholesterol (mmol/l)	1.01 ± 0.24	1.16 ± 0.22	1.03 ± 0.25	1.06 ± 0.21	p<0.01	ns	p<0.05
Serum urate (mmol/l)	313 ± 70	315 ± 73	351 ± 89	332 ± 84	ns	ns	ns

Means ± SD given. ns = not significant

RESULTS

Treatment with alphacalcidol did not induce any significant changes in the indices of glucose or lipid metabolism measured in any of the groups (Table 1-3) except for an increase in HDL cholesterol in the HPT patients. Neither was serum urate altered by vitamin D treatment in any of the groups. No significant changes in the metabolic variables were found when the data from the three studies were analysed together.

No significant correlations were found between the pretreatment blood pressure or

the change in blood pressure induced by treatment and the changes in metabolic variables induced by vitamin D.

DISCUSSION

It has previously been found that the hypotensive action of vitamin D supplementation seen in subjects with IGT is not associated with any effects on glucose or lipid metabolism (5, 8). In those studies, the effect of vitamin D on glucose tolerance was evaluated by an intravenous glucose tolerance test.

In the studies reported in this paper glucose metabolism was evaluated by measurements of fasting glucose and insulin in two of the groups (HPT and IntHC) while also HbA1c was measured in the hypertensive group. Vitamin D treatment was not associated with any effects on the measured indices of glucose metabolism. Furthermore, alphacalcidol had no effect on the serum or HDL fraction of triglycerides or cholesterol, as previously reported (5, 8), except for inducing a slight rise in HDL cholesterol in the HPT subjects.

Vitamin D is known to cause a natriuresis secondary to an increased excretion of calcium. As a diuretic action is a main characteristic of the thiazides, which is known to raise the levels of serum urate, this variable was also measured. However, no effects on serum urate was reduced by vitamin D.

Table 2
Effect of treatment on glucose and lipid metabolism and serum urate in the group with intermittent hypercalcemia, n=26.

	Treatment group		Placebo group			Treatment	
Time	Placebo 0 months	Treat- 6 months	0 months	6 months	effect	effect	ment vs placebo
Serum glucose (mmol/l)	4.8 ± 0.45	4.5 ± 0.57	6.2 ± 1.3	5.6 ± 1.7	p<0.05	p<0.01	ns
Fasting insulin (mU/l)	8.3 ± 6.4	10 ± 14	12 ± 10	12 ± 8.2	ns	ns	ns
Serum triglycerides (mmol/l)	2.0 ± 0.97	1 .9 ± 1.0	2.4 ± 0.97	2.0 ± 0.79	ns	ns	ns
Serum cholesterol (mmol/l)	6.9 ± 1.2	6.6 ± 1.0	7.3 ± 0.88	6.7 ± 0.93	ns	p<0.01	ns
HDL triglycerides (mmol/l)	0.27 ± 0.098	0.20 ± 0.073	0.24 ± 0.075	0.21 ± 0.064	p<0.05	ns	ns
HDL cholesterol (mmol/l)	1.05 ± 0.20	1.09 ± 0.18	0.88 ± 0.25	1.04 ± 0.29	ns	p<0.01	ns
Serum urate (mmol/l)	317 ± 66	307 ± 64	336 ± 54	314 ± 78	ns	ns	ns

Means ± SD given. ns = not significant

Table 3
Treatment effects on glucose and lipid metabolism and serum urate in patients with essential hypertension, n=42.

Time	Treatment group Treat- 0 months	6 months	Placebo group 0 months	6 months	Treatment effect	Placebo effect	Treatment vs placebo
Serum glucose (mmol/l)	4.7 ± 0.58	5.3 ± 2.2	4.6 ± 0.67	4.7 ± 0.47	ns	ns	ns
Fasting insulin (mU/l)	7.1 ± 4.8	6.7 ± 2.7	7.7 ± 5.5	9.7 ± 8.3	ns	ns	ns
Hba1c (%)	6.5 ± 0.68	6.6 ± 0.86	6.3 ± 0.45	6.2 ± 0.53	ns	ns	ns
Serum urate (mmol/l)	340 ± 77	349 ± 71	331 ± 47	335 ± 47	ns	ns	ns
HDL triglycerides (mmol/l)	0.19 ± 0.090	0.23 ± 0.060	0.18 ± 0.053	0.23 ± 0.053	p<0.05	p<0.01	ns
HDL cholesterol (mmol/l)	1.17 ± 0.32	1.24 ± 0.32	1.10 ± 0.27	1.14 ± 0.30	p<0.05	ns	ns
Serum triglycerides (mmol/l)	1.92 ± 1.85	1.75 ± 0.55	1.76 ± 0.95	1.75 ± 0.97	ns	ns	ns
Serum cholesterol (mmol/l)	5.99 ± 1.22	5.64 ± 1.24	5.88 ± 1.0	5.56 ± 1.10	ns	p<0.05	ns

Means ± SD given. ns = not significant. Number in parenthesis denotes number of observations, if observations are lacking.

In summary, a hypotensive action of vitamin D supplementation has been found in several studies. This effect of vitamin D was, however, in the present study not associated with any major metabolic alterations in glucose or lipid homeostasis, while the most commonly used antihypertensice drugs, thiazides and betablockers, cause impairments in these important cardiovascular risk factors. This difference in metabolic effects suggests the mechanisms involved in the hypotensive action of vitamin D differ from those with beta-blockers and diuretics and deserve further investigation.

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