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Serum vitamin D and the risk of Parkinson's disease

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Abstract

Context—Low vitamin D status has been suggested to be related to Parkinson's disease risk.

Objective—To investigate whether serum vitamin D level predicts the risk of Parkinson's disease.

Design, Setting and Participants—The study was based on the Mini–Finland Health survey, which was conducted in 1978–1980, and followed-up for Parkinson's disease occurrence through the end of 2007. The study population consisted of 3173 men and women, aged 50–79 years and free from Parkinson's disease at baseline. During the 29–year follow–up period, 50 incident Parkinson's disease cases occurred. Serum vitamin D (25(OH)D) was determined from frozen samples, stored at baseline. Estimates of the relationship between serum vitamin D concentration and Parkinson's disease incidence were calculated using Cox's model.

Main Outcome Measure—Parkinson's disease incidence

Results—Individuals with higher serum vitamin D concentrations showed a reduced risk of Parkinson's disease. The relative risk between the highest and lowest quartiles was 0.33 (95% CI 0.14–0.80) after adjustment for sex, age, marital status, education, alcohol consumption, leisure-time physical activity, smoking, body mass index, and month of blood draw.

Conclusions—The results are consistent with the suggestion that high vitamin D status provides protection against Parkinson's disease. It cannot, however, be excluded that the finding is due to residual confounding and further studies are thus needed.

Vitamin D plays an important role in the pathogenesis of skeletal disorders and calcium homeostasis.[1] Vitamin D inadequacy also predicts increased risk of other chronic conditions e.g. cancer[2], cardiovascular diseases[3], and type 2 diabetes.[4] Recently, chronically inadequate vitamin D intake was proposed to play a significant role in the pathogenesis of Parkinson's disease [5] According to the suggested biological mechanism, the Parkinson's disease may be caused by a continuously inadequate vitamin D status leading to a chronic loss of dopaminergic neurons in the brain. The epidemiological evidence of an association between

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Professor Knekt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Knekt, Heliövaara
Acquisition of data: Knekt, Heliövaara, Marniemi
Analysis and interpretation of data: Knekt, Kilkkinen, Rissanen, Marniemi, Sääksjärvi, Heliövaara
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vitamin D and Parkinson's disease is, however, limited to cross–sectional studies[6–8] showing lower vitamin D status in patients of Parkinson's disease compared with healthy controls.

The Parkinson's disease is a major cause of disability in the elderly. Its risk factors are relatively unknown. However, both biological plausibility and epidemiological data indicate that vitamin D deficiency may contribute to its development[5]. The present cohort study investigated whether serum 25-hydroxyvitamin D (25(OH)D) predicts Parkinson's disease incidence in a population from northern latitudes where exposure to the sun is limited and therefore vitamin D status is continuously low.

METHODS

The Mini–Finland Health Survey, carried out in 1978–1980 in 40 areas of Finland, was based on a two–stage cluster sample (n=3637 men and n=4363 women), drawn from the population register to represent Finnish adults aged 30 years and over.[9] A total of 7217 individuals (90% of the sample) participated in the survey. Of these, 3173 individuals, aged 50–79 years, free from Parkinson's disease and not using antipsychotic medication due to psychotic disorders (ICD–10 (International Classification of Diseases) codes F20–F39), were included in the present study.

Information on socioeconomic background, diseases, medications and lifestyle was collected via questionnaires and interviews.[9] At the baseline examinations, height and weight were measured, and the body mass index (kg/m^2) was calculated. Casual blood pressure was measured with the auscultatory method and hypertension was defined as systolic blood pressure ≥160 mmHg and diastolic blood pressure ≥95 mmHg or the use of antihypertensive medication. Blood samples were taken and the cholesterol concentrations determined by an autoanalyzer modification (Auto–Analyzer Methodology N–24a and N–77; Technicon, Tarrytown, NY) of the Liebermann–Burchard reaction. The serum samples were kept frozen at –20 °C until 2002, when serum 25(OH)D concentrations were determined using the radioimmunoassay (DiaSorin, Stillwater, Minnesota, USA). The inter–assay coefficient of variation of 25(OH)D determination was 7.8% at the mean level of 47.3 nmol/l (n=167). The intra-assay CV was 6.4 %. The samples were run as single samples. The right level of the assay was assured by using the reference serum validated by NIST (Gaithersburg, MD, USA; Fat-Soluble Vitamins, serum 968c). The laboratory also participates in the external quality control program run by Labquality Oy (Helsinki, Finland). In addition, this vitamin D method of the laboratory is accreditated by the Finnish Accreditation Service (FINAS, T077).

Parkinson's disease cases (ICD-10 code G20) were identified through linkage with the nationwide Drug Imbursement Register of the Social Insurance Institution (SSI), using individual social security codes as the identity link. All individuals in Finland with Parkinson's disease are eligible for medication free of charge. In order to obtain this allowance, the patient must apply for it and attach a certificate written by the treating neurologist stating that all the diagnostic criteria for Parkinson's disease are met. This certificate must include symptom history and reports of clinical findings, including the presence of resting tremor, bradykinesia and/or muscle rigidity. An SSI neurologist must agree with the diagnosis as described on the certificate for medication costs to be reimbursed. In an ongoing validation of the register, the certificates for Parkinson's disease drug reimbursement and selected hospital records were re-evaluated retrospectively by a neurologist according to the National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria for PD [10, 11]. Of the originally identified Parkinson's disease cases reviewed, 80% met criteria for Parkinson's disease (Jukka Lyytinen, personal

communications) consistent with other estimates of the percentage of people clinically diagnosed with Parkinsonism in a general population that meet strict PD criteria [12]. The follow–up time was defined as the number of days from the baseline examination to the dates of Parkinson's disease occurrence, death, or end of follow–up, whichever came first. During a 29-year follow–up from 1978–2007, 50 Parkinson's disease cases were identified.

Cox's proportional hazards model was used to estimate the strength of association between serum vitamin D level and Parkinson's disease incidence as relative risks (RR) and their 95% confidence intervals (95% CI) between quartiles of serum vitamin D.[13] Test for trend was based on the likelihood ratio test by including serum vitamin D as a continuous variable in the three models. The first model included age and sex as potential confounders. The second model further included marital status, education, alcohol consumption, leisure–time physical activity, smoking status, body mass index and month of blood drawn. In a third model the eventually intermediary variables hypertension and total serum cholesterol, were further included. Potential effect modification of sex, age, season, hypertension, body mass index, and serum cholesterol on the association between vitamin D and Parkinson's disease incidence was studied by including interaction terms in the second model. All analyses were carried out using SAS software version 9 (SAS Institute Inc., Cary, North Carolina).

RESULTS

At baseline, Parkinson's disease cases were more often non-smokers, non–hypertensive, and non–diabetics than subjects who were free from the disease (Table 1). Serum vitamin D concentration was lower among Parkinson's disease cases and it was also associated with age, sex, marital status, education, leisure–time physical activity, smoking, alcohol consumption, body mass index, diabetes, hypertension, serum cholesterol and the season of measurement (Table 2).

A significant inverse association between sex– and age–adjusted serum vitamin D and Parkinson's disease incidence was found (Table 3). The RR of the disease between the highest and lowest quartiles of vitamin D concentration was 0.35 (95% CI 0.15–0.81, p for trend=0.006). After further adjustment for the potential confounders, including body mass index, leisure-time physical activity, smoking, education, marital status, alcohol consumption, and month of blood drawn, the association persisted (RR 0.33, CI 0.14–0.80, p for trend=0.006). Further adjustment for serum cholesterol and hypertension or exclusion of the disease cases occurring during the first two years of follow–up did not notably alter the results either. Inclusion of an interaction term between vitamin D and sex, age, body mass index, serum cholesterol, blood pressure, and the season of measurement did not notably alter the results (data not shown).

COMMENT

This cohort study shows that low serum vitamin D level predicts an elevated risk of Parkinson's disease incidence. Individuals with a serum vitamin D concentration of at least 50 nmol/l had a 65% lower risk than those with values under 25 nmol/l after adjustment for several potential confounders. Despite the overall low vitamin D levels in the study population, a dose–response relationship was also found.

Vitamin D is obtained from diet and is photosynthesized in the skin by the action of solar ultraviolet B radiation. This study was carried out in Finland, an area with restricted sunlight exposure and is thus based on a population with a continuously low vitamin D status. Accordingly, the mean serum vitamin D level in the present population was about 50% of

the suggested optimal level (75–80 nmol/l).[14] Our findings are thus consistent with the hypothesis[5] that chronic inadequacy of vitamin D is a risk factor of Parkinson's disease.

As far as we know this is the first longitudinal study to investigate the association between vitamin D status and subsequent Parkinson's disease occurrence. In line with our finding, however, previous cross–sectional studies demonstrated the higher prevalence of hypovitaminosis D in patients with Parkinson's disease than in healthy controls.[6–8] The exact mechanisms by which vitamin D may protect against Parkinson disease are not fully understood. Vitamin D has, however, shown to exhibit neuroprotective effects through antioxidative mechanisms, neuronal calcium regulation, immunomodulation, enhanced nerve conduction and detoxification mechanisms.[5, 15, 16]

The vitamin D receptors and an enzyme responsible for the formation of the active form $1,25(OH)_2D$ have been found in high levels in the substantia nigra, the region of the brain affected most by Parkinson's disease.[15] This raises the possibility that chronic inadequacy of vitamin D leads to the loss of dopaminergic neurons in the substantia nigra region and further Parkinson's disease.

The strengths of the present study are the apparent long–term inadequacy of vitamin D[17], and the prospective design. There are, however, some weaknesses to be considered. First, the small number of cases may have caused instable results. Second, only a single measurement of serum 25-OHD was available which fails to take into account the intraindividual seasonal variation. However, no measurements were carried out during July and no interaction between serum vitamin D concentration and the season (sunny vs. dark period) was observed. Serum vitamin D is relatively stable over time.[18] The possibility that levels have changed during long-term storage cannot, however, be excluded.[19, 20] Third, it is possible that the study population includes undefined Parkinson's disease cases and also that all diagnosed patients are not definite cases. Because of the low prevalence of the disease, the former error is not of great importance. The latter error may however have biased the estimates of the strength of association. Fourth, the limited information on dietary intake of vitamin D is of potential concern. The major dietary source of vitamin D is fatty fish, whose consumption is also suggested to be beneficial against Parkinson's disease, due to n–3 polyunsaturated fatty acids.[21] The findings are, however, contradictory[22] and vitamin D has several other determinants.[23] Fifth, the risk factors of Parkinson's disease are not well known, and therefore despite comprehensive adjustments for potential confounders residual confounding may still remain.

In conclusion, our results are in line with the hypothesis that low vitamin D status predicts the development of Parkinson disease. Because of the small number of cases and the possibility of residual confounding, large cohort studies are needed. In intervention trials focusing on effects of vitamin D supplements, the incidence of Parkinson's disease merits to be followed up.

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TABLE 1

Selected sex– and age–adjusted baseline characteristics by Parkinson's disease.

	Parkinson's disease		
	Noncases (N=3123)	**Cases (N=50)**	**p for heterogeneity**
Age[1] (yrs)	61·8 (8·0)	60·4 (6·5)	0·23
Males[2] (%)	43.1	47.2	0.56
Summer season (Jun–Sep) (%)	18.3	12.7	0.25
More than basic education (%)	19.8	23.2	0.55
Married (%)	65.9	68.7	0.66
Regular leisure time physical activity (%)	11.3	7.6	0.42
Smokers (%)	18.7	6.2	0.02
Alcohol consumption (g ethanol/week)	29.6 (86.2)	13.1 (51.1)	0.15
Hypertensive (%)	35.7	21.1	0.03
Body mass index (kg/m2)	26.8 (4.2)	26.5 (3.3)	0.62
Diabetes (%)	8.7	2.7	0.13
Serum total cholesterol (mmol/l)	7.34 (1.37)	7.25 (1.34)	0.65
Serum 25(OH)D (nmol/l)	41.8 (19.5)	36.3 (18.5)	0.05

[1] Adjusted for sex

[2] Adjusted for age

TABLE 2

Selected sex– and age–adjusted baseline characteristics by serum 25(OH)D quartiles.

	Serum 25(OH)D mean (SD)				
	1st quartile (N=774)	**2nd quartile (N=819)**	**3rd quartile (N=778)**	**4th quartile (N=792)**	**p for trend**
Age[1] (yrs)	63.8 (8.1)	62.2 (8.1)	61.2 (7.8)	60.0 (7.6)	<0.001
Male sex[2] (%)	45.1	43.4	42.6	41.8	0.18
Summer season (Jun–Sep) (%)	2.7	12.7	21.1	36.1	<0.001
More than basic education (%)	12.7	18.3	24.6	23.7	<0.001
Married (%)	61.9	65.6	65.8	70.5	<0.001
Regular leisure time physical activity (%)	5.5	10.3	12.9	15.9	<0.001
Smokers (%)	22.3	17.3	18.8	15.6	0.002
Alcohol consumption (g ethanol/week)	22.0 (71.3)	25.9 (72.1)	32.0 (96.1)	37.6 (98.8)	<0.001
Hypertension (%)	37.2	36.6	35.5	32.4	0.04
Body mass index (kg/m^2)	26.7 (4.6)	27.1 (4.3)	27.1 (4.0)	26.2 (3.6)	0.03
Diabetes (%)	11.2	8.9	8.2	6.1	<0.001
Serum total cholesterol (mmol/l)	7.19 (1.41)	7.30 (1.35)	7.39 (1.37)	7.48 (1.32)	<0.001

[1] Adjusted for sex

[2] Adjusted for age

Quartiles for men 8–28, 29–41, 42–56, 57–159 nmol/l; for women 7–25, 26–36, 37–49, 50–151 nmol/l

TABLE 3

Relative risks (RRs) with 95% confidence intervals (CIs) for Parkinson's disease cases by baseline serum 25(OH)D.

	Serum 25(OH)D				
	1st quartile	**2nd quartile**	**3rd quartile**	**4th quartile**	**p for trend**
Number of Parkinson's disease cases	17	15	10	8	
Sex– and age–adjusted model	1.00	0.73 (0.36–1.46)	0.47 (0.21–1.03)	0.35 (0.15–0.81)	0.006
Multivariate model A	1.00	0.72 (0.36–1.46)	0.48 (0.22–1.08)	0.33 (0.14–0.80)	0.006
Multivariate model B	1.00	0.72 (0.36–1.45)	0.48 (0.21–1.07)	0.33 (0.14–0.78)	0.005

Model A further included marital status (married, others), education (basic, intermediate or high), alcohol consumption (0, <5, ≥5 g/day), leisure-time physical activity (no or light, heavy), smoking status (none, current), body mass index, and month of blood drawn.

Model B further included hypertension and serum cholesterol.

Quartiles for men 8–28, 29–41, 42–56, 57–159 nmol/l; for women 7–25, 26–36, 37–49, 50–151 nmol