Route of Insulin Does Not Influence 25-Hydroxyvitamin D Concentrations in Type 1 Diabetes: A Brief Report

Peter R. van Dijk,[1,2] Susan J. J. Logtenberg,[3] Femke Waanders,[4] Klaas H. Groenier,[1] Harry van Goor,[5] Nanne Kleefstra,[2,6] and Henk J. G. Bilo[1,2,4]

[1]Diabetes Centre, Isala, Zwolle 8000, Netherlands; [2]Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen 9700, Netherlands; [3]Department of Internal Medicine, Diakonessenhuis, Utrecht 3582, Netherlands; [4]Department of Internal Medicine, Isala, Zwolle 8000, Netherlands; [5]Department of Pathology and Medical Biology, University Medical Centter Groningen, University of Groningen, Groningen 9700, Netherlands; and [6]Medical Research Group, Langerhans, Ommen 9700 RB, Netherlands

ORCiD numbers: 0000-0002-9702-6551 (P. R. van Dijk).

The increased prevalence of vitamin D [25(OH)D] deficiency in type 1 diabetes mellitus (T1DM) may be related to low insulin levels in the hepatic portal venous system. In this prospective matched-control study, we demonstrate that long-term intraperitoneal insulin does not influence 25(OH)D concentrations in patients with T1DM as compared with subcutaneous insulin administration.

Type 1 diabetes mellitus (T1DM) is associated with an increased prevalence of vitamin D deficiency [1]. As insulin influences the activity of (hepatic) 25-hydroxylase, the enzyme that converts dietary vitamin D into calcidiol [25-hydroxyvitamin D, or 25(OH)D], a lower insulin concentration in the hepatic portal vein may influence vitamin D metabolism [2–4]. With continuous intraperitoneal insulin infusion (CIPII), insulin is infused in the intraperitoneal space, where insulin is absorbed via the capillaries of the visceral peritoneum and to a large extent into the portal vein [5–7]. We hypothesized that 25(OH)D concentrations are affected by the route of insulin administration [CIPII or subcutaneous (SC)] and that CIPII results in higher concentrations of 25(OH)D as compared with SC insulin administration.

1. Patients and Methods

This study is a *post hoc* analysis of a multicenter investigator-initiated study with a prospective, observational matched case-control design. The full study design is described elsewhere [8]. In short, patients with T1DM, aged 18 to 70 years, HbA$_{1c}$ ≥58 mmol/mol, and/or five or more incidents of hypoglycemia (defined as glucose concentrations <4.0 mmol/L) per week were eligible. Cases were subjects on CIPII using an implanted insulin pump (MIP

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CIPII, continuous intraperitoneal insulin infusion; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injection; SC, subcutaneous; T1DM, type 1 diabetes mellitus.

2007D; Medtronic/MiniMed, Northridge, CA) for at least 4 years before inclusion in the study. The SC control group, using multiple daily injections (MDIs) or continuous subcutaneous insulin infusion (CSII), was age- and sex-matched to the cases. Measurements were made at baseline and after 6 months. A 25(OH)D deficiency was defined as concentrations <50 nmol/L. Using a general linear model, to adjust for possible baseline differences, the difference in 25(OH)D between the CIPII and SC groups over time was analyzed. Multivariate regression analysis was performed with 25(OH)D averaged over the study period as dependent variable and the average HbA_{1c}, calcium, PTH, total insulin plasma concentrations, and insulin mode (CIPII or SC) as covariates. Results are expressed as mean (with SD) or median (with interquartile range) for normally distributed and nonnormally distributed data, respectively. The study protocol was registered prior to the start of the study (NCT01621308 and NL41037.075.12) and approved by the local medical ethics committee. All patients gave informed consent.

2. Results

Of the 183 patients eligible for analysis, 11 patients (3 CIPII, 7 MDI, and 1 CSII) were excluded because of insufficient blood samples and 25 patients (7 CIPII, 9 MDI, and 9 CSII) were excluded because of the use of vitamin D supplements. Subsequently, 147 patients (29 CIPII, 54 MDI, and 64 CSII) were analyzed. Of these patients, 41% were male with a mean age 49 (12) years, diabetes duration 23 (17, 35) years, BMI 26 (4) kg/m^2, HbA_{1c} of 64 (11) mmol/mol, and a total insulin dose of 0.6 (0.5, 0.8) units/kg/d. There were no differences in baseline characteristics between the CIPII and SC group.

A 25(OH)D deficiency was present in 61 (42%) of the patients included in the analysis: 16 of these patients were treated with CIPII and 45 with SC insulin (19 MDI and 26 CSII) (P = 0.15). As presented in Table 1, concentrations of calcium, phosphate, magnesium, and PTH changed significantly during the study period within the SC treatment group, whereas they remained stable in the CIPII group. The estimated mean 25(OH)D concentration over the study period was not significantly lower in the CIPII group as compared with the SC group: 58.3 (95% CI 51.1, 65.6) vs 64.6 (95% CI 60.8, 65.6) with a mean difference of 6.3 (95% CI −1.9 to 14.5) nmol/L. Except for higher alkaline phosphatase concentrations in the CIPII group, there were no other significant differences between groups. In multivariable analysis with 25(OH)D as the dependent variable, only calcium was significant [β: 43.4; SE: 8.0 (95% CI 27.5, 59.2) with R^2 = 0.19 for the model].

Comparisons between CIPII and the MDI and CSII groups and the comparisons between included and excluded patients also revealed no differences between groups.

3. Discussion

No considerable differences between CIPII and SC insulin administration regarding 25(OH)D concentrations and related parameters were observed in the current study. Moreover, in multivariate regression, no influence of both the route as the total daily dose of insulin on 25(OH)D concentrations was present. These findings are in contrast to those of Colette et al. [3], who observed higher 25(OH)D, but identical 1,25(OH)2D, levels among 13 patients treated with CIPII as compared with 28 persons treated with SC insulin. The 25(OH)D concentrations among the patients treated with SC insulin in the study by Colette et al. [3] were lower as compared with our study (∼32 nmol/L vs 65 nmol/L), whereas concentrations among CIPII-treated patients were similar. Although differences in study design may account for these discrepancies, we hypothesize that the duration of insulin therapy (≥4 years in the current study as compared with several months in the study by Colette et al. [3]) may have induced adaption of 25-hydroxylase enzyme activity and thereby normalization of 25(OH)D. Because decreased bone synthesis and strength are already present early in the course T1DM, we cannot exclude that the lack of influence of long-term treatment with CIPII on vitamin D metabolism as found in this study has no clinical consequences on bone mineral density [9]. Previous experiments in rodents suggested that insulin influences (bone- and liver-derived) alkaline phosphatase concentrations [10, 11]. As such, it could be

Table 1. Outcomes of Parameters of Vitamin D Metabolism During Baseline and Last Visit and Changes Between the CIPII and SC Insulin Therapy Groups

	CIPII Baseline	End	Change Within Group	SC Baseline	End	Change Within Group	Difference Between SC vs CIPII (Baseline Adjusted)
Calcium, mmol/L	2.17	2.16	−0.01 (−0.15, 0.13)	2.16	2.09	−0.08 (−0.15, −0.01)	−0.04 (−0.1, 0.4)
Albumin, g/L	41.8	42.2	0.35 (−2.51, 3.22)	40.9	40.1	−0.78 (−2.28, 0.73)	−1.48 (−3.10, 0.15)
Phosphate, mmol/L	0.98	0.96	−0.02 (−0.12, 0.09)	1.03	0.96	−0.07 (−0.13, −0.01)	−0.03 (−0.03, 0.90)
Alkaline phosphatase, U/L	78.1	78.3	0.2 (−9.1, 9.7)	71.8	71.6	−0.24 (−5.1, 4.7)	−6.5 (−11.8, −1.1)
Magnesium, mmol/L	0.75	0.73	−0.02 (−0.07, 0.03)	0.75	0.72	−0.03 (−0.06, −0.01)	−0.01 (−0.03, 0.03)
25(OH)D, nmol/L	51.8	64.9	13.0 (−1.5, 27.5)	58.5	65.9	12.3 (4.6, 19.8)	6.3 (−1.9, 14.5)
PTH, pmol/L	4.67	4.32	−0.33 (−1.12, 0.45)	4.81	4.18	−0.63 (−1.04, 0.22)	−0.07 (−0.45, 0.44)

Data are presented as estimated mean (SD), median (interquartile range), or mean change (95% CI) within and between groups.

hypothesized that the higher alkaline phosphatase concentrations among patients treated with CIPII, as compared with patients treated with SC insulin, are a result of differences of insulin concentrations in the portal vein and/or the peripheral circulation. Nevertheless, it should be emphasized that our data are unable to explain this finding. Besides the lack of information on bone mineral density, other limitations should be taken into account when interpreting the results of this study, including the nonrandomized design, small numbers, direct insulin measurements, and the lack of information on other indices of vitamin D metabolism, including 1,25(OH)2D and FGF-23. In contrast, we included parameters of vitamin D metabolism that are routinely used in clinical practice; furthermore, plasma insulin concentrations and all other measurements were made on two separate occasions.

Taken together, these findings may indicate that after long-term treatment, the route of insulin administration does not influence 25(OH)D concentrations in T1DM.

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Additional Information

Correspondence: Peter R. van Dijk, MD, PhD, Department of Internal Medicine, University Medical Center Groningen, University of Groningen, HPA AA41, Groningen 9700 RB, Netherlands. E-mail: p.r.van.dijk@umcg.nl.

Disclosure Summary: The authors have nothing to disclose.

Data Availability: The data sets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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