NEFROLOGO IN CORSIA

Severe 25-OH vitamin D deficiency in patients on chronic hemodialysis

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Abstract

Introduction: 25-OH vitamin D deficiency is associated with increased cardiovascular mortality in general population and in chronic kidney disease. The aim of this study was to evaluate 25-OH-Vitamin D (25-D) serum levels in chronic hemodialysis (HD) patients and its relationship with cardiovascular and non-cardiovascular risk factors.

Material and Methods: we performed a cross-sectional study with 187 prevalent HD patients (106 M/ 81 F) in chronic hemodialysis. 25-D were measured in January and blood samples were collected for analysis before a midweek HD session.

Results and conclusions: the mean age of patients was 67 ± 15 years with the mean HD time of 73 ± 68 months. Forty-six patients (25%) were diabetics. 31% of the patients were taking i.v. paricalcitol and 22% were taking calciomimetics. None of patients were receiving native vitamin D. Serum levels of 25-OH-Vitamin D were low (11,7±7,5 ng/ml). Only 4% of patients had values of 25- OH-Vitamin D considered normal by the guidelines KDOQI. Levels of 25-D were deficient and insufficient respectively in 73% and 23% of the patients. In univariate analysis, serum levels of 25-D were negatively correlated with female sex and diabetes and positively correlated with albumin. In multivariate analysis dialysis vintage, lower serum calcium, hypoalbuminemia, higher BMI and treatment with paricalcitol were independently associated with lower levels of 25-OH-Vitamin D.

Deficiency of 25-D is extremely common in chronic hemodialysis. It is still to be investigated by randomized prospective studies if native vitamin D supplementation is able to improve clinical outcomes in dialysis.

Key words: 25-OH-Vitamin D, haemodialysis, vitamin d

Introduction

Vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) are almost totally synthesized by the skin in response to ultra-violet radiation, and are only minimally ingested with the diet. Both undergo liver hydroxylation, leading to the formation of 25-OH vitamin D (calcifediol), and then kidney hydroxylation [1] (full text), which leads to the synthesis of

1,25-OH vitamin D (calcitriol), the active form of vitamin D. The synthesis of calcitriol is therefore deficient in patients with chronic kidney disease, although a small amount of vitamin D is still synthesized peripherally.

The enzyme 1-α hydroxylase has been identified in extra-renal tissues such as brain, heart, pancreas, smooth muscle and lymphocytes [2], but its activity is directly regulated by parathyroid hormone (PTH) and FGF23 exclusively at renal level [3] (full text).

Both 25- and 1,25-OH vitamin D control calcium and phosphorus metabolism and regulate other systems (renin-angiotensin, insulin resistance, inflammation) by binding to vitamin D nuclear receptors (VDRs) in the cells of extra-renal tissues [4], but the affinity of 25-OH vitamin D for VDRs is 100 times less, its serum levels are one thousand times, and it has a much longer half-life (2-3 weeks against the 4-7 hours of calcitriol) [5] (full text).

Vitamin D (particularly 25-OH vitamin D) has aroused increasing interest over recent years because of its association with some types of neoplasias, auto-immune diseases, and diabetes mellitus [6]. Observational studies of the general population have also shown that the risk of mortality due to cardiovascular and other causes is greater in subjects with low levels of 25-OH vitamin D [7] [8] [9] [10].

However, only a few studies of 25-OH vitamin D levels in patients undergoing chronic hemodialysis have been carried out in Italy [11].

The aim of study was therefore to evaluate serum 25-OH vitamin D levels in patients on chronic hemodialysis, and investigate their associations with cardiovascular and non-cardiovascular risk factors.

Materials and methods

This observational study involved 187 patients undergoing chronic hemodialysis in four dialysis centres in Lazio, Italy. The causes of end-stage renal disease were glomerulonephritis (23 cases), tubulo-interstitial nephropathy (15 cases), diabetic nephropathy (26 cases), nephroangiosclerosis (61 cases), other (14 cases) and undetermined (48 cases).

The samples for blood chemistry measurements were drawn during the winter (January 2011), before a mid-week dialytic session. The levels of 25-OH vitamin D, intact PTH, C-reactive protein and albuminemia were assayed in a single centralised laboratory within four hours of the samples being taken; the other parameters (calcemia corrected for hypoalbuminemia, phophoremia, total and HDL cholesterol, and hematocrit) were analysed by the laboratories of the dialysis centres.

The serum levels of 25-OH vitamin D and intact PTH 1-84 were determined by means of chemiluminescence (DiaSorin LIAISON, Stillwater, MN). In accordance with the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, 25-OH vitamin D levels of <5 ng/mL were considered severely deficient, those of 5-15 ng/mL as slightly deficient, and those of 15-30 ng/mL as insufficient [12] (full text).

Statistics

In order to describe the characteristics of the studied population, categorical variables were expressed as absolute and relative frequency distributions, and quantitative variables as mean values and standard deviations.

Simple linear regression was used to evaluate the associations between 25-OH vitamin D levels and some demographic and clinical characteristics and blood chemistry parameters. A multivariate linear regression model was used to evaluate each variable as a potential con-

founder using an automated stepwise method and setting a p value of ≤0.10 as a threshold for entering model variables; the variables of age and gender were forced into the model.

Results

Figura 1 shows the demographic characteristics and blood chemistry parameters of the 187 patients (57% males), 25% of whom were affected by diabetes mellitus. Their mean age at the time of the study was 67 ± 15 years, and their mean dialytic age was 73 ± 68 months.

All of the patients were hemodialysed using a synthetic membrane: vascular access was provided by an arteriovenous fistula in 92% of cases, and by a central venous catheter in 8%.

Seventy-one percent were being treated with vitamin D analogues (40% with calcitriol, and 31% with paricalcitol), and 22% with cinacalcet; none were being treated with native vitamin D. In addition, 51% were receiving sevelamer, 13% calcium-based binding-phosphate and 7% lanthanum carbonate.

Figura 2 shows that 25-OH vitamin D levels were below the range considered normal by the KDIGO guidelines in 96% of the patients. They were significantly higher among males, and increased for unit albuminemia values, and significantly lower among diabetics (Figura 3). There was no association with phosphoremia or PTHi levels.

Multivariate linear regression analysis, which was carried out taking some potentially confounding factors into account, showed that dialytic age, an increased body mass index (BMI) and higher HDL cholesterol levels, hypocalcemia, hypoalbuminemia, and treatment with

VARIABLE	All patients (n=187)
Age (years)	67,3±14,5
Sex	Maschi=106 (56,7%) / Femmine=81 (43,3%)
HD duration (months)	73 ± 68
Diabetes	46 (24,5%)
BMI (kg/m2)	24,2 ± 3,9
Vascular Access	AV fistula=172 (92,0%) / CVC=15 (8,0%)
Dialysis technique	HD =146 (78,1%) / HDF=41 (21,9%)
Sevelamer	96 (51,1%)
Calcium-Carbonate	24 (12,8%)
Lanthanium carbonate	13 (6,9%)
Cinacalcet	41 (21,8%)
Calcitriol	76 (40,4%)
Paricalcitol (iv)	59 (31,4%)
Hematocrit	34 ± 5 (%)
C –reactive protein mg/dl	1,11 ± 1,94
Total cholesterol mg/dl	163 ± 44
HDL-cholesterol mg/dl	44 ± 13
Albumin g/dl	3,98 ± 0,42
Calcium (albumin adjusted) mg/dl	9,02 ± 0,69
Phosphorus mg/dl	5,00 ±1,27
iPTHi pg/mL (nv < 38 pg/ml)	129 ± 143
25-OH-Vitamina D ng/mL	11,77 ± 7,50

Figura 1.
Caratteristiche demografiche, cliniche e di laboratorio della popolazione studiata (N=187)

Demographic, clinical and laboratory characteristics of the study population (n = 187)

paricalcitol were independently associated with lower 25-OH vitamin D levels, whereas calciomimetic treatment was associated with higher 25-OH vitamin D levels (Figura 4).

Discussion

The results of this study show that patients undergoing chronic hemodialysis lack 25-OH vitamin D as only 4% had levels within the range considered normal by the KDOQI guidelines [12] (full text), and are similar to the findings of other studies [13] (full text) [14] [15] (full text).

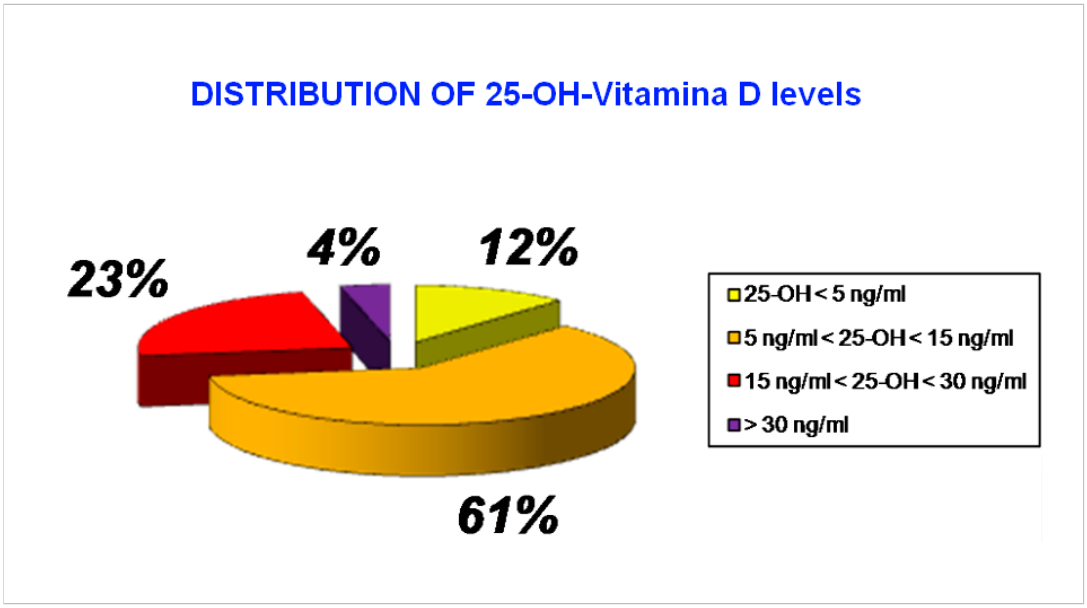

Figura 2.
Distribuzione dei livelli di 25-OH Vitamina D

Distribution of 25-OH vitamin D levels

VARIABLE	coefficient	CI95%	P
Age (each year more)	-0,04	-0,11; 0,04	0,33
Male vs Female	3,09	0,95; 5,24	0,01
Diabetes (YES vs NO)	-2,46	-4,95; 0,04	0,05
Albumin (each g/dl more)	3,75	1,23; 6,27	< 0,01
AV fistula vs CVC	3,54	-0.42; 7,50	0,08
BMI (each kg/m^2 more)	-0,24	-0,52; 0,03	0,09
Calcium albumin adjusted (each mg/dl more)	0,79	-0,79; 2,37	0,33
Phosphorus (each mg/dl more)	-0,25	-1,10 ; 0,60	0,56
iPTH (each pg/ml more)	0,00	-0,01; 0,01	0,75
Paricalcitol (YES vs NO)	-1,66	-3,99; 0,65	0,15
Cinacalcet (YES vs NO)	2,43	-0,20; 5,05	0,07

Figura 3.
Associazione tra alcune caratteristiche demografiche e alcuni parametri ematochimici e livello di 25-OH Vitamina D (modelli di regressione lineare)

Associations between 25-OH vitamin D levels, some demographic characteristics and some blood chemistry parameters (linear regression models)

The deficiency is particularly marked if compared with the data of another Italian study published in 2005 [11] indicating that 50% of the subjects had levels of <30 ng/mL, although these were measured over a period of 12 months and not only during the winter. Seventy-three percent of our patients had levels of <15 ng/mL, a percentage that is similar to that reported by Wolf *et al.* [16], with respectively 12% and 61% showing severe or mild deficiency.

The deficiency in 25-OH vitamin D in hemodialysed is multifactorial, and due to the inactivity of patients undergoing replacement therapy, limited exposure to sunlight, a minimal dietary intake of foods containing vitamin D_2 [17] (full text), and the altered skin synthesis of vitamin D related to uremia [18] (full text).

It is known that patients with chronic kidney disease undergoing hemodialysis are at greater risk of death due to cardiovascular causes than healthy controls [19]. Numerous studies published over the last few years have shown that there is a close association between reduced 25-OH vitamin D levels and all-cause and cardiovascular mortality in subjects with chronic renal insufficiency who have not yet started dialysis [20], those undergoing peritoneal dialysis [21] (full text), and incident [22] (full text) and prevalent patients [23] (full text) undergoing hemodialysis. Furthermore, Bienaime *et al.* [24] (full text) have shown an association between low 25-OH vitamin D levels, interstitial fibrosis, and a 12-month worsening in renal function in kidney transplant recipients. Low 25-OH vitamin D levels in hemodialysed patients are also associated with the development of vascular calcifications [25] (full text) [26].

This study was carried out in winter, during which 25-OH vitamin D levels are lower than those measured in the summer [27] (full text), but almost all of our patients had levels that were lower than the 30 ng/mL recommended in the KDOQI guidelines [12] (full text).

Previous studies have shown that 25-OH vitamin D levels are associated with dialytic age [28] (full text) but not chronological age [29], and others that low levels correlate with the presence of diabetes [16] [22] (full text) [25] (full text) and higher BMI values [17] (full text) [30]. It seems that 25-OH vitamin D deficiency plays a role in the pathogenesis of diabetes by determining a dysfunction in pancreatic β cells and as a result of increased insulin resistance [31] (full text) [32] [33] (full text),and the autonomic neuropathy associated with diabetes can alter the intestinal absorption of vitamin D [34] (full text).

Linear regression analysis confirmed that females were more predisposed to lower 25-OH vitamin D levels [15] (full text), probably because of hormonal factors.

VARIABLES	coefficient	95%CI	p
Age (each year more)	-0,03	-0,11 0,05	0,43
Sex (male vs female)	1,64	-0,55 ; 3,84	0,14
BMI (each kg/m² more)	-0,36	-0,64; -0,08	0,01
HDL – cholesterol (each mg/dl more)	-0,10	-0,18 ; -0,01	0,03
Albumin (each g/dl more)	3,23	0,75 ; 5,72	0,01
Calcium (albumin adjusted)(each mg/dl more)	1,65	0,08 ; 3,22	0,04
Paricalcitol (YES vs. NO)	-3,60	-6,12 ; -1,09	0,01
Cinacalcet (YES vs. NO)	3,35	0,52 ; 6,19	0,02
AV fistula vs CVC	3,83	-0,19; 7,85	0,06
HD duration (months) (each month more)	-0,02	-0,03; 0,00	0,05
All variables have been adjusted for each other.			

Figura 4.
Fattori associati al livello di 25-OH Vitamina D (modello multivariato di regressione lineare)

Factors associated with 25-OH vitamin D levels (multivariate linear regression model)

Like other authors, we did not find a correlation between 25-OH vitamin D levels and parameters of bone metabolism such as phosphorus and PTHi [11] [16] [29], but there was an association between low vitamin levels and hypocalcemia [36] (full text).

In relation to the treatment of secondary hyperparathyroidism, unlike Matias *et al.* [25] (full text), we found that the patients treated with paricalcitol had significantly lower 25-OH vitamin D levels, whereas those treated with calciomimetics had higher levels.

Hypoalbuminemia is usually associated with chronic micro-inflammation, and 25-OH vitamin D levels did correlate with albuminemia [13] (full text) [25] (full text) but not with c-reactive protein levels. Peterson *et al.* [37] (full text) have observed an inverse correlation between 25-OH vitamin D and TNF-α levels in women, whereas Wasse *et al.* [36] (full text) found higher C-reactive protein but not TNF-α levels in hemodialysed subjects with 25-OH vitamin D levels of <15 ng/mL.

Vitamin D supplementation improves plasma 25-OH vitamin D levels [38] (full text), but the improvement is inadequate in some patients, particularly those with diabetes [39] [40] (full text).

The limitations of this study include its observational nature and small sample size. Furthermore, there are data concerning the presence of arterial hypertension, ischemic heart disease, peripheral vasculopathy or the use of statins.

In conclusion, subjects undergoing chronic hemodialysis show severe 25-OH vitamin D deficiency and, given the association between low vitamin D levels and increased mortality, vitamin D levels should be assayed at least once a year in everyday clinical practice. Furthermore, given the extremely low levels encountered in winter, the measurements should be principally made during the winter in order to identify the most affected patients. The assay should be repeated even in patients receiving exogenous supplementation (particularly if diabetic) because of the variability in response. Finally, the low cost of calcidiol therapy would allow it to be widely used.

Although randomised clinical trials are necessary in order to verify whether the use of supplementation to reach “normal” 25-OH vitamin D levels really prolongs the survival of dialysed patients, this remains one of the few studies of 25-OH vitamin D levels in patients undergoing chronic hemodialysis.

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