

Circulating 1,25-Dihydroxyvitamin D And Its Ratio With PTH(1-84) Are Predictors Of Worsening Renal Function In CKD3 Patients

Prof. Mario Cozzolino
September, 2020

Introduction

- Chronic Kidney Disease (CKD) patients have to be monitored closely and frequently in order to delay the progression to end stage kidney failure that requires transplantation or dialysis.
- The most common approach for kidney function monitoring is the eGFR, which utilizes the relatively simpler and less expensive measurement of blood creatinine clearance.
- eGFR still maintains two significant limitations:
 - it can neither anticipate nor predict kidney damage
 - creatinine levels in blood are compromised by several parameters, including age, gender, muscle metabolism and mass, diet and fluid balance.

Introduction

- In CKD, deficiency of 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$) develops during the progression of kidney failure due to the decreased capability of the renal proximal tubule cells to mediate the final hydroxylation step of 25-hydroxyvitamin D ($25(\text{OH})\text{D}$) to $1,25(\text{OH})_2\text{D}$.
- the reduced levels of $1,25(\text{OH})_2\text{D}$ also induce hyperplasia of the parathyroid glands with consequent enhanced synthesis and secretion of parathyroid hormone (PTH).
- High PTH levels are responsible for secondary hyperparathyroidism and its subsequent manifestations of bone disease consequent to the appearance of abnormal calcium and phosphorus balances.

Introduction

- No significant correlation between 25(OH)D levels and its active form $1,25(\text{OH})_2\text{D}$ are found in CKD or in normal subjects
- During the last few years, literature reports have explored the ratio of $1,25(\text{OH})_2\text{D}$ to PTH(1-84) as a predictor of worsening renal function:
 - $1,25(\text{OH})_2\text{D}/\text{PTH}(1-84)$ ratio was a strong predictor of mortality in a cohort of chronic heart failure patients (Gruson et al., 2015)
 - The ratio predicted incident worsening of renal function in 1,200 patients with chronic HF, independent of serum creatinine (Masson et al., 2016).
 - The $1,25(\text{OH})_2\text{D}/\text{PTH}(1-84)$ ratio was strongly predictive of composite renal events in CKD 3b-5 patients (Levin et al, ASN 2017).

Study Aim

The aim of this study was to explore the predictive value and utility of bone and mineral biomarkers in the earlier stages of CKD.

Study Design

- This monocentric study was observational, prospective and descriptive, with a longitudinal approach.
- 71 patients under nephrologist care were enrolled from with follow-up care at 3 and 6 months.
- eGFR were between 15 and 59 mL/min/1.73 m² (CKD stages 3a, 3b and 4), calculated using the CKD-EPI formula.
- **Included subjects:** receiving maintenance therapy for diabetes and hypertension and patients on treatment with vitamin D or vitamin D analogues.
- **Excluded subjects:** with primary hyperparathyroidism, previous parathyroidectomy or active bisphosphonate, denosumab, PTH analogue and or strontium ranelate regimens, as well as pregnant and lactating subjects. Demographic variables including age, sex and ethnicity were recorded.
- The primary outcome used was 20% worsening of renal function based on eGFR, evaluated at 3 and 6 months.

Methods

- Blood samples were collected at fasting between 7:00 and 10:00 a.m.
- Routine measurements such as serum creatinine, total alkaline phosphatase, total calcium, phosphorus were made at the corresponding local accredited laboratories using standardized assays.
- mGFR was determined at baseline by renal scintigraphy (^{99m}Tc -diethylenetriamine-pentaacetic acid)
- Measurement of bone mineral biomarkers was performed at DiaSorin Inc. (Stillwater MN, USA) on a LIAISON® XL analyzer using the fully-automated LIAISON® assays

General Characteristics Results

	CKD3	CKD4	P value
Gender %M	83%	66%	0.0774
Age	73.6 ± 8.9	72.4 ± 12.8	0.67
Cardiovascular events N (%)	25 (69%)	23 (72%)	0.83
Diabetes	15 (42%)	12 (37%)	0.73
CKD cause (N)			
Diabetes	11 (30%)	10 (31%)	0.95
Hypertension	31 (86%)	29 (91%)	0.57
Glomerulonephritis	4 (11%)	1 (3%)	0.21
Inherited diseases	1 (3%)	1 (3%)	0.93
Malformations	15 (42%)	17 (53%)	0.35
Lupus /autoimm	3 (8%)	2 (6%)	0.74
Obstructions	4 (11%)	5 (16%)	0.59
Repeated urinary infections	0	5 (16%)	0.0145
Other	12 (33%)	8 (25%)	0.45
Weight (kg)	74.4 ± 13.7	76.7 ± 14.1	0.51
Height (cm)	164.5 ± 8.6	163.4 ± 8.8	0.63
BSA (kg/m²)	1.81 ± 0.19	1.83 ± 0.19	0.64
BMI	27.4 ± 4.0	28.8 ± 5.3	0.22
Blood pressure (mmHg)			
systolic	137 ± 20	139 ± 22	0.69
diastolic	72.4 ± 11.5	73.9 ± 11.2	0.58

Biomarker Results

	CKD3	CKD4	P value
mGFR (re-I scintigraphy mL/min)	43.9 ± 13.0	25.3 ± 9.6	<0.0001
eGFR (mL/min/1.73m ²)	40.2 ± 7.7	22.1 ± 4.1	<0.0001
Serum creatinine (mg/dL)	1.63 ± 0.27	2.60 ± 0.48	<0.0001
ALP (IU/L)	73.3 ± 20.4	81.8 ± 22.6	0.11
Calcium (total, mg/dL)	9.50 ± 0.33	9.38 ± 0.46	0.24
Phosphorus (mg/dL)	3.44 ± 0.50	3.91 ± 0.73	0.0026
Intact PTH (pg/mL)	110 ± 45	169 ± 81	0.0004
24h urine creatinine (g/24h)	1.15 ± 0.36	1.06 ± 0.38	0.34
24h urine phosphorus (g/24h)	0.64 ± 0.19	0.60 ± 0.27	0.45
24h urine calcium (mg/24h)	53.2 ± 48.3	32.2 ± 38.4	0.0586
24h urine sodium (mEq/L)	101.4 ± 31.4	91.4 ± 31.9	0.21
urine spot creatinine (mg/dL)	83.2 ± 43.3	83.0 ± 37.6	0.98
urine spot albumin (mg/L)	197 ± 438	423 ± 477	0.0504
ACR (mg/g)	37.4 ± 114	59.7 ± 81.2	0.3701
Vitamin D supplements (N)			0.0265
none	18 (50%)	5 (16%)	
inactive	16 (44%)	14 (44%)	
active	0	2 (6%)	
both	2 (6%)	11 (34%)	

No significant differences were observed except for those directly related to the severity of kidney disease

Univariate Regression

Variable	P value
1,25(OH)₂D	0.0029
1,25(OH) ₂ D/PTH1-84 ratio	0.0504
24h urine sodium	0.0686
25OHD	0.0776
ALP	0.1102
24h urine calcium	0.1908
BAP	0.2031
1,25(OH) ₂ D/FGF23 ratio	0.3024
PTH1-84	0.3599
24h urine creatinine	0.4629
24h urine phosphorus	0.6947
eGFR	0.7193
FGF23	0.7626
calcium	0.8649
sclerostin	0.9123
phosphorus	0.9985

1,25(OH)₂D was the single and strongest predictor of a 20% worsening renal function endpoint

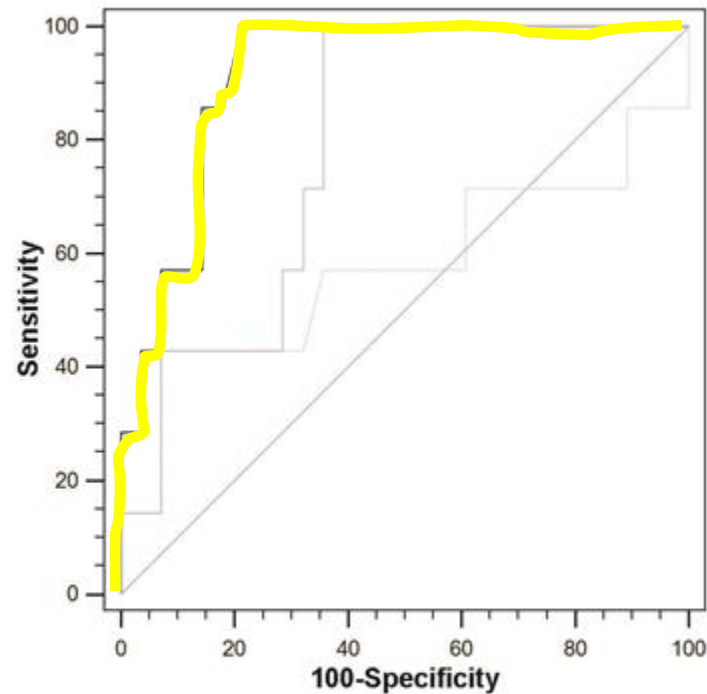
Multivariate Regression

Variable	P value
1,25(OH) ₂ D/PTH1-84 ratio	0.0032
PTH1-84	0.0086

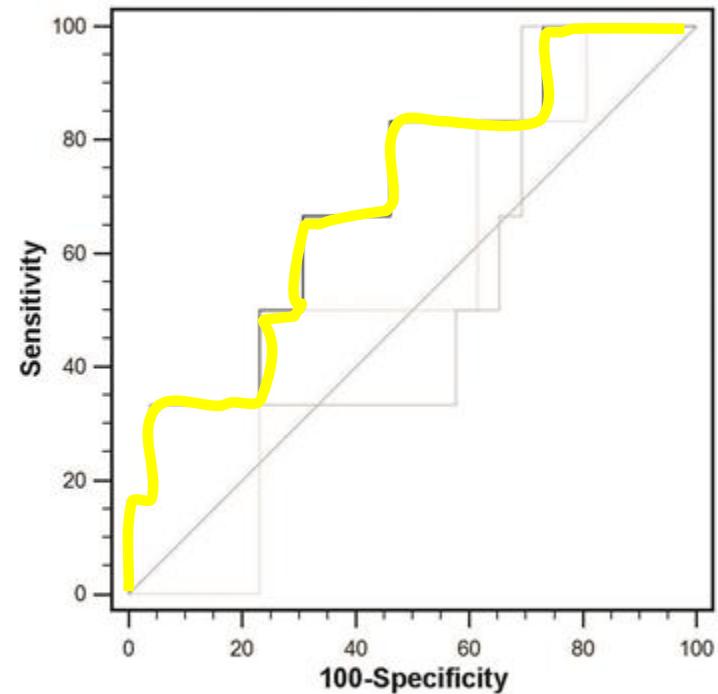
- **Backward elimination multivariate regression left 1,25(OH)₂D/PTH(1-84) ratio and PTH(1-84) as significant predictors**
- **Variable elimination was done in the order of calcium, BAP, phosphorus, FGF23, 24h urine creatinine, eGFR, 1,25(OH)₂D/FGF23 ratio, 24h urine phosphorus, 25OHD, 1,25(OH)₂D, 24h urine calcium, 24h urine sodium, sclerostin and lastly, total alkaline phosphate.**

ROC Analysis 1,25(OH)₂D

CKD3



CKD4



— 1,25(OH)₂D
— 1,25(OH)₂D/PTH1-84 ratio
- - - eGFR

1,25(OH)₂D was a better predictor in CKD3 patients suggesting better prediction earlier in the disease course

ROC Analysis 1,25(OH)₂D

Subgroup	N	AUC	Criterion	Sensitivity	Specificity	P
All patients	71	0.806	≤29.0 pg/mL	92.3	65.5	<0.001
CKD3	35	0.916	≤29.0 pg/mL	100	78.6	<0.0001
CKD4	32	0.770	≤29.0 pg/mL	83.3	53.8	0.0967
≤70 years	19	0.883	≤27.8 pg/mL	100	73.3	<0.0001
>70 years	52	0.770	≤29.0 pg/mL	88.9	65.1	0.0003

1,25(OH)₂D was a better predictor in CKD3 patients suggesting better prediction earlier in the disease course as well as in younger patients.

ROC Analysis

1,25(OH)₂D/PTH(1-84) Ratio

Subgroup	N	AUC	Criterion	Sensitivity	Specificity	P
All patients	71	0.653	≤0.844	100	48.2	<0.028
CKD3	35	0.791	≤0.844	100	64.3	0.0004
CKD4	32	0.558	≤0.840	100	30.8	0.697

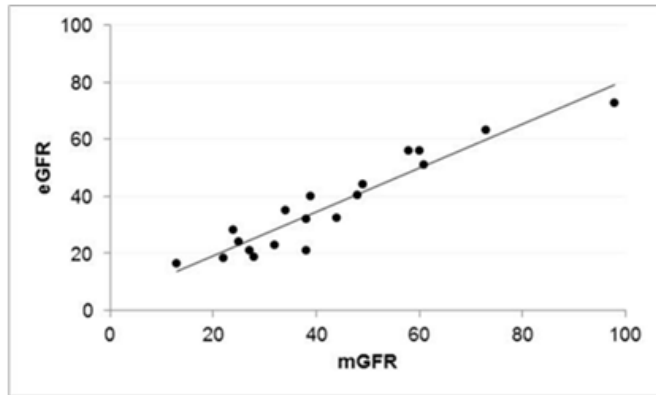
The 1,25(OH)₂D/PTH(1-84) ratio was also a good predictor of 20% worsening renal function and also better in CKD3 patients.

Correlations With eGFR

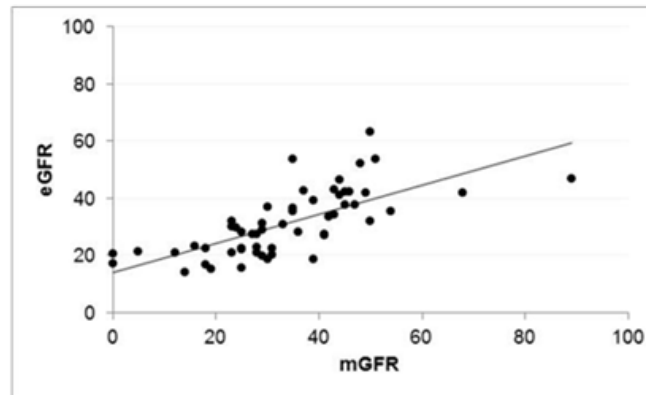
≤70 years old

>70 years old

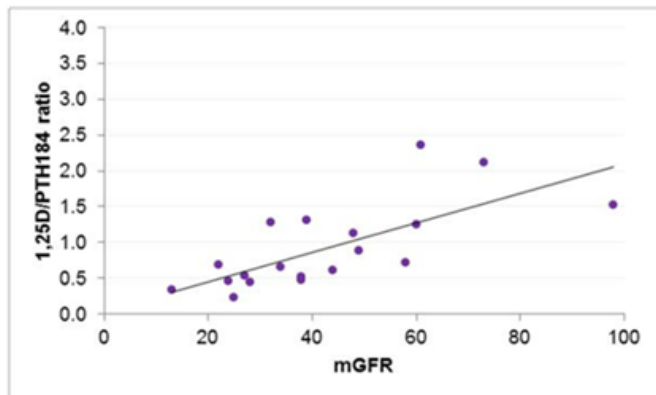
A



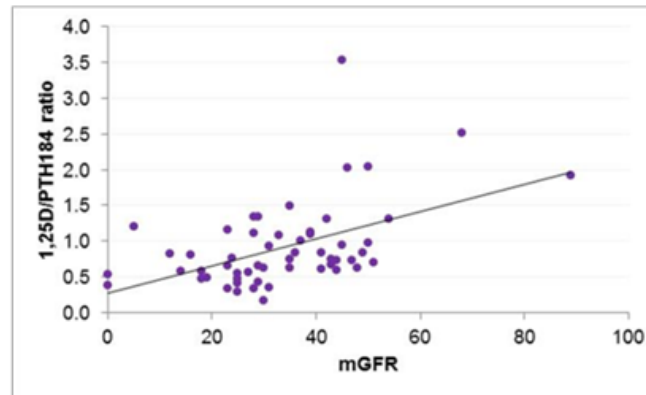
B



C



D



The 1,25(OH)₂D/PTH ratio was the variable most strongly correlated to mGFR after eGFR (R=0.71 and R=0.50 for younger and older patients, respectively).

1,25(OH)₂D alone was not correlated to eGFR (R≤0.16)

Conclusions

In a prospective clinical trial examining bone and mineral biomarkers in CKD patients we observed:

- In univariate regression analysis $1,25(\text{OH})_2\text{D}$ was the single and strongest predictor of a 20% worsening renal function endpoint.
- Backward elimination multivariate regression left $1,25(\text{OH})_2\text{D}/\text{PTH}(1-84)$ ratio and $\text{PTH}(1-84)$ as significant predictors.
- In ROC analysis $1,25(\text{OH})_2\text{D}$ and the $1,25(\text{OH})_2\text{D}/\text{PTH}(1-84)$ ratio were better predictors in CKD3 patients suggesting better prediction earlier in the disease course.
- The $1,25(\text{OH})_2\text{D}/\text{PTH}$ ratio was the variable most strongly correlated to mGFR after eGFR.

Limitations

Although the main limitation of this study is the relatively small subject numbers, especially for subgroups, it nonetheless affords proof of concept for further research of these markers in expanded populations, both in terms of size, ethnicity, age and clinical etiology.