Insulin Resistance and Vitamin D Deficiency in Patients with Chronic Kidney Disease Stage 2-3

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Type of manuscript: Original Article

Short Title: Insulin Resistance and Vitamin D Deficiency in Kidney Disease

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Summary

Vitamin D status and the relationship between serum 25(OH) vitamin D concentrations and the components of insulin resistance were examined in 120 patients with chronic kidney disease stage 2 and 3. Insulin sensitivity/resistance was calculated by the quantitative insulin sensitivity check index (QUICKI). In this analysis, the prevalence of insulin resistance was 42%. Only 17% of patients had serum 25(OH) vitamin D concentration in the reccomended range (≥ 30 ng/ml), 42% suffered from vitamin D insufficiency and 41% had moderate vitamin D deficiency. Insulin resistance significantly correlated with serum 25(OH)D and $1,25(OH)_2D$ concentrations, renal function and protein excretion rate. Our results support the increasing evidence that vitamin D deficiency may be one of the factors participating in the development of insulin resistance already in the early stages of chronic kidney disease.

Key Words

Chronic kidney disease • Insulin resistance • 25(OH) vitamin D • $1,25(OH)_2$ vitamin D • Proteinuria

Introduction

Chronic kidney disease (CKD) is associated with insulin resistance (Fliser *et al. 1998*, Kato *et al.* 2000, Chen *et al.* 2003) which plays an important role in the pathogenesis of cardiovascular diseases. Insulin resistance is a risk factor of metabolic syndrome (Tuttle, 2005). According to WHO classsification, microalbuminuria is also a clinical criterion for the metabolic syndrome (Chen *et al. 2004*, Grundy *et al.* 2004). Analysis of a subsample of NHANES III (National Health and Nutrition Examination Survey) participants revealed a strong, positive, and significant relationship between the insulin resistance and a risk for CKD (Chen *et al.* 2003). Vitamin D deficiency has long been considered as a risk factor for glucose intolerance (Boucher *et al.* 1995, Chiu *et al.* 2004, Foroughi *et al.* 2008). An inverse correlation between serum concentration of vitamin D and insulin resistance was found in NHANES III participants (Ford *et al.* 2002, Chonchol and Scragg, 2007). There is an increasing evidence that vitamin D metabolism affects insulin resistance. Previous studies reported reduced serum 25(OH) vitamin D concentration in patients with CKD (Ishimura *et al.* 1999, Gonzales *et al.* 2004, Chonchol and

Scragg, 2007), although the relationship between vitamin D status and insulin resistance has not been examined.

Therefore, the aim of our study was to evaluate the relation of insulin sensitivity/resistance to vitamin D status in CKD patients with mild to moderate decrease in renal function.

Subjects and Methods

One hundred and twenty patients with CKD, 71 women and 49 men, aged 22–83 years, (mean age 64 ± 10 years) were included into the examination. The patient diagnoses are summarized in Table 1. Patient with diabetes mellitus type 2 (DM) treatead with any insulin therapy were excluded, but 19 diabetic patients on sulfonylurea treatment or diet were included. Hypertension was present in 97 patients (81%) and was predominantly treated with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers. Dyslipidemia was treated by statins or fibrates in 49 patients (41%). The therapy of hypertension, diabetes and dyslipidemia was not changed at least two months before the examination. Chronic kidney disease was defined according to K/DOQI guidelines (K/DOQI, 2002). Glomerular filtration rate (GFR) was assessed by the abbreviated modification of MDRD equation (http://www.kidney.org/, Okša *et al.* 2008) and patients with stable GFR of 0.50-1.49 ml/s (CKD stage 2-3) were eligible for enrollment. Proteinuria was determined in the 24 hour urine collection by a routine method. Patients with an acute impairment of renal function, nephrotic proteinuria, malignancies, and derangements of mineral metabolism were excluded before enrolment to the study. Vitamin D, calcitriol or any over-the-counter vitamin D preparations had to be cancelled at least 2 months before examination.

Insulin resistance was calculated by the Quantitative Insulin Sensitivity Check Index (QUICKI) (Katz *et al.* 2000) from fasting glucose and insulin concentrations. Each subject was classified as either insulin sensitive (IS) or insulin resistant (IR) based on the QUICKI index above or below 0.356, respectively. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Serum concentrations of 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydoxyvitamin D ($1,25(OH)_2D$) (Immuno Diagnostic System, UK) were analysed by RIA methods. Intact PTH (Immunotech, France) and insuline (Immunotech, Czech Republic) were evaluated by IRMA methods.

The Ethics Committee of the Slovak Medical University approved the study, and all participants gave their written informed consent.

Statistical evaluation

The statistical software SPSS (release 13.0) was used for analysis. After testing for normality of data distribution, the data of three patients groups divided according to insulin sensitivity/resistance and DM were tested by Kruskal-Wallis test. Two groups of patient divided according to GFR were tested by Mann-Whitney test. Pearson´s correlation analysis between QUICKI on one hand and age, BMI, GFR, 25(OH)D and $1,25(OH)_2D$, PTH, blood pressure on other hand was done in pooled patient data only. All data are presented as median and inter quartile reange unless otherwise stated. Differences at a P - value < 0.05 were considered significant.

Results

Patients were devided into three groups according to QUICKI index. Fourty seven patients were insulin sensitive with the average QUICKI value of 0.377 (39%), 50 patients were insulin resistant with the average QUICKI value of 0.321 (42%) and 23 patients suffered from diabetes mellitus type II with the average QUICKI value 0.304 (19%) (Table 2). In addition to QUICKI, significant differences in fasting plasma glucose and insulin concentrations, as components for the calculation of QUICKI were detected among individual groups. Insulin resistant and DM patients had significantly higher BMI in comparison with IS group. Glomerular filtration rate was significantly lower in IR and DM patients. Insulin sensitive and IR patients had an urinary protein excretion in the range of microalbuminuria and diabetic patients in the range of proteinuria. Median serum 25(OH)D concentration was in the range of vitamin D insufficiency in all three groups. The serum concentration of $1,25(OH)_2D$ significantly decreased with diminution of insulin sensitivity. The serum PTH concentration was in the normal range in the all three groups. Median systolic blood pressure was 130 (120-140) mmHg and median diastolic blood pressure was 80 (78-85) mmHg, with nonsignificant decrease in IR and DM groups.

25(OH) vitamin D

Serum 25(OH)D concentrations were distributed in log-normal fashion (Fig.1). Vitamin D insufficiency/deficiency was evaluated according to K/DOQI guidelines (K/DOQI,

2003). Only 20 patients (17%) had serum 25(OH)D concentration in the recommended range (≥30 ng/ml), 51 patients (42%) suffered from vitamin D insufficiency (16-30 ng/ml) and 49 patients (41%) from moderete vitamin D deficiency (5-15 ng/ml). Nobody had severe vitamin D deficiency (<5 ng/ml) (Fig. 2).

Renal function

To evaluate the differences of individual parameters according to renal function, patients were devided into two groups, CKD stage 2 (n=45, 46%) and CKD stage 3 (n=52, 54%) (Table 3). Patients with diabetes mellitus were excluded. Urinary protein excretion was in the range of microalbuminuria in both groups. Patients with CKD stage 3 were older, had significantly higher plasma fasting glucose and insulin concentrations and higher insulin resistance. The serum concentrations of 25(OH)D and $1,25(OH)_2D$ were significantly lower in patients with CKD stage 3. In spite of lower vitamin D concentrations, median PTH levels were in the normal range, though at the upper normal limit in CKD stage 3 group. Patients with lower renal function had significantly higher systolic blood pressure without differences in diastolic blood pressure.

Correlations between QUICKI index, serum 25(OH)D concentration and other variables

Insulin resistance evaluated by the QUICKI index significantly correlated with serum 25(OH)D and $1,25(OH)_2D$ concentrations, GFR and protein excretion rate (Table 4). Expected negative and highly significant correlations were found between QUICKI, BMI and systolic blood pressure. In addition to correlation of serum 25(OH)D concentration with QUICKI, it correlated with fasting insulin concentration, but not with fasting glucose concentration. Significant possitive correlation was found between serum 25(OH)D and $1,25(OH)_2D$ concentrations, renal function and negative correlation with systolic blood pressure. No significant correlation was determined between serum 25(OH)D concentration and proteinuria.

Discussion

Insulin resistance and renal function

The principal finding in the present study is the demonstration that CKD is accompanied by insulin resistance even in stages 2 and 3. Our study identified a strong and significant relationship between QUICKI, renal function and proteinuria. Several large studies

examined the association between insulin resistance and risk of chronic kidney disease (Fliser *et al. 1998,* Chen *et al.* 2003). Hoechner and colleagues (2002) found that persons with 3 or more symptoms of the metabolic sydrome had 2,3-fold higher odds for microalbuminuria than persons with no symptoms. Chen and colleagues (2003) reported that insulin resistance estimated by homeostasis model assessment was associated with increased risk for chronic kidney disease in nondiabetic participants. Our results are in accordance with these observations and supports the notion that kidney disease is associated with insulin resistance, hyperinsulinemia and hyperglycemia, and that insulin resistance might be an important factor in the cause of chronic kidney disease.

Vitamin D, insulin resistance and renal function

Serum concentrations of 25(OH)D are the measure of the vitamin D body stores. The most well-known role of vitamin D is the regulation of calcium absorption and bone metabolism. It is becoming clear that this hormone has pleiotropic effects (Dusso *et al.* 2005) with possible roles in the pathogenesis of cancer, cardiovascular disease, multiple sclerosis (Holick, 2004), and type I diabetes (Holick, 2004). Recent epidemiological evidence (Boucher 1998, Chiu *et al.* 2004, Ford *et al.* 2005) also points to a potential association of vitamin D insufficiency with type 2 diabetes. Among these, vitamin D seems to be implicated in the development and progression of chronic renal disease and the risk of insulin resistance and diabetes (Chonchol and Scragg, 2007, Remuzzi 2007, Mehrotra *et al.* 2008) In this study we have demonstrated a high prevalence of vitamin D insufficiency/deficiency in patients with the mild and moderate CKD. Hypovitaminosis D significantly correlated with the renal function and insulin resistance evaluated by QUICKI index.

In conclusion, our results support the increasing evidence that vitamin D deficiency may affect also non-calcemic vitamin D functions, i.e. insulin resistance. More experimental and clinical data are required to elucidate pathophysiological mechanisms of non-calcemic vitamin D functions.

Conflict of Interest

There is no conflict of interest.

Acknowledgement

This work was supported by the Slovak Research and Development Agency under the contrat No. APVT-21-033002.

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Table 1. Patient renal diagnoses

Diagnosis	**n**	**%**
Tubulointerstitial nephritis	28	23.3
Hypertensive nephroangiosclerosis	6	5.0
Glomerulonephritis	7	5.8
Diabetic nephropathy	7	5,8
Atherosclerotic / ischemic nephropathy	13	10.8
Polycystic kidney disease	4	3.3
Other	10	8.3
Combination of ≥ 2 diagnoses[*]	30	25.0
Non-differentiated	15	12.5

[*] In 8/30 combined diagnoses, diabetic nephropathy was suggested.

Table 2. Characteristics in patients grouped by insulin sensitivity and diabetes mellitus according to insulin sensitivity

	Total (n=120)	**IS (n=47)**	**IR (n=50)**	**DM (n=23)**	**p values°**
Age (years)	**66** (58-72)	**66** (54-72)	**65** (59-72)	**68** (59-71)	NS
BMI (kg/m^2)	**27.1** (24.2-29.4)	**24.7** (22.6-26.6)	**28.7** (25.5-31.1)	**28.7** (27.7-31.8)	<0.001
Blood glucose (mmol/l)	**5.75** (5.37-6.54)	**5.37** (5.20-5.67)	**5.81** (5.46-6.29)	**7.86** (6.74-10.30)	<0.001
Insulin (IU/ml)	**7.81** (5.26-13.30)	**5.12** (3.85-6.11)	**12.50** (8.00-16.50)	**12.40** (9.61-20.34)	<0.001
*QUICKI**	**0.339**±0.038	**0.377**±0.023	**0.321**±0.023	**0.304**±0.027	<0.001
Serum creatinine (umol/l)	**109.5** (80.8-131.4)	**90.3** (75.6-118.4)	**116.1** (81.8-133.9)	**123.6** (99.8-140.4)	<0.01
GFR (ml/s)	**0.910** (0.725-1.145)	**1.050** (0.870-1.220)	**0.855** (0.705-1.113)	**0.850** (0.720-0.900)	<0.02
Proteinuria (g/24 h)	**0.110** (0.060-0.260)	**0.070** (0.040-0.150)	**0.110** (0.060-0.155)	**0.820** (0.260-2.000)	<0.001
25(OH)D (ng/ml)	**18.23** (12.39-27.16)	**25.20** (13.01-31.30)	**17.92** (12.56-25.67)	**15.90** (10.60-23.10)	NS
1,25(OH)$_2$D (pg/ml)	**30.47** (20.40-43.83)	**35.01** (22.03-44.50)	**31.27** (22.54-44.05)	**20.57** (15.04-29.22)	<0.008
iPTH (pg/ml)	**52.40** (40.11-72.64)	**47.56** (40.10-66.11)	**54.86** (42.21-72.80)	**52.20** (34.50-79.50)	NS
Blood pressure (mm Hg)					
systolic	**130** (120-140)	**125** (113-130)	**130** (120-140)	**142** (135-160)	<0.001
diastolic	**80** (78-85)	**80** (75-80)	**80** (80-86)	**84** (80-90)	<0.05

All values are medians and interquartile ranges unless otherwise indicated

* values are mean±SD; ° Kruskal Wallis test; NS – not significant

IS – insulin sensitivity; IR – insulin resistance; DM – diabetes mellitus type II

Table 3. Characteristics in patients grouped by renal function without diabetics

	CKD stage 2 (n=45)	**CKD stage 3 (n=52)**	**p values°**
Age (years)	**62** (54-69)	**69** (61-75)	<0.004
BMI (kg/m^2)	**24.9** (23.4-27.2)	**27.6** (24.4-30.4)	<0.005
Blood glucose (mmol/l)	**5.46** (5.27-5.83)	**5.71** (5.38-6.18)	<0.01
Insulin (IU/ml)	**6.20** (4.60-8.19)	**8.2** (5.8-13.9)	<0.005
*QUICKI**	**0.358**±0.037	**0.338**±0.032	<0.002
Serum creatinine (umol/l)	**77.7** (72.3-84.1)	**126.9** (112.7-141.7)	<0.001
GFR (ml/s)	**1.170** (1.075-1.260)	**0.760** (0.680-0.885)	<0.001
Proteinuria (g/24 h)	**0.080** (0.045-0.145)	**0.100** (0.060-0.160)	<0.04
25(OH)D (ng/ml)	**23.62** (14.41-31.70)	**16.47** (12.39-27.07)	<0.05
1,25(OH)$_2$ D (pg/ml)	**38.56** (28.72-48.26)	**28.32** (20.04-40.54)	<0.001
iPTH (pg/ml)	**47.56** (39.90-63.65)	**56.65** (41.37-75.40)	NS
Blood pressure (mm Hg)			
systolic	**127** (115-131)	**130** (120-140)	<0.05
diastolic	**80** (79-80)	**80** (76-85)	NS

All values are medians and interquartile ranges unless otherwise indicated;

* values are mean±SD; NS - not significant; ° Mann-Whitney test

CKD - chronic kidney disease

Table 4. Spearman correlations between serum 25(OH)D, QUICKI and other variables

	QUICKI		25(OH)D	
	r	**p values**	**r**	**p values**
25(OH)D (ng/ml)	0.200	<0.03	-	-
1,25(OH)$_2$D (pg/ml)	0.213	<0.02	0.246	<0.01
GFR (ml/s)	0.253	<0.005	0.201	<0.03
Protein exretion rate (g/24 h)	- 0.326	<0.001	- 0.07	NS
BMI (kg/m^2)	- 0.522	<0.001	- 0.120	NS
Systolic blood pressure (mm Hg)	- 0.440	<0.001	- 0.216	<0.03
Blood glucose (mmol/l)	- 0.621	<0.001	- 0.109	NS
Insulin (IU/ml)	- 0.953	<0.001	- 0.196	<0.03

r – correlation coefficient

NS - not significant

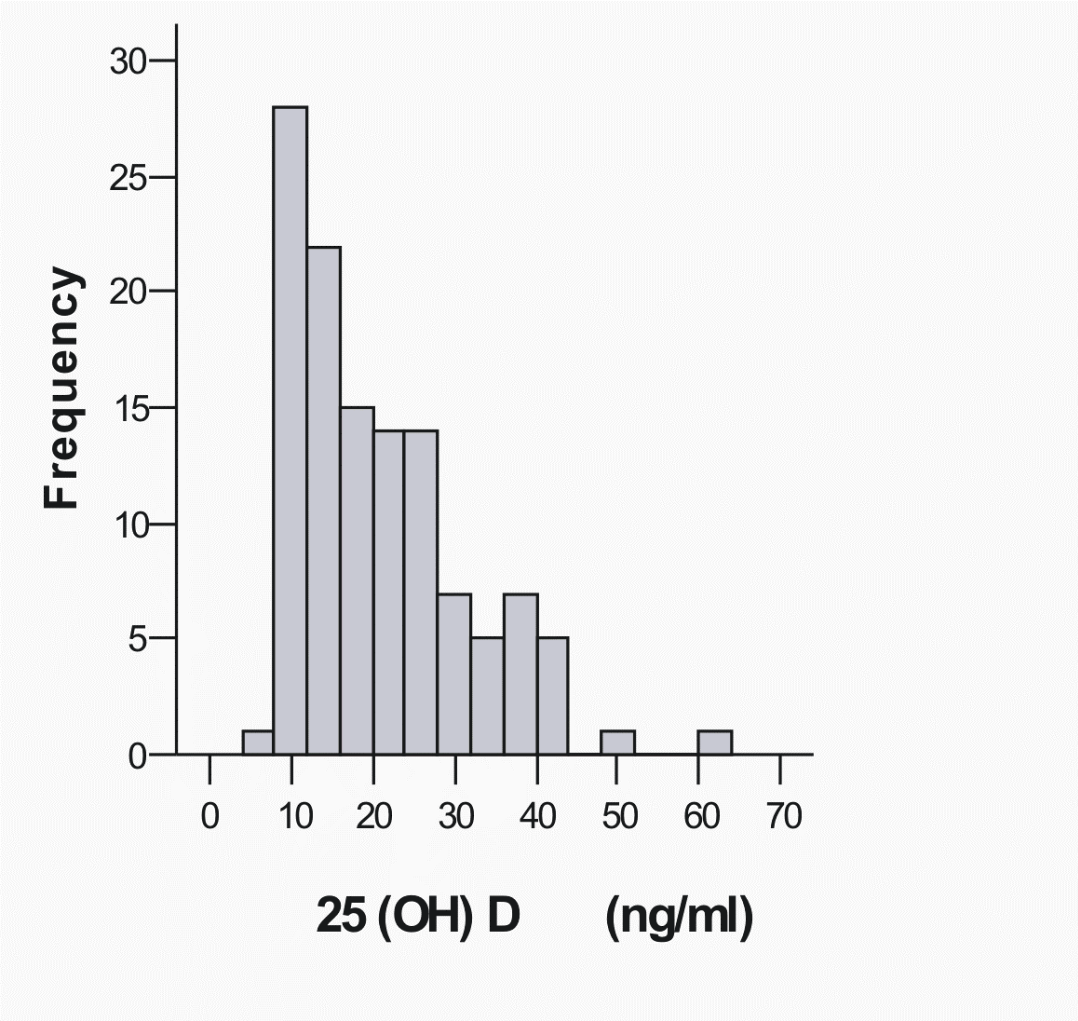

Fig. 1. Distribution of 25(OH)D serum concentration among study participants

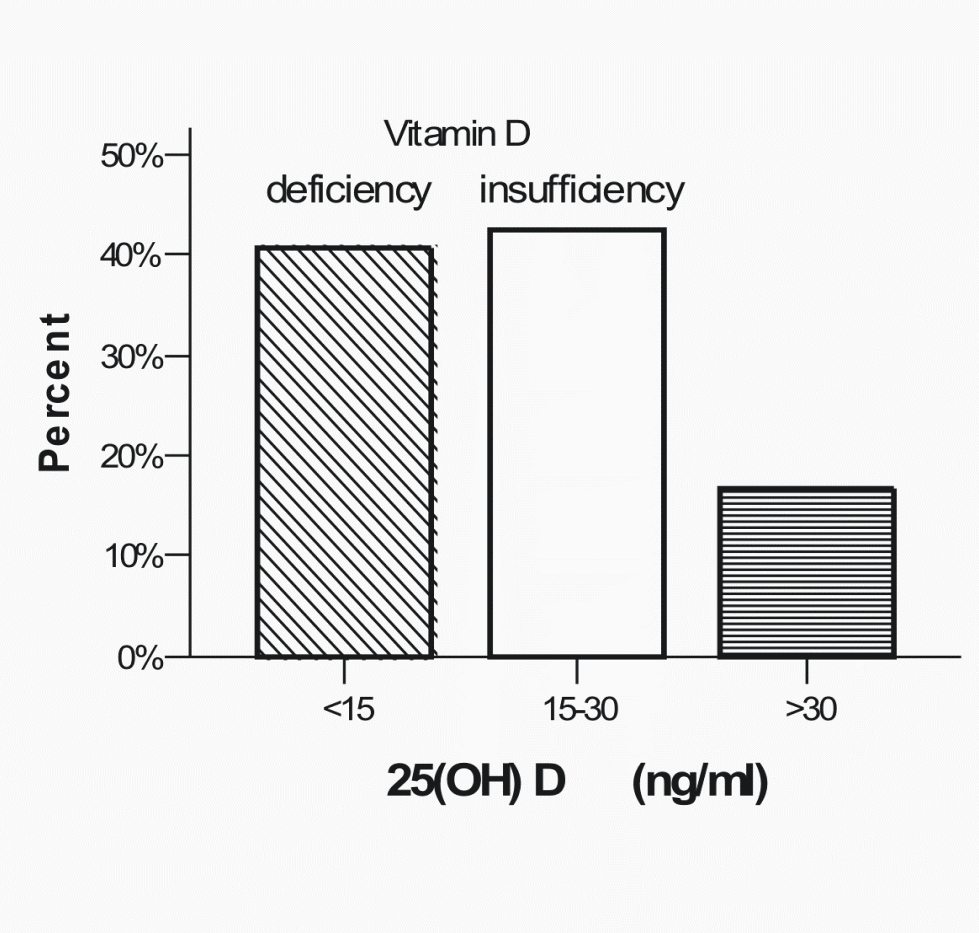

Fig. 2. Prevalence of vitamin D insufficiency/deficiency according K/DOQI guidelines