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Effect of paricalcitol on endothelial function and inflammation in type 2 diabetes and chronic kidney disease

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Abstract

Aims—Patients with type 2 diabetes (T2DM) and chronic kidney disease (CKD) have impaired endothelial function. Vitamin D and its analogs may play a role in regulation of endothelial function and inflammation. We studied effects of paricalcitol compared to placebo on endothelial function and markers of inflammation and oxidative stress in patients with T2DM and CKD.

Methods—A double blind, randomized, placebo-controlled trial was conducted in 60 patients with T2DM and stage 3 or 4 CKD. Paricalcitol 1 mcg or placebo was administered orally once daily for three months. Brachial artery flow mediated dilatation (FMD), nitroglycerine mediated dilation (NMD), and plasma concentrations of inflammatory cytokines, tumor necrosis factor –α and interleukin-6, highly-sensitive C-reactive protein; endothelial surface proteins, intercellular adhesion molecule –1 and monocyte chemo attractant protein-1, and plasma glucose, insulin, free fatty acids, and urinary isoprostane were measured at baseline and end of three months.

Results—27 patients in the paricalcitol group and 28 patients in the control group completed the study, though analysis of FMD at both time points was possible in 23 patients in each group. There was no significant difference in the change in FMD, NMD or the biomarkers examined after paricalcitol or placebo treatment.

Conclusions—Treatment with paricalcitol at this dose and duration did not affect brachial artery FMD or biomarkers of inflammation and oxidative stress. The lack of significance may be due to

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the fact that the study patients had advanced CKD and that effects of paricalcitol are not additive to the effects of glycemic, lipid and anti-hypertensive therapies.

Keywords

Diabetes mellitus; Chronic kidney disease; Paricalcitol; Endothelial dysfunction; Inflammation

1. Introduction

Type 2 diabetes (T2DM) is associated with an increased risk for cardiovascular disease. Traditional risk factors for cardiovascular disease such as age, gender, hypertension, dyslipidemia and smoking, do not fully explain this increased risk for patients with T2DM, and other factors including endothelial dysfunction, microalbuminuria and inflammation may be important (Fonseca, Desouza, Asnani, & Jialal, 2004). Cardiovascular disease is also the leading cause of death among patients with chronic kidney disease (CKD). The cardiovascular risk factors in patients with CKD patients include conventional factors and non-conventional factors, such as anemia, uremia, reduced vascular compliance, inflammation and various hormonal factors. Microalbuminuria/Proteinuria and renal insufficiency are also independent cardiovascular disease risk factors (Fonseca et al., 2004). We have previously demonstrated that these patients with T2DM and CKD have significantly impaired endothelial function (Jawa, Nachimuthu, Pendergrass, Asnani, & Fonseca, 2006).

Accumulating body of evidence suggests that vitamin D plays a role in cardiovascular disease (Achinger & Ayus, 2005; Chonchol, Cigolini, & Targher, 2008; Giovannucci, Liu, Hollis, & Rimm, 2008; Pittas et al., 2006; Wu-Wong et al., 2005) and regulation of vascular function and inflammation (McGreevy & Williams, 2011; Sanchez-Niño et al., 2012). Patients with chronic renal failure frequently develop secondary hyperparathyroidism, due to phosphate retention and low serum 1, 25(OH) 2D3. The combined increase in calcium and phosphate has been correlated with vascular calcification. There is a high prevalence of 25-hydroxyvitamin D deficiency in patients with T2DM and CKD (Chonchol et al., 2008).

Several vitamin D analogs have been developed that retain the direct suppressive action of calcitriol on the parathyroid glands but have less calcemic activity, thereby offering a safer and more effective means of controlling secondary hyperparathyroidism. One of these vitamin D analogs is paricalcitol [19-nor-1, 25(OH) 2D2] (Brown & Coyne, 2002). Recent clinical data show that these analogs provide survival benefit for CKD patients, independent of parathyroid hormone and calcium (Reinhart, 2004; Wu-Wong et al., 2005). In vitro data suggest that vitamin D and its analogs may play a role in endothelial function (Wu-Wong et al., 2005), but very little data are available from *in vivo* animal and human studies. Preliminary data suggest a reduction in risk factors for cardiovascular disease with paricalcitol compared to other vitamin D related compounds (Duplancic et al., 2013; Gonzalez-Parra et al., 2012; Ortiz, Sanchez Niño, Rojas, & Egido, 2011; Reinhart, 2004; Wu-Wong et al., 2005).

We therefore conducted a study of the effects of paricalcitol compared to placebo on endothelial function and markers of inflammation and oxidative stress in patients with

T2DM and stage 3–4 CKD. We hypothesized that administration of paricalcitol compared to placebo would improve endothelial function and suppress oxidative stress and inflammation in these patients.

2. Materials & methods

It was a double-masked, randomized, placebo-controlled multicenter trial of 60 patients with T2DM and stage 3 or 4 CKD having estimated glomerular filtration rate (eGFR) between 15 and 59 ml/min/1.73 m^2, calculated using the modification of diet in renal disease (MDRD) equation. Clinical assessment attributed CKD to either diabetic and hypertensive nephropathy but biopsy proven diagnosis was not required. The primary aim of the study was to demonstrate whether administration of paricalcitol (1 mcg/day) for 3 months would improve brachial artery flow mediated dilation (FMD) in patients with CKD. Secondary endpoints included the effect of paricalcitol on the plasma concentration of pro-inflammatory mediators including, interleukin 6 (IL-6) and highly sensitive C-reactive protein (hs-CRP) and urinary isoprostane. Endothelial surface proteins that are increased in association with inflammation such as monocyte chemoattactan protein –1 (MCP-1) and intercellular adhesion molecule 1 (ICAM-1) were also measured as secondary endpoints.

Each clinical site obtained local IRB approval. The trial was registered at clinicaltrials.gov (NCT01792206). All the participants were diagnosed with both T2DM and CKD, stage 3 or 4, aged 18–70 years, and were on stable anti-hypertensive and lipid lowering therapy for at least two months. Changes in statin therapy were not allowed during the trial except for safety reasons. Ongoing use of vitamin D analogs and vitamin D preparations was contraindicated. Other exclusion criteria were plasma calcium > 9 mg/dl, a known allergy to the study drug; pregnancy or lactation, or severe co morbid conditions—e.g. cancer; congestive heart failure.

Patients were randomized (1:1) to either paricalcitol 1 mcg or identical appearing placebo to be taken once daily with breakfast for 3 months. Paricalcitol has been used in the dose of 1 mcg daily in patients with DM and CKD in other studies as well. The randomization schedule was maintained by an unblinded member of study staff, but investigators providing participant care, and participants were masked to treatment assignment, as were those performing and interpreting findings. Calcium supplementation was discontinued prior to study entry. Addition of other treatments known to affect endothelial function such as estrogen, arginine, statins and ACE inhibitors were not permitted. However, patients who were on stable doses of these medications for at least 2 months prior to entry were allowed to participate, and no changes in dosage of these medications were made during the study period. Study visits occurred in a fasting state at baseline and 12 weeks after randomization. At these visits endothelial function studies were performed, and blood was drawn for markers of inflammation and oxidative stress. The last dose of paricalcitol was at 12 weeks, the day prior to these tests being done at the last visit. Samples were processed to separate serum and plasma and were stored at −80 ° C till further analyses. Twenty four hour urine was collected at the beginning and end of the study for microalbumin and isoprostane measurement. All samples were shipped on dry ice for the assays to be done.

2.1. Brachial flow-mediated dilatation (FMD)

A 7.5–10 MHz broadband multi-frequency linear array transducer was used to acquire images. Patients were positioned supine with the arm in a comfortable position for imaging the brachial artery. The brachial artery was imaged longitudinally just proximal to the ante-cubital fossa with the transducer position adjusted to obtain optimal images of the near and far wall of the intima. The 'R' wave on the electrocardiogram served as a trigger to acquire digitalized image frames at end-diastole. Vessel diameter was measured at a fixed distance from an anatomical marker, such as a bifurcation, by two observers unaware of treatment status. Vessel diameters in scans of reactive hyperemia, 15 min rest, and nitroglycerin were expressed as percentages of the first control scan. To create a flow stimulus, a blood pressure cuff was placed on the upper portion of the arm and inflated to supra-systolic pressure (at least 50 mm Hg above systolic pressure or 200 mm Hg whichever was greater) for 5 min. The resultant ischemia triggered dilatation of downstream resistance vessels via auto regulatory mechanisms. Following 5 min of occlusion, the cuff was deflated. The recording of the arterial image was done continuously from 30 s before to 2 min following cuff deflation (Corretti et al., 2002). Cuff deflation resulted in reactive hyperemia (a brief high-flow state) in the brachial artery to accommodate the dilated resistance vessels. The shear stress that resulted caused dilatation of the brachial artery. The velocity time integral was assessed by pulse Doppler within 15 s of cuff release to assess peak hyperemic blood flow velocity. FMD of the brachial artery was determined with images acquired 1 min after cuff deflation. All sites underwent central training and certification procedures to establish uniform methodology.

Ten minutes after cuff release, the brachial artery was re-imaged to ensure a return to basal conditions. Then, to determine nitroglycer-in-mediated endothelium-independent vasodilation (NMD), subjects received 0.4 mg of nitroglycerin, sublingually. The brachial artery was imaged 3 min later. Nitroglycerin was not administered if the systolic blood pressure was below 100 mm Hg. The brachial artery images were reviewed independently by one of the investigators (MB), who was blinded to the treatment allocation. Only subjects whose image quality at every measurement was considered adequate are reported in the results. In order to further minimize bias, we analyzed the results when the other FMD calculations were included, and it did not change the results or conclusions.

2.2. Plasma concentrations of inflammatory cytokines

Plasma concentrations of intercellular adhesion molecule –1 (ICAM-1), monocyte chemo attractant protein-1 (MCP-1), tumor necrosis factor –α (TNF-α) and interleukin-6 (IL-6) were measured using sensitive and high sensitive ELISA kits (R&D Systems, MN). Highly sensitive C-reactive protein (hs-CRP) concentrations were measured using an ELISA kit from Alpha Diagnostics International Inc. (San Antonio, TX) at a central laboratory.

2.3. Urinary isoprostane measurement

Urinary isoprostane was measured from 24 h urine samples and were analyzed using an EIA kit from Oxford Biomedical Research (Oxford, MI) at a central laboratory. Urine was collected at room temperature with 0.02% thimerosal and 0.005% butylated hydroxytoluene

as preservatives to prevent oxidation, aliquotted, and stored immediately at −80° Celsius till further analyses.

2.4. Plasma glucose, insulin and free fatty acids (FFA) measurements

Insulin levels were determined using an ELISA kit from EMD Millipore. (Billerica, MA). Glucose levels are measured in plasma by YSI 2300 STAT Plus glucose analyzer (Yellow Springs, OH). FFA concentrations were measured by HR series reagents (Wako Chemicals Inc., Richmond, VA) at a central laboratory.

3. Statistical analysis

The primary outcome was the percent change of reactive hyperemia from baseline to the follow up in 12 weeks. Medians and ranges were used to describe continuous variables, and percentages were used for categorical variables. Transformations of variables were used to ensure that normality assumptions are satisfied. If necessary, a non-parametric test such as Mann–Whitney's test was used. A chi-square test was used to compare categorical variables between paracalcitol group and the placebo group. Where the sample size was small, a Fisher's exact text was performed. Additionally, tests for statistically significant changes within groups were conducted, such as McNemar's test for categorical data and paired t-test for continuous data. Statistical significance was set at $P < 0.05$.

4. Results

Baseline characteristics of study participants by treatment group are listed in Table 1. We randomized 30 patients to paricalcitol and 30 to placebo. Twenty-seven patients in the paricalcitol group and 28 patients on placebo completed the study, though paired analysis of FMD at both time points was only possible in 23 patients in each group. Thus, the data in Table 1 are of those 23 patients that had completed the study and had adequate FMD results. There was no significant difference in the baseline serum iPTH level (median, 62.0; 13.0–144.0 pg/ml in the paricalcitol arm vs. 69.0, 18.0–231.0 pg/ml in the placebo arm, $P = 0.33$). Similarly, there was no significant difference in the baseline serum 1, 25-OH vitamin D level (median, 45.0; 27.0–91.0 pg/ml in the paricalcitol arm vs. 35.0; 9.0–88.0 pg/ml in the placebo arm) between the two groups. Five patients did not complete the study. There were nine patients for whom the quality of the images during the FMD procedure did not meet the standards, and therefore those results could not be used in analysis. This was due to inter-operator differences as the technician had changed. There were no differences at baseline between the patients who completed the study and those that did not complete the study. At baseline, the FMD was 3.9 ± 5.3% in the paricalcitol and 3.9 ± 8.9% in the placebo arm. There was no significant difference in the change in FMD after 12 weeks in either arm. The NMD was 8.4 ± 7.1% in the paricalcitol group and 11.5 ± 9.2% in the placebo group and did not change at the end of the study. Similarly, there were no significant differences between the two groups for all the biomarkers examined. There was no significant reduction in microalbuminuria either with paricalcitol. Results are summarized in Table 2.

Additionally, at the end of 12 weeks, there was no significant change in body weight, systolic or the diastolic blood pressure. One patient experienced chest pressure, and another

patient had atypical chest pain. One other patient had a heart rate less than 45. None of these events were deemed related to the study drug, and there were no other adverse events reported by the patients during the study.

5. Discussion

Our study results show that paricalcitol does not affect endothelial function measured by brachial artery flow mediated dilatation or plasma biomarkers of inflammation and oxidative stress in patients with type 2 diabetes and established chronic kidney disease with eGFR between 15 and 59 ml/min/1.73 m^2. In our study, the FMD at baseline was 3.9% in both groups which was lower than the baseline of 10.1% in a previous study in patients with diabetes without nephropathy (Pradhan, Manson, Rifai, Buring, & Ridker, 2001). After 12 weeks of treatment with paricalcitol, there was no significant decrease in urinary isoprostane, FFA, insulin levels, MCP-1, TNFa, IL-6, ICAM-1, MCP-1, and hs-CRP. Notably, endothelial function and hs-CRP were abnormal at baseline in this high risk population compared with healthy controls and patients with diabetes but without CKD. The baseline levels of plasma FFA, insulin, TNFα and IL-6 of the study subjects were higher than those in healthy controls but similar to those in subjects with diabetes without CKD (Pradhan et al., 2001). Given the variation in the urine microalbumin creatinine ratio among the patients, in an exploratory analyses we compared urinary isoprostane, IL_6 and TNFα levels at baseline and at week 12 in patients that had urine microalbumin creatinine ratio > 30 μg/mg in both the groups. For urinary isoprostane, there was no significant difference before and after the study in the paricalcitol arm (median 2.82; 0.6–4.46 ng/ml at baseline vs. 2.34; 0.65–4.42 ng/ml at week 12, P = 0.77) or the placebo arm (median 2.30; 0.32–5.22 ng/ml at baseline vs. 1.92; 0.65–4.59 ng/ml at week 12).

There is an accumulating body of evidence that suggests that vitamin D plays a role in cardiovascular disease (Achinger & Ayus, 2005; Giovannucci et al., 2008; Pittas et al., 2006; Wu-Wong et al., 2005). Deficiency of the active form of vitamin D, 1,25-dihydroxyvitamin D (Giovannucci et al., 2008), and acquired vitamin D resistance through the uremic state, have both been shown to be important in CKD. Patients with CKD have a much higher risk for cardiovascular disease as compared to those without CKD. Vitamin D deficiency impacts cardiovascular risk through multiple potential mechanisms that include previously underappreciated non-mineral homeostatic effects of vitamin D. Several vitamin D analogs are currently available for the treatment of secondary hyperparathyroidism.

Paricalcitol has been demonstrated to suppress inflammation (Duplancic et al., 2013; Navarro-González et al., 2013) as well. In an open-label, prospective pilot trial, Navarro-González et al. (2013) studied the effect of oral paricalcitol for 12 weeks in 25 patients on hemodialysis. There was a significant mean percent decrease in hs-CRP, TNF-α, and IL-6, (14.3%, 4.7%, and 5%, respectively). Notably, these patients had been on intravenous calcitriol prior to undergoing washout for 3 weeks upon entering the study. While only 36% of the subjects in this study had DM, all the patients in our study had DM which itself may be contributing factor for insignificant increase in the inflammatory markers. The role of vitamin D on endothelial function has also been explored and tested in several trials. Sokol et al. conducted a study assessing the effect of weekly 50,000 international units (IU) of

ergocalciferol versus placebo on endothelial function using tonometry in patients with coronary artery disease in those that had a 25-OH vitamin D level of < 20 ng/ml. At the end of 12 weeks, there was no significant difference in the reactive hyperemia peripheral arterial tonometry score or in the amount of reduction of hs-CRP and IL-6. Less than half the patients in this study had DM, and those with eGFR < 20 ml/min were excluded (Sokol et al., 2012). Contrary to this are the results of the study by Chitalia et al. (2014) which assessed the effected of oral ergocalcalciferol on brachial artery FMD in CKD stage 3 and 4 patients who did not have DM. Ergocalciferol 300,000 IU were given at baseline and at eight weeks. At eight weeks, FMD improved from 3.1 ± 3.3% to 6.1 ± 3.7%, P = 0.001.

Paricalcitol and ENdothelial function in chronic kidneY (PENNY) disease trial (Zoccali et al., 2014) is a double-blinded randomized controlled trial that tested the effect of paricalcitol on endothelium-dependent and endothelium-independent vasodilation in 88 patients with stage 3 or 4 CKD and PTH >65 pg/ml. After 12 weeks of treatment, FMD increased in the paricalcitol group but not in the placebo group. The significant between-group difference in FMD changes was 1.8%, with 95% CI, 0.3–3.1%, P = 0.016. The mean proportional change in FMD was 61% higher in paricalcitol group. The dose of paricalcitol used in this study was 2 μg/day, and not all the patients in the study had DM.

Other investigators have also studied the role of paricalcitol on urinary albumin excretion with varying results. A recent study by Joergensen, Tarnow, Goetze, & Rossing (2014) showed a significant reduction in urinary albumin excretion rate in the paricalcitol group as compared to placebo in a cross over study of 12 weeks. Patients in this study had type 1 DM and CKD with the mean eGFR of 47 ± 15 ml/min/1.73 m^2. There were total of 48 participants in this study with 24 subjects in each group. Our study patients had type 2 DM and CKD stage 3 or 4. We did not see a significant decline in the microalbumin in the paricalcitol group in our study.

6. Limitations

Our study did not demonstrate a significant difference in endothelial between the two groups at the end of 12 weeks which was the primary endpoint. Using our own data we would need a sample size of 332 per group to achieve 80% power to detect a mean difference of −1.1 with standard deviations of 5.2 for paricalcitol group and 4.9 for control group, and with a significance level (alpha) of 5% using a two-sample t-test. Thus, even if there was a benefit from such treatment a very large number of patients would be needed to be treated in order to see any benefit in this endpoint. There were no significant reductions in the urinary microalbumin or the inflammatory markers and markers of oxidative stress. The study was however not powered to detect significant changes in the secondary outcomes. The lack of statistical significance may also be due to the fact the subjects were in the late stage of disease. Nevertheless, there are other reports of microalbuminuria reduction with this drug in patients with less severe kidney disease (Ortiz et al., 2011). Another limitation of the study is that it is not known if the dose of paricalcitol used was sufficient. 1 mcg is the lowest dose of paricalcitol though it has been used in prior studies in patients with CKD. Patients in our study were on paricalcitol only for 12 weeks which may not be long enough

to demonstrate the anti-inflammatory effects of paricalcitol especially in patients with both DM and CKD.

Additionally, participants in this study were well managed in terms of glycemic, lipid and blood pressure control. It is possible that effects of paracalcitrol are not additive to the effects of glycemic, lipid and anti-hypertensive therapies. Studies in patients similar to ours have not been shown to benefit from lipid lowering with statins in cardiovascular outcome trials (Slinin et al., 2012); thus our patients may have been too far advanced in disease to demonstrate improvements.

To summarize, in patients with advanced diabetic nephropathy, markers of endothelial function and inflammation remained markedly abnormal, and were not improved by treatment with the vitamin D analog paricalcitol. Other modalities of treatment that target these cardiovascular risk factors and pathways need to be developed in order to attempt to reduce cardiovascular risk in these patients.

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Table 1

Baseline characteristics of the two groups.

	Paricalcitol	Placebo	P value
N (female/male)*	10/18	8/19	0.63
Age (years)	64, 53.0–71.0	61.0, 51.0–71.0	0.11
Weight (in pounds)	241.1, 136.4–345.2	225.6, 141.8–321.2	0.39
Systolic blood pressure (mm/Hg)	133.5, 98.0–182.0	138.0, 98.0–167.0	0.86
Diastolic blood pressure (mm/Hg)	71.5, 57.0–103.0	76.0, 48.0–103.0	0.72
Blood urea nitrogen (mg/dL)	26.0, 15.0–68.0	27.0, 12.0–52.0	0.43
Serum creatinine (mg/dL)	1.6, 1.0–3.0	1.6, 1.0–2.4	0.83
Estimated glomerular filtration rate (eGFR)	43.0, 19.0–56.0	48.0, 25.0–57.0	0.35
Urine microalbumin creatinine ratio (μg/mg)*	28.0, 3.0–1723.0	78.0, 4.0–184.0	0.23
Fasting plasma glucose (mg/dL)	130.0, 76.0–243.0	119.0, 60.0–268.0	0.73
Hemoglobin A1c (%)	7.4, 5.9–9.4	7.3, 5.8–10.6	0.74
Intact PTH (pg/ml)	62.0, 13.0–144.0	69.0, 18.0–231.0	0.33
1,25-OH vitamin D (pg/ml)	45.0, 27.0–91.0	24.0, 9.0–44.0	0.22
Patients on Ace Inh/ARB*	19 (68)	19 (70)	0.99
Patients on statin*	18 (64)	20 (74)	0.62

Data are median with range unless otherwise stated.

*Data are n and percentages.

Table 2

Results of the various variables in each group.

Variable	Week	Paricalcitol (N = 23)	P value	Placebo (N = 23)	P value
Hemoglobin A1c (%)	0	7.4, 5.2–9.4	0.28	7.3, 5.8–10.6	0.36
	12	7.2, 5.9–11.1		7.5, 5.7–10.2	
F M dilation (%)	0	3.4, −10.1–17.9	0.73	2.4, −30.1–21.3	0.85
	12	3.3, −7.5–14.4		3.6, −3.4–17.1	
N G dilation (%)	0	7.8, 0.9–30.3	0.18	9.7, −1.7–33.3	0.36
	12	4.2, 0.3–24.3		9.8, −2.5–30.0	
Microalbumin/Cr (μg/mg)	0	41.0, 1.9–1806	0.35	83.3, 1.3–7713.9	0.60
	12	69.1, 1.7–8405		56.1, 1.7–8332.0	
Urinary Isoprostane/Cr (ng/ml)	0	2.5, 0.7–6.3	0.17	1.8, 0.3–5.0	0.70
	12	2.0, 0.8–5.2		2.3, 0.4–5.5	
FFA (mM)	0	0.6, 0.1–1.5	0.03	0.4, 0.1–0.9	0.73
	12	0.4, 0.1–1.4		0.4, 0.1–1.0	
Insulin (mU/ml)	0	9.9,1.6–60.2	0.56	6.1, 0.5–38.5	0.28
	12	8.8, 0.5–53.9		5.4, 0.3–21.9	
MCP–1 (pg/m)l	0	246.8, 75.6–674.9	0.46	275.9, 120.4–781.4	0.93
	12	268.0, 83.1–585.0		300.9, 120.4–637.6	
TNF-α (pg/ml)	0	2.5, 1.5–3.6	0.58	2.5, 1.6–4.5	0.13
	12	2.6, 1.6–3.9		2.6, 1.1–4.2	
IL-6 (pg/ml)	0	2.8, 0.8–25.4	0.11	2.5, 1.1–26.0	0.27
	12	2.5, 0.4–24.0		2.7, 1.2–25.0	
ICAM-1 (ng/ml)	0	242.8, 72.8–521.2	0.34	179.8, 64.9–612.8	0.34
	12	225.4, 78.2–387.8		182.0, 69.2–366.9	
CRP (mg/ml)	0	7.4, 0.2–13.2	0.32	4.3, 0.2–13.1	0.02
	12	5.8, 0.3–12.9		6.9, 0.8–13.0	

Data are median with range.