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META-ANALYSIS

Vitamin D receptor activation by paricalcitol and insulin resistance in CKD

B. Spoto [a], P. Pizzini [a], S. Cutrupi [a], G. Tripepi [a], G. Curatola [a], F. Mallamaci [a,b], C. Zoccali [a,*]

[a] CNR-IFC, Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension, Reggio Calabria, Italy
[b] Nephrology Dialysis and Renal Transplantation Unit, Reggio Calabria, Italy

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KEYWORDS
Chronic kidney disease;
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Insulin sensitivity

Abstracts *Background and aims:* The nature of the link (causal vs non-causal) between low 1,25-OH vitamin D and insulin resistance (IR) in patients with chronic kidney disease (CKD) remains elusive. We have now made a post hoc analysis of the effect of vitamin D receptor activation by paricalcitol on IR in the complete dataset of a double-blind, randomized, placebo controlled trial, the Paricalcitol and ENdothelial fuNction in chronic kidneY disease (PENNY).
Methods and results: Eighty-eight patients with stage 3–4 CKD were randomized (1:1) to receive 2 μg/day paricalcitol or matching placebo for 12 weeks. IR was measured by five IR indices: the homeostasis model assessment of insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI), the McAuley index, the HOMA corrected for adiponectin (HOMA-AD) and the Leptin-adiponectin ratio (LAR).

As compared to placebo, paricalcitol produced the expected small rise in serum calcium (+0.07 mmol/L, P = 0.01) and phosphate (+0.08 mmol/L, P = 0.034) and the expected parathyroid hormone suppression (−96 pg/ml, P < 0.001). However, the drug largely failed to affect the five indices of IR which remained unchanged both in the active and the placebo arm (paricalcitol vs placebo, P ranging from 0.25 to 0.62) and no effect modification of paricalcitol on IR by vitamin D or other parameters was registered.
Conclusion: Paricalcitol treatment for 12 weeks does not improve IR in patients with stage 3–4 CKD. Low vitamin D receptor activation is not a causal factor for IR in the CKD population.

Introduction

The biologically active form of vitamin D, 1,25-dihydroxyvitamin D (1,25-OH VD), is a pleiotropic hormone modulating a wide range of biological processes including glucose metabolism [1]. Stimulation of vitamin D receptor (VDR) has a beneficial effect on insulin sensitivity (IS) [2], since it induces insulin release from pancreatic β cells through modulation of intracellular free calcium [3] and increases the expression of the insulin receptor thus enhancing glucose transport [4]. Accordingly, large community-based studies, reported an association between the deficiency/insufficiency of the vitamin parent to 1,25-OH VD, i.e. 25 hydroxy vitamin D (25-OH VD), and insulin resistance (IR) [5].

* Corresponding author. CNR-IFC, Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension, Ospedali Riuniti, c/o EUROLINE Via Vallone Petrara 55-57, 89100, Reggio Calabria, Italy. Fax: +0039 0965 26879.
E-mail address: carmine.zoccali@tin.it (C. Zoccali).

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Deficiency of 1,25-OH VD is a hallmark of chronic kidney disease (CKD) and occurs early in the course of this condition. Similarly, IR may start when the glomerular filtration rate (GFR) is still within the normal range [6] to become almost universal in chronic kidney failure [7]. IR has been implicated in progression to kidney failure [8] and in cardiovascular (CV) disease in stage G3-4 CKD patients [9] and in stage G5D CKD patients maintained on hemodialysis [10] or peritoneal dialysis [11]. Serum levels of 1,25-OH VD are inversely related to indices of IR like the homeostatic model assessment of insulin resistance (HOMA-IR) and fasting insulin across all CKD stages including stage G5D [12 13 14]. However, the relevance of vitamin D on glucose metabolism in CKD remains uncertain because results of clinical trials performed so far are conflicting [15–17].

With this background in mind, we have taken the opportunity of a recent double-blind, randomized, controlled clinical trial, the Paricalcitol and ENdothelial fuNction in chronic kidneY disease (PENNY) study (clinicaltrials.gov identifier: NCT01680198) [18], to perform a post hoc analysis aimed at testing the effect of VDR activation by paricalcitol in patients with stage G3 to 4 CKD. In the present study, IR was estimated by 5 indices whose validity was specifically assessed in CKD patients in comparison to a golden standard test like the euglycemic hyperinsulinemic clamp technique [19].

Methods

The study protocol was approved by the ethics committee of our Institution and a written informed consent was obtained from each participant.

Patients

The protocol of the PENNY trial and the CONSORT flow diagram of this trial are reported into detail in the source study [18]. Briefly, PENNY is a double-blind, randomized, parallel group trial (ClinicalTrials.gov identifier, NCT01680198) enrolling 88 patients with CKD stage 3–4, age ranging between 18 and 80 years, parathyroid hormone $\geq$ 65 pg/ml, serum total Ca between 2.2 and 2.5 mmol/L and phosphate levels between 1.0 nmol/L and 1.5 nmol/L, not in treatment with vitamin D compounds or anti-epileptic drugs, without neoplasia or symptomatic CV disease or liver disease. Patients who met the inclusion criteria were randomized (1:1) to receive 2 μg paricalcitol once daily or matching placebo for 12 weeks after a 2-week run-in. The dose of paricalcitol was adjusted on the basis of serum parathyroid hormone and calcium and the maximum dose allowed was 2 μg daily. No vitamin D compounds were allowed during the trial. Demographic, clinical and biochemical characteristics of the study population distributed in the two study arms are listed in Table 1. CKD etiology in the two study arms is reported in Supplementary Table 1.

Laboratory measurements and IR indices

Serum calcium, phosphate, glucose, lipids were measured in the routine clinical pathology laboratory at our Institution. Serum parathyroid hormone (DiaSorin Stillwater, MN, USA), 25-OH VD and 1,25-OH VD (Immunodiagnostic Systems, Boldon, UK) were measured by immunoradiometric assay kits. Serum intact FGF23 was measured by ELISA kit (Kainos Laboratories, Bunkyo, Tokyo, Japan). Serum creatinine was measured by the Roche enzymatic, IDMS calibrated method and serum cystatin C by the Siemens Dade Behring kit which is traceable to the International Federation of Clinical Chemistry Working Group for Standardization of Serum Cystatin C and the GFR was calculated by the CKD-Epi creatinine-cystatin formula [20]. Insulin (MP Biomedicals, Ohio, USA), adiponectin and leptin (Linco Research, USA) were measured by immunoradiometric assay kits. IR was estimated by 5 indices that have been previously tested in comparison with the euglicemic hyperinsulinemic clamp technique in CKD [19] and calculated according to the following formulas: homeostasis model assessment of insulin resistance, HOMA-IR = [insulin (μU/mL) × glucose (mg/dL)]/405; quantitative insulin sensitivity check index, QUICKI = 1/[log(-glucose (mg/dl) + insulin (μU/mL)]; McAuley index = exp [2.63−0.28 ln insulin (μU/mL) − 0.31 ln triglycerides (mmol/mL)]; homeostasis model assessment corrected by adiponectin, HOMA-AD = [insulin (μU/mL) × glucose (mg/dL)]/[405 × adiponectin (μg/mL)] and leptin-adiponectin ratio, LAR = leptin (ng/mL)/adiponectin (μg/mL). In the validation study mentioned above [19], these indices showed a fair to moderate agreement with the glucose disposal rate measured by the euglicemic hyperinsulinemic clamp technique and good to excellent reproducibility. The reference values for IR indices in the healthy general population are: HOMA-IR$\geq$2.6 [19], QUICKI$\leq$0.33 [19], McAuley index$\leq$5.8 [19], HOMA-AD$>$0.95 [21] and Leptin to Adiponectin Ratio (LAR) $>$ 0.59 in men and $>$1.04 in women [22]. Plasma samples for these measurements were available in all patients who participated into the PENNY study and there were no missing values for any of the five IR indices considered in this study.

Statistical analysis

Data are reported as mean ± standard deviation (normally distributed data), median and inter-quartile range (non-normally distributed data) or as percent frequency, and comparison between groups were made by independent *t*-Test, Mann–Whitney Test, or Chi Square test. Correlates of IR indices and of paricalcitol-induced changes in IR indices were analyzed by using the Pearson's correlation coefficient (on $\log_{10}$ transformed data, when appropriate). Within- and between-group differences in changes over time of mineral and IR biomarkers as well as in glucose and insulin levels were expressed as mean difference and 95% CI. Along with the analytical approach adopted in the source study [18], between-group comparisons were made

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