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A low plasma 1,25(OH)$_2$ vitamin D/PTH (1–84) ratio predicts worsening of renal function in patients with chronic heart failure

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ABSTRACT

Background: Dysregulation of the vitamin D system promotes renal dysfunction and has direct detrimental effects on the heart. Progressive deterioration of renal function is common in patients with chronic heart failure (HF) and is invariably associated with unfavorable outcomes which can be improved by early identification and timely interventions. We examined the relation between two plasma markers of vitamin D metabolism and worsening of renal function (WRF) in a large cohort of patients with chronic HF.

Methods: Plasma levels of 1,25-dihydroxyvitamin D (1,25(OH)$_2$D) and parathyroid hormone PTH (1–84) were measured in 1237 patients with clinical evidence of chronic and stable HF enrolled in the multicentre GISSI-HF trial and followed for 3.9 years. We examined the relation of 1,25(OH)$_2$D, PTH(1–84), and their ratio with WRF, defined as first increase in serum creatinine concentration ≥0.3 mg/dL and ≥25% at two consecutive measurements at any time during the study.

Results: Lower 1,25(OH)$_2$D/PTH(1–84) ratio was associated with a higher baseline serum concentration of creatinine, winter season, female sex and older age; 335 patients (29.6%) experienced an episode of WRF. After adjustment, a lower 1,25(OH)$_2$D/PTH(1–84) ratio remained significantly associated with a higher risk of WRF (HR = 0.75 [0.62–0.90], p = 0.002) and correctly reclassified events. This ratio also independently predicted mortality and admission to hospital for cardiovascular reasons.

Conclusions: The plasma 1,25(OH)$_2$D/PTH(1–84) ratio is a promising indicator of future risk of deterioration of renal function in patients with chronic HF and mild renal impairment, that may serve to optimize therapies and improve outcomes.

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1. Introduction

Some degree of renal impairment is common in patients with chronic heart failure (HF) and is associated with unfavorable outcomes [1]. The cross-talk between the diseased heart and kidney is a growing burden for health care systems as the incidences of HF and chronic kidney disease (CKD) have been steadily rising and will grow further due to the aging of the general population and better treatment of acute cardiac and renal diseases [2]. It has also been realized that the progressive development of worsening renal function (WRF) over time carries an increased risk of death and hospitalization [3].

Early identification of patients with chronic HF at risk of developing WRF may be useful to optimize therapies (*i.e.* RAAS inhibitors *vs.* beta-blockers, intensification of diuretics) [4,5], and thus to improve outcomes. In the absence of a consensus definition of WRF [3,6], new circulating biomarkers may provide a simple and objective means to predict deterioration in renal function in patients with chronic HF earlier than serum creatinine.

Disturbances of the mineral metabolism, particularly of the parathyroid hormone (PTH)/vitamin D axis, are characteristic of loss of renal function [7]. Vitamin D-deficiency may promote or accelerate the progression of CKD [8]. Cross-sectional studies have shown higher circulating levels of PTH and lower levels of vitamin D metabolites with worse CKD stages (lower estimated glomerular filtration rate, eGFR) [9]. To our knowledge, however there are few reports on whether circulating markers of the bone mineral metabolism can predict deterioration of renal function over time. We therefore examined the relation between

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two markers of the vitamin D/PTH axis and WRF in a large cohort of patients with chronic HF. Since there is evidence of a role of vitamin D and PTH in cardiac remodeling and worsening HF [10,11], and to predict cardiovascular events in patients with chronic HF [12], we also assessed their relation with mortality and cardiovascular hospitalization.

2. Patients and methods

The GISSI-HF trial was a randomized, double-blind, placebo-controlled, multicenter study that enrolled 6975 patients with clinical evidence of chronic and stable HF (NYHA II-IV), irrespective of the cause and the left ventricular ejection fraction (LVEF). Protocols and results of the main trial have been published in detail [13–15]. In a subset of 1237 patients recruited in 50 clinical centers in Italy and one in Switzerland, venous blood samples were drawn on EDTA at randomization and after three months of follow-up. Patients rested supine for at least 15 min before blood sampling. Blood was centrifuged at 4 °C within 10 min and plasma was shipped on dry ice to a central laboratory. Samples were stored at −70 °C until assayed. The study was approved by local ethics committees, and informed consent was obtained from all patients before the study started.

2.1. Biomarker measurements

The plasma concentrations of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) and PTH(1–84) were assayed in a central laboratory in a blinded fashion and in a single batch. $1,25(OH)_2D$ was determined with a new, fully automated, sensitive immunoassay that uses a recombinant fusion construct of the vitamin D receptor ligand binding domain for specific capture of $1,25(OH)_2D$ (DiaSorin, Saluggia, Italy) [16]. The limit of quantitation for this $1,25(OH)_2D$ assay is 5 pg/mL and the reference interval in healthy volunteers ranged between 25.0 and 86.5 pg/mL with a median of 48.1 pg/mL. PTH(1–84) was measured with a chemiluminescent immunoassay (CLIA, LIAISON®, DiaSorin, [17]) with an observed range of normality 5.7–45.4 ng/L.

2.2. Renal function, definition of worsening renal function

Serum creatinine was measured in local laboratories as part of national quality control surveillance, at randomization and during follow-up after 1, 3, 6, 12, 24, 36, 48 and 60 months. Glomerular filtration rate (eGFR, mL/min/1.73m^2) was calculated using the simplified modification of diet in renal disease (MDRD) formula. WRF was defined as the first increase in serum creatinine ≥0.3 mg/dL and ≥25% at two consecutive measurements at any time during the study [3].

2.3. Outcomes

The primary analysis of this study was the ability of the $1,25(OH)_2D$/PTH ratio to predict the first occurrence of WRF. Secondary outcomes included time to death for any cause or worsening of HF, hospitalization for cardiovascular reasons or for worsening of HF; these were adjudicated blindly by an *ad-hoc* committee on the basis of pre-agreed definitions and procedures [13].

2.4. Statistical methods

Continuous variables were expressed as mean ± SD if normally distributed or median [Q1–Q3], as appropriate; categorical variables were reported as absolute numbers and percentages. The non-parametric Kruskal-Wallis test was used to establish the association between season of blood collection, NYHA and KDOQI classes at baseline and $1,25(OH)_2D$, PTH(1–84) levels and their ratio.

Linear multilevel analysis was used to assess the association of patients' baseline characteristics with decreasing baseline $1,25(OH)_2D$/PTH(1–84) ratios transformed on a natural logarithmic scale. The model considered variables regarding patients' characteristics as fixed effects and clinical centers as random effects.

Classification and regression trees (CART), a model-free approach used to find the best splitting criterion, was adopted to identify the best cut-off for the $1,25(OH)_2D$/PTH(1–84) ratio and mortality. This method, a form of recursive partitioning, developed on nine tenths of the data can validate the best on the remaining tenth. A Cox proportional hazards model was built to assess the independent prognostic value of the $1,25(OH)_2D$/PTH(1–84) ratio on the occurrence of WRF, adjusting for the covariates that were significant in the univariate analysis ($p < 0.05$). Similarly, multivariable Cox models were adopted for the secondary outcomes.

For all the categorical variables, the proportionality of risk required by the Cox model was assessed using Schoenfeld residuals. The ratio was initially fitted as a single continuous measurement. Because clear evidence of non-linearity of the risk was detected by the restricted cubic splines technique (RCS) [18], it was transformed into the natural logarithm, thus satisfying the linearity assumption required by the Cox model.

To establish the incremental prognostic value of the $1,25(OH)_2D$/PTH(1–84) ratio on the occurrence of WRF, on top of the conventional risk factors that emerged as significant in the multivariable Cox model, we calculated the category-free Net Reclassification Index (cfNRI) for survival outcomes (http://ncook.bwh.harvard.edu/sas-macros.html).

A two-sided p value of <0.05 was considered significant. Statistical analyses were done with SAS software, version 9.3 (SAS Institute, Inc., Cary, NC) and with the R program and the rms package (http://CRAN.R-project.org/package=rms).

3. Results

3.1. Variables associated with the $1,25(OH)_2D$/PTH(1–84) ratio

In the overall population of 1130 patients, the baseline concentration of $1,25(OH)_2D$ was 31.3 [23.0–42.2] pg/mL (median [Q1–Q3]), and 33.8 [24.3–49.3] pg/mL for PTH(1–84), corresponding to a ratio of 0.89 [0.55–1.45]. Baseline concentrations of $1,25(OH)_2D$ and PTH(1–84), but not serum creatinine, were significantly different across seasons, resulting in a lower $1,25(OH)_2D$/PTH(1–84) ratio in winter ($p < 0.0001$, Table 1). The $1,25(OH)_2D$/PTH(1–84) ratio showed significant inverse relations with stages of CKD (KDOQI stages) and severity of HF symptoms (NYHA classes, Fig. 1). In linear multilevel analysis, the variables most strongly associated with a lower, log-transformed $1,25(OH)_2D$/PTH(1–84) ratio were higher baseline serum concentration of creatinine, season of blood collection, female sex and age (Table 2).

3.2. Worsening of renal function and the $1,25(OH)_2D$/PTH(1–84) ratio

In all, 335 patients (29.6%) experienced an episode of WRF, on average 6.2 [2.7–24.1] months after randomization. They were older, had higher serum creatinine and lower LDL- and HDL cholesterol, and were more often prescribed diuretics, spironolactone and amiodarone at randomization than those without WRF (Table 3). Patients with WRF had a lower baseline concentration of $1,25(OH)_2D$, and higher PTH(1–84), resulting in a significantly lower $1,25(OH)_2D$/PTH(1–84) ratio (Table 3). A restricted cubic splines approach shows the relation between the baseline $1,25(OH)_2D$/PTH(1–84) ratio as a continuous variable and the relative hazard for WRF (Fig. S1). There was a biphasic, non-linear effect with an inflection point corresponding to a ratio of about 1.63. After transformation of the $1,25(OH)_2D$/PTH(1–84) ratio on a natural logarithmic scale, the relation became linear (Fig. S1). Fig. S2 shows the relations between $1,25(OH)_2D$ and PTH(1–84), separately, with WRF. Kaplan–Meier curves for the first occurrence of WRF according to the $1,25(OH)_2$ vitamin D/PTH (1–84) ratio are presented in Fig. 2.

At an optimal cut-off of 0.98, the $1,25(OH)_2D$/PTH(1–84) ratio had sensitivity of 68.2%, specificity of 50.3%, negative predictive value 0.79

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