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Full Length Article

Impact of high-dose statins on vitamin D levels and platelet function in patients with coronary artery disease

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ABSTRACT

Background: Statins represent a pivotal treatment in coronary artery disease, offering a reduction in cardiovascular risk even beyond their lipid-lowering action. However, the mechanism of these "pleiotropic" benefits of statins is poorly understood. Vitamin D has been suggested as a potential mediator of the anti-inflammatory, anti-thrombotic and vascular protecting effects of statins. Aim of present study was to assess the impact of a high-intensity statin therapy on vitamin D levels and platelet function in patients with coronary artery disease.
Methods: Patients discharged on dual antiplatelet therapy and high-intensity statins after an ACS or elective PCI were scheduled for main chemistry and vitamin D levels assessment at 30–90 days post-discharge. Vitamin D (25-OHD) dosing was performed by chemiluminescence method through the LIAISON® Vitamin D assay (Diasorin Inc). Platelet function was assessed by Multiplate® (multiple platelet function analyser; Roche Diagnostics AG).
Results: Among 246 patients included, 142 were discharged on a new statin therapy or with an increase in previous dose (Inc-S), while 104 were already receiving a high-dose statin at admission, that remained unchanged (Eq-S). Median follow-up was 75.5 days. Patients in the Inc-S group were younger ($p = 0.01$), smokers ($p < 0.001$), with a less frequent history of hypercholesterolemia ($p = 0.05$), diabetes ($p = 0.03$), hypertension ($p = 0.02$), or previous cardiovascular events ($p < 0.001$). They were more often admitted for an acute coronary syndrome ($p < 0.001$) and used less anti-hypertensive drugs or nitrates. Higher total circulating calcium was observed in the Inc-S group ($p = 0.004$), while baseline vitamin D levels were similar in the 2 groups ($p = 0.30$). A significant reduction in the circulating low-density lipoprotein (LDL) cholesterol was observed in the Inc-S group. Vitamin D levels increased in the Inc-S patients but not in the Eq-S group (delta-25OHD: 23.2 ± 20.5% vs 3.1 ± 4.7%, $p = 0.003$), with a linear relationship between the magnitude of vitamin D elevation and the reduction of LDL cholesterol ($r = -0.17$, $p = 0.01$). Platelet reactivity was significantly lower in the Inc-S patients, when evaluating aggregation with different platelet activating stimuli (arachidonic acid, $p = 0.02$, collagen, $p = 0.004$, thrombin-activating peptide, $p = 0.07$, ADP, $p = 0.002$).
Conclusions: In patients with coronary artery disease, the addition of a high-intensity statin treatment, besides the lipid-lowering effects, is associated to a significant increase in vitamin D levels and lower platelet reactivity, potentially providing explanation of the "pleiotropic" benefits of statins therapy in cardiovascular disease.

1. Introduction

In the era of interventional cardiology representing the first treatment option for the majority of patients with coronary artery disease (CAD), a crucial role in cardiovascular prevention is still played by pharmacological therapy [1–3]. Statins, the inhibitors of cholesterol synthesis, are strongly recommended in all patients with coronary artery

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disease, having demonstrated in several trials a 25–40% reduction in cardiovascular risk [4], directly related to the magnitude of low-density lipoprotein cholesterol (LDL-C) lowering [5]. Moreover, a relevant regression in the volume of atheromasic plaque has been demonstrated with high-intensity statins, those achieving over 40% cholesterol reduction [6,7]. However, the benefits of this therapy in CAD has been ascribed not only to an aggressive reduction of circulating pro-atherogenic lipid particles, but also to its "pleiotropic" effects, including an improvement in endothelial function, anti-inflammatory and anti-oxidant actions, whose mechanism is still largely undefined [8,9].

Previous reports have suggested a role of vitamin D in explaining the pleiotropic effects of statins [10,11]. In fact, vitamin D (25-OHD) is the precursor of a hormone with a widespread cardio-protective function, modulating inflammatory and thrombotic processes [12]. Hypovitaminosis D, indeed, has been linked to the development of main established cardiovascular risk factors, as hypertension or diabetes, and to an increased risk of CAD and acute myocardial infarction [13–15]. However, despite, in certain studies, statin administration could raise the circulating levels of 25-OHD in patients with dyslipidaemia or diabetes [16,17], confirming a potential vitamin D-statin interplay in cardiovascular prevention, results were not confirmed by other reports [18], with even few data in patients with established CAD.

Therefore, aim of present study was to evaluate the impact of a high-intensity statin therapy on vitamin D levels and platelet function in patients with a recent acute coronary syndrome or percutaneous coronary intervention.

2. Methods

We included patients admitted to the Division of Cardiology, "Maggiore della Carità" Hospital, Università del Piemonte Orientale in Novara, Italy, from September 2013 to December 2014 requiring dual antiplatelet therapy for an acute coronary syndrome or after PCI for stable coronary artery disease. Invasive treatment with coronary angiography and eventual coronary stenting was not a required inclusion criterion. All patients receiving at discharge high-intensity statins and a dual antiplatelet therapy with ASA (100 to 160 mg daily) and an ADP-antagonist (clopidogrel 75 mg daily or ticagrelor 90 mg b.i.d) were scheduled for chemistry and platelet function tests evaluation at 30–90 days from discharge.

High-intensity statin therapy was considered for atorvastatin ≥20 mg/daily, rosuvastatin ≥10 mg/daily or simvastatin ≥40 mg daily according to literature [19].

The study was approved by our local Ethical Committee and informed consent was obtained by all patients. The study was conducted in accordance with the Declaration of Helsinki.

Main demographic, clinical and angiographic data, together with the indication to dual antiplatelet therapy were recorded at discharge and included in a dedicated database, protected by password. Patients receiving concomitant vitamin D supplementation were excluded. As previously described [20] hypertension was defined as systolic pressure >140 mm Hg and/or diastolic pressure >90 mm Hg or if the individual was taking antihypertensive medications. Diabetes mellitus was defined as previous diagnosis, specific treatment administration (oral drug or insulin), fasting glycemia > 126 mg/dL or HbA1c > 6.5%. Chronic renal failure was considered for a history of renal failure or an admission glomerular filtrate (GFR) < 60 mol/min/1.73 m^2 by MDRD (Modification of Diet in renal Disease) formula.

2.1. Biochemical measurements

Fasting blood samples were drawn from all patients for main chemistry and vitamin D levels assessment at baseline, at admission, and at planned follow-up. Vitamin D dosing was performed by the chemiluminescence method through the LIAISON® Vitamin D assay (Diasorin Inc). The normal range for 25-OH D3 levels in our laboratory is from 30 to 100 ng/ml, according to literature reference [21].

2.2. Platelet function assessment

Platelet aggregation was measured by a whole blood test, the impedance aggregometry (Multiplate®- multiple platelet function analyser; Roche Diagnostics AG) a whole blood sample was stored in Vacutainer standard lithium heparin tubes and analyzed within 1–2 h from collection [22]. Tests with different agonists were performed: arachidonic acid (AA), collagen, ADP and prostaglandin E1 and thrombin receptor activating peptide (TRAP-6). Results were expressed as arbitrary Aggregation Units (AU) and plotted against time, defining platelet function as the area under curve (AUC or AU ∗ min).

2.3. Statistical analysis

Statistical analysis was performed using SPSS 17.0 statistical package. Continuous data were expressed as mean ± SD and categorical data as percentage. Patients were divided in 2 groups: in the "Eq-S" group we included patients already receiving at admission a high-intensity statin, that was maintained on discharge, while the "Inc-S" were considered patients who started a high-intensity statin therapy or increased the dose or a previous treatment on discharge. Analysis of variance and the chi-square test were used for continuous and categorical variables, respectively. Linear regression analysis was performed to evaluate the relationship between changes in vitamin D levels and the reduction in low-density lipoprotein (LDL) cholesterol. The Mann-Whitney *U* test was used to compare median follow-up values. The changes in vitamin D and LDL cholesterol levels were considered both as an absolute difference or as % variation, as compared to baseline. A p value < 0.05 was considered statistically significant.

3. Results

Our population is represented by a total of 246 patients. Among them, 142 patients were discharged on a new statin therapy or with an increase in previous dose (Inc-S), while 104 were receiving at admission a high-intensity statin, that remained unchanged (Eq-S). As shown in Fig. 1, in the Inc-S group 69.8% of patients received atorvastatin and 30.2% rosuvastatin, while in the Eq-S group, 52.9% of patients received atorvastatin, 43.3% rosuvastatin and 2.8% simvastatin. Median follow-up was 75.5 days [Interquartile Range (IQR): 38–84.8]; not being different in the Eq-S group (median: 65.5 days; IQR [42–83]) or the Inc-S group (median 79 days; IQR [41–87], p value = 0.19).

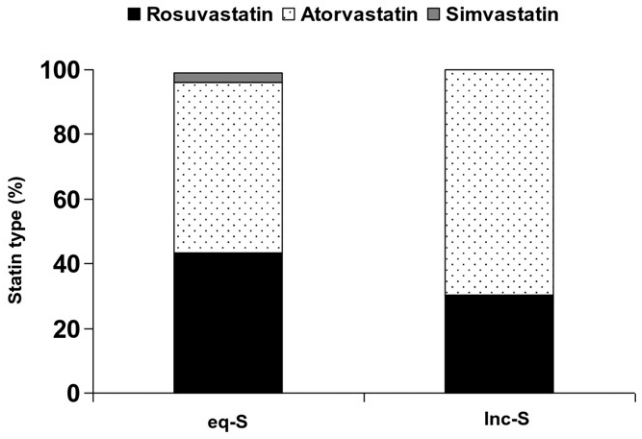

Fig. 1. Distribution of statin therapy in study population (Eq-S = statin dose unchanged, Inc-S = statin dose increased or new therapy started).