Endocrine (2019) 66:699–700
https://doi.org/10.1007/s12020-019-02105-6

RESEARCH LETTER

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Body mass index predicts resistance to active vitamin D in patients with hypoparathyroidism

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Received: 1 April 2019 / Accepted: 26 September 2019 / Published online: 26 October 2019

Persistent hypoparathyroidism (PH) is a severe disease mostly occurring as a surgical complication of total thyroidectomy [1]. The primary goal of chronic management is to maintain serum calcium within an asymptomatic range avoiding significant hypo- or hyper-calcemia; calcium and active vitamin D (calcitriol) are the most common and low-cost therapies used in this setting. However, choice of doses and strategies of follow-up are predominantly based on an empirical approach, which reflects huge variability among patients in the amount of calcium and calcitriol needed to correct biochemical and clinical profile. In fact, several patients do not achieve control of the disease under conventional therapy or need heavy up-titration, with high risk of poor compliance and side effects [2]. To overcome the current limitation, human recombinant PTH (rhPTH) (1–84) —identical in structure to full-length endogenous hormone —has been recently introduced in clinical practice and is currently indicated, due to its elevated cost, only in PH patients "resistant" to conventional therapy [3, 4]. Notably, so far there is no chance to predict resistance to conventional treatment, impairing the opportunity of personalized follow-up and adequate up-titration modalities.

Methods

Seventy-one Caucasian patients, (68 with postsurgical, 3 with autoimmune PH; F/M: 60/11) attending the Nuclear Medicine Unit, were retrospectively and consecutively enrolled. We evaluated the anthropometric characteristics assessed at the diagnosis of PH; all patients were followed up for at least 1 year, and were under stable conventional treatment with calcium and calcitriol from at least 6 months. We arbitrarily defined as resistant (R) to conventional therapy those patients in need to take 1 μg of calcitriol daily or more [2]. Based on the body mass index (BMI) we divided patients into four groups: group 0, normal weight (<25 Kg/m^2); group 1, overweight (25 to <30 Kg/m^2); group 2, obesity class I (30 to <35 Kg/m^2); group 3, obesity class II (35 to <40 Kg/m^2) and III (≥40 Kg/m^2). Statistical analyses were performed using the Stata 12 software (Stata Statistical Software: Release 12; StataCorp LP, College Station, TX, USA).

Results

When we compared R ($n = 24$) and nonresistant (NR) ($n = 47$) groups, we found no difference in age (R: 58 ± 13 vs. NR: 56 ± 13 years, p = NS), sex (female percentage: R 83% vs. NR 85%, p = NS), and disease duration (R: 12 ± 8 vs. NR: 11 ± 9 years, p = NS) between the two groups. Conversely, BMI was higher in R patients (28 ± 5 vs. 25 ± 5 kg/m^2, $p = 0.005$) (Fig. 1). Furthermore, logistic regression analysis showed that BMI was independently associated with resistance to conventional therapy (OR 2.07, 95% CI 1.04–3.92; $p = 0.02$), in face of similar serum calcium levels obtained by therapy (R: 8.8 ± 0.9 mg/dl vs. NR: 8.7 ± 0.6 mg/dl, p = NS). Among the 24 R patients, 21% were normal weight, whereas 79% were obese ($p = 0.026$). On the other hand, we found no significant difference in daily supplemental calcium intake between BMI

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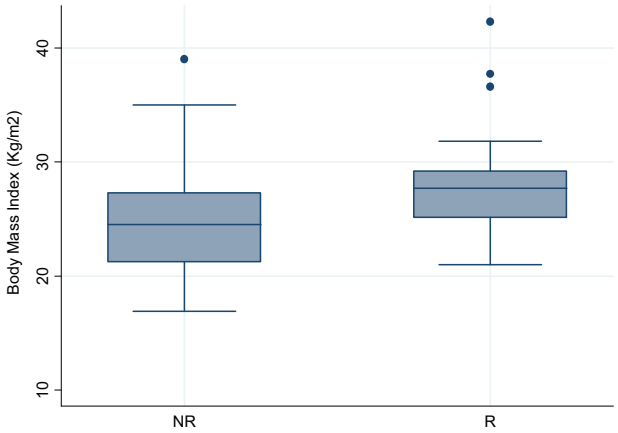

Fig. 1 Body mass index in nonresistant (NR)$^{\text{PTH sensitive}}$ vs. resistant (R) patients. Whisker-box plot showing the difference in BMI (kg/m^2) between NR and R patients ($p = 0.005$). Patients were classified as NR or R based on calcitriol daily dosage below or above 1 mcg/day, respectively. Data are represented as median, 25–75, and 10–90 interquartile range; full circles represent outliers. Statistical analysis was performed using Student's *t* test

groups (group 0: 882 ± 644 mg; group 1: 1235 ± 1366 mg; group 2: 741 ± 756 mg; group 3: 1250 ± 500 mg).

Discussion

This is the first study showing that elevated BMI at diagnosis, a variable not related to the disease per se, can predict calcitriol resistance in PH. The observation that patients with high body mass require higher doses of calcitriol might be explained by accumulation of 1,25(OH)2D3 (perhaps in esterified form) in the adipose tissue [5]. Alternatively, adipose tissue does have increased expression of the vitamin D receptor [6], which may be hypothesized to be dysfunctional. If the predictive power of BMI will be confirmed by larger studies, our data may help clinicians in three ways: (1) Adapt from the beginning the active vitamin D dose, and the schedule of possible dose escalation, to BMI; (2) Advise towards lifestyle modifications, never previously recommended by guidelines in this setting, leading to weight loss in PH [4]; (3) If body weight reduction is not obtained, consider an earlier addition of low-dose rhPTH (1–84) in overweight/obese PH patients [7].

Funding This study was funded by the European Commission (grant number 795877 to F.T.).

Compliance with ethical standards

Conflict of interest A.G. has received research grants from Ipsen and Novartis and is a consultant for Ipsen, Pfizer, Astellas, and Shire. A.M. F. is consultant for Shire. F.T. declares that he has no conflict of interest. The remaining authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was waived.

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