Endocrine (2016) 52:183–186
DOI 10.1007/s12020-016-0890-0

EDITORIAL

Vitamin D-binding protein: one more piece in the puzzle of acromegalic osteopathy?

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Received: 22 January 2016 / Accepted: 2 February 2016 / Published online: 22 February 2016

In only 5 years, more than 20,000 papers (more than 300 in the last month) dealing with vitamin D have been published, reflecting the deep interest of the scientific community for the role of this hormone in health and disease. As a matter of fact, vitamin D has been shown to exert pleiotropic effects on different tissues and there has been growing evidence that low vitamin D may be associated with several pathological conditions, including fragility fractures [1], myopathy [2], diabetes [3], cardiovascular [4], autoimmune [5], and neoplastic diseases [6]. Despite this compelling evidence, there is still controversy on how hypovitaminosis D should be evaluated and defined in different clinical settings and whether and how supplementation of vitamin D deficiency may truly influence the different clinical outcomes.

There is an agreement that adequate vitamin D status should be defined by concentrations of serum 25-hydroxy-vitamin D [25(OH)-vitamin D] that is the immediate precursor of the active hormone 1,25 dihydroxy-vitamin D3 [7]. However, in some conditions such parameter may not represent a reliable marker of vitamin D activity due to modifications of free hormone levels independently of total hormone storage and amount [8–10]. Consistently with the free hormone hypothesis, only hormone not bound to protein vectors can exert biological actions [11]. More than 80 % of circulating vitamin D (i.e., both 25(OH)-vitamin D and 1,25-dihydroxy-vitamin D3) is bound to vitamin D-binding protein (VDBP) which acts as regulator of hormone bio-availability to target tissue [12]. Indeed, VDBP could be either a reservoir of vitamin D prolonging its half-life or a modulator of hormone biological activity [9, 10, 13]. In clinical conditions, the inhibitory effects of VDBP on vitamin D activity seem to be predominant and some individuals may be misclassified as vitamin D sufficient or insufficient by measurement of serum 25(OH)vitamin D alone in the presence of modifications in VDBP production. In fact, bio-available vitamin D is sufficient, despite low total 25(OH) vitamin D levels, in subjects with low levels of VDBP (e.g., patients with liver cirrhosis) [9, 10]. Conversely, an increase in serum VDBP may cause a functional vitamin D deficiency even in the presence of normal 25(OH) vitamin D values [14]. As a matter of fact, the potential benefit of measuring bio-available vitamin D concentrations, especially in the presence of abnormalities of VDBP, has been suggested [9, 10].

Growth hormone (GH) and insulin-like growth factor-1 (IGF-I) exert important effects on bone modeling and remodeling [15]. Patients with acromegaly are at high risk of fractures, despite they display largely preserved bone mineral density (BMD) [16], a novel specific bone metabolic disease that can be defined "acromegalic osteopathy." In this context, the effects of GH/IGF-I hypersecretion on vitamin D and calcium metabolism are still largely unclear. GH was shown to modulate parathyroid hormone secretion [17] and there has been also evidence that GH and IGF-I may stimulate the expression of 1-alpha-hydroxylase activity in the kidney, favoring the synthesis of 1,25 dihydroxy-vitamin D3 [18]. In fact, several studies have consistently demonstrated hypercalciuria, hypercalcemia, and mild hyperphosphatemia in acromegaly as an effect of increased synthesis of 1,25 dihydroxy-vitamin D3 [18]. On the other

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hand, vitamin D deficiency has been consistently reported in patients with acromegaly [19].

In this issue of the Journal, Altinova et al. investigated vitamin D status in a cohort of 54 patients with controlled or active acromegaly in comparison to 32 control subjects, matched for gender, age, and body mass index [20]. The novelty of this study concerns the evaluation of 25(OH)-vitamin D along with serum VDBP values. The main result of this study was the higher serum VDBP values in acromegaly patients as compared to control subjects, the difference being more pronounced when only patients with active acromegaly were investigated [20]. Indeed, the entity of VDBP increase was not defined, since the authors did not provide information on the normal reference values in their own laboratory and the assay used in this study seems to be different from those already employed by others [8, 9]. However, looking at the distribution of VDBP values in patients and control subjects, one could argue that most of the acromegaly patients of Altinova study had elevated VDBP levels, since the median value reported in the patients was above the upper limit of range of control subjects [20]. The authors did not discuss potential mechanisms underlying the increase in serum VDBP in acromegaly. A direct effect of GH hypersecretion could be hypothesized, although no similar evidence has been provided so far for hepatic proteins, in general, and hormone carriers in particular [21]. On the other hand, a compensatory effect secondary to above-mentioned changes in vitamin D metabolism induced by GH and IGF-I excess may be hypothesized [18]. Accordingly, Altinova et al. found lower serum free vitamin D in patients with acromegaly as compared with control subjects notwithstanding the not statistically significant difference in serum total 25(OH) vitamin D between the two groups [20]. This result is noteworthy, since it provides suggestion that hypovitaminosis D could be likely more frequent and severe than that expected by total 25(OH)-vitamin D values in acromegaly.

Besides the mechanistic uncertainties, some methodological issues merit to be highlighted. Because of their low concentrations, direct measurement of free vitamin D by laborious ultrafiltration and dialysis methods may be challenging. For this reason, Altinova et al. performed an indirect estimation of free vitamin D based on the measurement of 25(OH)-vitamin D, albumin, and VDBP values [12]. This method is easily applied in the clinical practice but some methodological shortcomings may affect the reliability of results. The algorithms used for estimating bio-available vitamin D are unable to capture eventual changes in VDBP affinity which may influence the amount of vitamin D bound to the carrier protein. As a matter of fact, affinity of VDBP for vitamin D metabolites is greatly influenced by gene polymorphisms [22] which were not investigated by Altinova et al. in their acromegaly patients [20]. Specifically, three main phenotypic alleles have been described and there is convincing evidence that VDBP polymorphism may influence the impact of hypovitaminosis D on different clinical outcomes [23, 24]. Moreover, polymorphisms of VDBP may also influence the results of immunoassays using monoclonal antibodies against VDBP epitopes near the polymorphic regions of the protein [25]. From this point of view, either evaluation of VDBP polymorphism or direct measurement of free vitamin D is expected to provide more reliable results on vitamin D status in different clinical settings. However, it is noteworthy that in studies comparing the two methods, indirect measurement of bio-available vitamin D was shown to overestimate directly measured free hormone [9]. Therefore, it is reasonable to hypothesize that applying direct assays in acromegaly, free vitamin D levels may be even lower than those observed by Altinova et al. somewhat corroborating the results of this study. On the other hand, in some conditions, VDBP values may be accompanied by a decrease in its affinity for vitamin D ligands with consequent no change in free vitamin D as measured by a direct assay [26]. If this was the case, the indirect evaluation of free vitamin D may underestimate vitamin D bio-availability, and the acromegaly data presented in this study may not have a relevant clinical role.

Based on the aforementioned methodological uncertainties, the question is could the results of Altinova et al. have relevant implications in the context of "acromegalic osteopathy"? Although the exact role of vitamin D deficiency in the pathogenesis of GH excess-induced skeletal fragility is still unknown, low vitamin D values were associated with vertebral fractures in post-menopausal women [27] but not in males [28] with acromegaly and correction of vitamin D deficiency has been recommended as one of main measures in the management of skeletal fragility in this clinical setting [29]. Unfortunately, the study of Altinova et al. did not provide data concerning skeletal health in their acromegaly patients [20]. In the case of a GH-induced effect, one can hypothesize that high VDBP and low free vitamin D may play a role in predisposing to skeletal fragility, in agreement with the experimental evidence that VDBP is an inhibitor of vitamin D activity [30] and the clinical finding of association between high VDBP and low BMD in general population [8]. Moreover, it was also observed that VDBP may directly stimulate osteoclastogenesis and bone resorption in experimental conditions [31]. Future studies are, however, needed to test and confirm this hypothesis.

Somatostatin analogs are the primary medical treatment option in acromegaly [32, 33]. There is evidence that somatostatin analogs may cause intestinal malabsorption [34] potentially contributing to development of

hypovitaminosis D in acromegaly. Altinova et al. found no difference in serum VDBP and free vitamin D between patients treated with somatostatin analogs and those who were not treated with these drugs [20]. This result was in agreement with another recent retrospective study that did not observe any effect of long-term somatostatin analogs treatment on serum 25(OH)-vitamin D values in acromegaly [35]. However, the retrospective [35] and cross-sectional [20] designs, as well as the small number of enrolled patients [20] did not allow to draw definitive conclusions on this issue, and further prospective studies on larger number of patients evaluated for both total and free vitamin D are needed to definitely clarify whether or not somatostatin analogs may have an impact on vitamin D metabolism and activity in acromegaly, regardless of biochemical control of disease, such as already demonstrated for other clinical outcomes [36].

Finally, since all patients enrolled in the study of Altinova et al. were untreated for hypovitaminosis D, it is unclear whether VDBP levels may influence the effectiveness of vitamin D supplementation in acromegaly. In fact, in the presence of high VDBP, 25(OH)vitamin D normalization may occur before reaching normal levels of bio-active vitamin D, hampering the correct assessment of adequacy of replacement therapy.

In conclusion, Altinova et al. provide a novel element of discussion in the area of what we have defined acromegalic osteopathy. However, the rather preliminary nature of this study does not allow to understand if the VDBP levels change described may be directly correlated to GH hypersecretion and may have a relevant pathophysiological and clinical impact on the vitamin D system in acromegaly.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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