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Editorial: Vitamin D Binding Protein, Total and Free Vitamin D Levels in Different Physiological and Pathophysiological Conditions

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Editorial on the Research Topic

Vitamin D Binding Protein, Total and Free Vitamin D Levels in Different Physiological and Pathophysiological Conditions

Vitamin D binding protein (DBP) is a major plasma carrier for vitamin D and its metabolites. In recent years, there has been growing interest in understanding the physiological functions and attributes of DBP. The current issue is comprised of five review articles and two original research papers concerning the physiology of DBP and its role in different disorders.

Poor vitamin D status is highly prevalent in many different countries (1–4), but the exact definition of vitamin D status is controversial. The plasma concentration of total 25-hydroxyvitamin D [25(OH)D] is currently used as an indicator of vitamin D status. In the past decades, however, there has been argument as to whether just measuring total 25(OH)D is appropriate for the assessment of vitamin D status in different physiological and pathophysiological conditions (5, 6). About 85% of the total circulating 25(OH)D is bound to DBP, and 15% is bound to albumin. About 0.03% of 25(OH)D circulates in free form. Since 25(OH)D is weakly bound to albumin and dissociates from it during tissue perfusion, the sum of the free and the albumin-bound 25(OH)D represents the bioavailable 25(OH)D, which may be readily available for metabolic function. In contrast, the DBP-bound vitamin D is relatively unavailable to target tissue, with the exception of a few tissues such as the kidney that express a megalin/cubilin transport system for DBP-bound 25(OH)D. The concept that it is the free hormone and not the DBP-bound hormone that enters cells is known as the free hormone hypothesis. In the review by Bikle and Schwartz it is highlighted that the DBP level is regulated by estrogen, glucocorticoids, and inflammatory cytokines but not by vitamin D itself, and therefore, these regulators would affect levels of total 25(OH)D. The review by Bikle and Schwartz focuses on the biological importance of DBP with emphasis on its regulation of total and free vitamin D metabolite levels in various clinical conditions. They also point out that attempts to calculate the free level using affinity constants generated in a normal individual along with measurement of DBP and total 25(OH)D have not accurately reflected directly measured free levels in a number of clinical conditions. The authors examine the impact of different clinical conditions as well as different DBP alleles on the relationship between total and free 25(OH)D, using only data in which the free 25(OH)D
level was directly measured. Following their previous review (7),
the review by Chun et al. discussed a number of important
questions including the following. Is the total 25(OH)D (bound
plus free) or the unbound free 25(OH)D the crucial determinant
of the non-classical actions of vitamin D? While DBP-bound
25(OH)D is important for renal handling of 25(OH)D and
endorcine synthesis of 1,25(OH)2D, how does DBP impact extra-
renal synthesis of 1,25(OH)2D and subsequent 1,25(OH)2D
actions? Are there pathophysiological contexts where total
25(OH)D and free 25(OH)D would diverge in value as a marker
of vitamin D status? This review aims to introduce the concept
of free 25(OH)D and the molecular biology and biochemistry
of vitamin D and DBP, which provides the context for free
25(OH)D, and surveys in vitro, animal, and human studies taking
free 25(OH)D into consideration.

Low DBP levels in patients with primary hyperparathyroidism
(PHPT) were first reported in 2013 by Wang's group (8) and
confirmed by Battista et al. (9). In the paper by Wang et al.,
the authors recruited 75 patients with PHPT and 75 healthy
control subjects. In addition, 25 PHPT patients underwent
parathyroidectomy and had a 3-month follow up visit. The
results showed that serum DBP levels were lower in patients with
PHPT but that parathyroidectomy restored DBP levels. Lower
DBP levels may be one of the contributing factors of low total
25(OH)D level in PHPT patients, and the total 25(OH)D levels
might not reflect true vitamin D status in patients with PHPT.

In the comprehensive review by Bouillon et al. it was noted
that DBP was originally discovered as a highly polymorphic
protein useful for population studies and originally called Group-
specific Component (GC). It is now known that DBP and
GC are the same protein and appeared early in the evolution
of vertebrates. DBP is genetically the oldest member of the
albuminoid family (which includes albumin, α-fetoprotein, and
afamin, all involved in the transport of fatty acids or hormones).
DBP has a single binding site for all vitamin D metabolites
with a high affinity for 25(OH)D, thereby creating a large
pool of circulating 25(OH)D, which prevents rapid vitamin D
deficiency. The review also highlighted the roles of DBP in
preventing the urinary loss of 25(OH)D and the formation of
polymeric actin fibrils in the circulation after tissue injury. DBP
also plays a minor role in transporting fatty acids. Based

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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