

Vitamin D and Insulin Resistance in Polycystic Ovarian Syndrome and Congenital Adrenal Hyperplasia-a Commentary and Natural Expansion

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In our previous focused review, the journal emphasized Type 2 diabetes (T2DM), excluding intimately associated disorders that should be considered integral components of the insulin resistance (IR) syndrome e.g., polycystic ovarian syndrome (PCOS), congenital adrenal hyperplasia (CAH), and gout [1]. In this expansion I'll highlight potential roles of vitamin D in PCOS and CAH. Before discussing these areas, I shall briefly summarize key points from our review:

- Low vitamin D levels are strongly and independently associated with IR, impaired insulin secretion, and higher incident T2DM risk, especially in people already at increased risk.
- In several species the association of hypovitaminosis D with incident T2DM risk is apparently causal.
- Causality of hypovitaminosis D in incident T2DM in humans is not established due to conflicting results of interventional trials and mendelian randomization studies on both incidence and glycemic control indices. Interventional trials varied widely in terms of dosage, preparations used, duration, and demographics.
- Low vitamin D status (VDS) is strongly correlated

with risk for several micro- and macrovascular T2DM complications including: peripheral neuropathy, erectile dysfunction (ED), retinopathy, kidney disease, and all-cause mortality, but not gastroparesis. The association between serum vitamin D level and diabetic cardiac neuropathy risk is U-shaped.

- Interventional studies in people with diabetic kidney disease reported significant therapeutic benefit when combining vitamin D analogues with renin angiotensin aldosterone system (RAAS) inhibitors. Causality of low VDS in T2DM complications, except for renal damage, remains unconfirmed.
- In people with prediabetes (unselected for hypovitaminosis D), vitamin D₃ supplementation at 4000 IU/ day did not significantly lower risk of incident diabetes in the much much-anticipated D2d trial [2].

Vitamin D & T2DM-Related Disorders Associated with IR

It is now settled science that PCOS is IR-associated and is a metabolic syndrome component [3]. Insulin-sensitizing interventions e.g., weight loss, exercise, metformin, thiazolidinediones, and inositol, were reported to clinically and biochemically ameliorate PCOS [3]. Vitamin D is a putative insulin sensitizer [1,4]. While less appreciated, CAH, like PCOS, is IR-associated and, as will be discussed,

IR-reducing interventions, including vitamin D repletion, show potential in treating CAH.

Vitamin D and Polycystic Ovarian Syndrome (PCOS)

Kim et al. studied the prevalence of Vitamin D deficiency in Korean women with PCOS and possible relationships between vitamin D levels and clinical/metabolic characteristics [5]. They recruited 38 women with PCOS using Rotterdam criteria and 109 BMI and age-matched controls. Serum 25-hydroxy vitamin D (25OHD) concentrations <20 ng/mL were considered deficient. Since hypovitaminosis D may play a key role in metabolic dysfunction in PCOS, correlations between clinical/metabolic indicators and vitamin D concentration were calculated separately for both groups. Women with PCOS did not differ significantly from controls regarding 25OHD concentration 19.6±6.6 (SD) ng /mL vs 20.1±7.4 ng/mL (controls), p=0.696) or in prevalence of vitamin D deficiency (57.9% in women with PCOS vs 56.5% controls, p=0.880). There was no significant correlation between serum vitamin D concentration and clinical/metabolic profiles in women with PCOS, controls, or the group as a whole.

In exploring associations between serum vitamin D concentration and IR or glucose homeostasis, several studies reported serum vitamin D levels in women with PCOS. While there is no consensus on whether or not VDS is different in women with PCOS and controls; an inverse association between serum vitamin D level and metabolic aberrations was reported in women with PCOS. In addition to low serum 25OHD levels, some vitamin D receptor gene polymorphisms are associated with increased risk of PCOS and similar metabolic/endocrine phenotypes, suggesting a vitamin D role in PCOS prevention [6-18]. Most prior studies involved Caucasian women; few were in Asian populations. In Kim's study, the authors investigated whether low VDS characterizes Korean women with PCOS and if there was a relationship between serum vitamin D concentration and their clinical/metabolic profiles.

Women with PCOS had higher mean serum calcium vs controls, but showed no difference in serum levels of 25OHD or in prevalence of vitamin D deficiency. Hypovitaminosis D was present in most subjects (92.1% PCOS vs 87.0% controls).

While Wehr et al. reported lower mean serum vitamin D levels in a large cohort with PCOS (n=545) vs controls (n=145) (25.7 vs. 32.0 ng/mL, respectively), some studies reported that serum vitamin D levels were similar in both groups [14, 18, 19]. Indeed, one reported that women with PCOS had significantly higher vitamin D levels than matched controls [9]. Thus, the literature is inconsistent

concerning relative vitamin D levels in women with PCOS.

In earlier studies, mean serum 25OHD levels in women with PCOS were reported to be between 11-31 ng/mL, with most studies reporting mean values <20 ng/mL [6-10, 14,16, 20-23]. In Kim et al.'s study, mean serum 25OHD level in women with PCOS was also <20 ng/mL (19.6±6.6 ng/mL) and vitamin D deficiency (< 20 ng/mL) was found in 57.9%, but vitamin D deficiency is very common in the general population, (10% - 60% of adults) [24-25]. Controls also had a high prevalence of vitamin D deficiency (56.5%), with a mean concentration of 20.1 ng/mL . While there is disagreement concerning whether vitamin D levels are different in women with or without PCOS, vitamin D deficiency is equally common in both groups. In Kim's study, hypovitaminosis D (<30 ng/mL) was noted in most women. This finding is consistent with reports that >90% of the non-white US population have hypovitaminosis D [26].

Several groups explored possible associations between VDS and hormonal/metabolic features in PCOS. In PCOS low serum vitamin D concentrations are believed to be associated with metabolic risk factors e.g., IR, elevated serum total cholesterol, blood pressure, glucose, C-reactive protein, triglycerides, and low HDL cholesterol [8,11]. Furthermore, vitamin D replacement was reported to reduce IR, fasting and post-meal glucose, and triglyceride levels in women with PCOS [10,15]. Several studies reported associations between low serum vitamin D levels and hyperandrogenism indices e.g., SHBG, Ferriman-Gallwey score, free androgen index, total serum testosterone, and serum dehydroepiandrosterone sulfate [7-8, 11, 20]. Kim did not find any correlations between VDS and hormonal/metabolic markers in women with PCOS or controls.

In Kim's study, serum calcium levels were higher in women with PCOS. Although some investigators found no differences [9,11], lower serum calcium concentrations in PCOS have also been reported [7, 15, 20]. Pre-clinical studies reported that a rise in intracellular free calcium is required for oocyte meiosis resumption and suggested that dysregulated calcium metabolism contributes to abnormal oocyte development in PCOS [18,21]. It is unclear from Kim's article why women with PCOS had higher serum calcium levels. This should be explored in future studies.

While Kim's study reported no differences in mean serum concentration of vitamin D or prevalence of vitamin D deficiency between women with PCOS and matched controls, these data should be interpreted cautiously as deficiency may be widespread in both groups and because inverse correlations between obesity indices and serum vitamin D concentrations were frequently reported [6-9,11,16,20]. As vitamin D is fat soluble, a greater percentage of it is sequestered in fat in overweight/obese

people, reducing serum concentrations. In this study there were no inter-group differences in obesity indices or whole body or visceral fat masses. Comparable degrees of obesity may obscure small differences in serum vitamin D concentrations between women with PCOS and controls. A limitation of Kim's study is the fairly small PCOS sample size, precluding firm conclusions. Finally, they did not control for other potential confounders, e.g., sunlight exposure, season, or dietary factors affecting VDS.

Summarizing, Kim found no significant difference in mean serum vitamin D level or prevalence of vitamin D deficiency between women with PCOS and controls, nor any correlation between serum vitamin D and hormonal/metabolic profiles in either group. Possible relationships between vitamin D and PCOS need further exploration, as vitamin D deficiency has often been reported to increase the risk of IR, a key part of PCOS pathophysiology.

Butts et al. reported that Vitamin D deficiency is associated with less successful ovarian stimulation in women with PCOS $n=607$, but not in those with idiopathic infertility $n=647$ [27]. Vitamin D deficient women with PCOS were less likely to ovulate, adjusted OR=0.82; 95% CI, 0.68-0.99 and had a 40% lower chance of live birth (adjusted OR=0.63; 95% CI, 0.41-0.98). Vitamin D deficiency was associated with greater risk of early miscarriage (OR, 1.6; 95% CI, 1.0-2.6; $P=0.05$).

Kuliczowska-Plaksej et al. investigated associations of serum vitamin D binding protein (VDBP) with cardiovascular/metabolic risk factors in women with PCOS [28]. Their goal was to determine serum concentrations of 25OHD and VDBP and their associations with several cardiovascular risk factors in women with PCOS. They studied 267 women, aged 20-35 years, mean \pm SD= (24.7 \pm 4.9): 167 with PCOS and 100 controls stratified by BMI. Biochemical/hormonal parameters were determined. Free and bioavailable serum 25OHD were calculated using mathematical equations. Whole body and visceral fat proportions were determined by DXA. In lean controls serum total, free, and bioavailable 25OHD ($p<0.001$ for all) were significantly higher than in overweight/obese controls, while VDBP levels were not different. In women with PCOS total 25OHD ($p<0.001$), and VDBP ($p=0.006$) were lower in overweight/obese subgroups than in lean ones. In both groups' serum VDBP concentrations were negatively associated with serum insulin and positively with SHBG. In women with PCOS, in contrast with controls, VDBP was negatively associated with abdominal fat content, BMI, and fasting blood glucose and positively with HDL. Regardless of lower serum total 25OHD in obese women with PCOS, all women with PCOS (lean and obese) had similar serum free/ bioavailable 25OHD, which could result from concomitantly lowered serum VDBP levels in obese women with PCOS. VDBP may be important in regulating availability of active 25OHD fractions in

women with PCOS. VDBP was negatively correlated with cardiovascular risk factors e.g., waist circumference and fasting serum insulin in women with PCOS.

Fang et al. conducted a meta-analysis and systematic review of randomized control trials (RCTs) of vitamin D administration in women with PCOS [29]. A literature search identified all RCTs published before 12/2015 comparing the effect of vitamin D administration with placebo or metformin in women with PCOS; 9/463 studies met criteria and were included, involving 502 women with PCOS. Vitamin D administration significantly improved follicular development with a higher number of dominant follicles (OR, 2.34; 95% CI, 1.39-3.92). Significant improvement in menstrual regularity occurred when metformin +vitamin D was compared with metformin alone (OR, 1.85; 95% CI;1.01-3.39).

Mogili et al. studied the prevalence of vitamin D deficiency in infertile women with PCOS and its association with metabolic syndrome [30]. They performed a prospective, observational study in a tertiary care setting from 03/2016-03/2017. The primary outcome was the prevalence of vitamin D deficiency in this group. Secondary outcomes were determination of associations of hypovitaminosis D with metabolic syndrome, obesity, and hypercholesterolemia. A total of 256 infertile women with PCOS participated. Vitamin D deficiency was noted in 70.3%; 20.3% had vitamin D insufficiency; only 9.4% were replete. Metabolic syndrome was noted in 31.3%. No associations were seen between hypovitaminosis D and metabolic syndrome, obesity or hyperlipidemia, save a strong association between waist circumference >80 cm and vitamin D deficiency ($p=0.02$).

Rashidi et al. studied the effects of calcium-vitamin D and metformin on the menstrual cycle and ovulation in Iranian women with PCOS [31]. In this pilot study, 60 infertile women with PCOS were recruited in a prospective trial and assigned to 3 groups of 20 each. Group 1 took 1,000 mg of calcium+400 IU vitamin D/day, orally. Group 2 took the same as Group 1+1,500 mg/day of metformin. Group 3 took just 1,500 mg/day of metformin. They were treated for 3 months and followed for 3 more months. Menstrual regularity, number of dominant follicles (≥ 14 mm), and conception rates were compared. Generalized estimating equation tests revealed that the number of dominant follicles during the 2-3 months of post-treatment follow-up was higher in the calcium-vitamin D +metformin women than in the other 2 groups ($p=0.03$). The observed effects of metformin +calcium-vitamin D on menstrual cycle regulation suggest that they may be effective for treatment of anovulation and oligomenorrhea, with possible gains for pregnancy rates in women with PCOS. (As this study was done in Iran, when most women observed strict purdah dress code, probably most participants had baseline hypovitaminosis D.)

Summarizing-with several notable exceptions, PCOS is reported to be associated with low VDS. Vitamin D interventions in women with low VDS are associated with improved follicular maturation, androgen profiles, menstrual regularity, and live birth rates. VDBP levels differ between obese and lean women with PCOS and may be important in regulating bioavailable vitamin D.

Vitamin D and Congenital Adrenal Hyperplasia

While the importance of IR in the pathogenesis, expression, and treatment of PCOS is widely acknowledged and PCOS is considered a component of metabolic (IR) syndrome, the ubiquity of IR in people with CAH (independently of glucocorticoid treatment) and the possibility of effective treatment via IR-reducing strategies, *often without glucocorticoids*, is scarcely appreciated [32-34]. As noted, before, numerous authors have reported IR reduction with vitamin D [4,35,36].

Even among the few investigators who recognize the ubiquity of IR/hyperinsulinemia in CAH, fewer still have used IR reduction to treat CAH, as is done in PCOS [37-38]. Such successful interventions include: metformin, thiazolidinediones, weight loss via lifestyle changes, bariatric surgery, Ashwagandha, and vitamin D replacement.

Thomas et al. reported normalization of serum 11-deoxycortisol in a man with classic 11-hydroxylase deficiency and vitamin D deficiency with vitamin D repletion without glucocorticoid/mineralocorticoid replacement [39].

Luis Lam et al. reported normalization of serum 11-deoxycortisol in a man with non-classic 11-hydroxylase deficiency and hypovitaminosis D with vitamin D repletion +the glucagon-like peptide-1 (GLP-1) receptor agonist, liraglutide [40]. They previously reported that vitamin D repletion may ameliorate both classic and non-classic adrenal hyperplasia (NCAH) due to 11-hydroxylase deficiency, as it does in PCOS, possibly due to reduced IR. Here they reported an apparent biochemical benefit that this man derived from the above combination. He is a 60-year-old man followed in Endocrine clinic since 03/2012, after hospitalization for bowel obstruction in

which hyperglycemia was noted. Past medical history was only remarkable for obesity and seizure disorder, for which he took oxcarbazepine 300mg and phenobarbital 30mg both, 3x/day. Phenobarbital may cause hypovitaminosis D via increased clearance [41].

At the time of his diabetes diagnosis BMI had been stable around 36 kg/m². His initial HbA1c on 03/20/2012=11.4% (normal 0-6.99%) He began basal/bolus insulin. His serum 25OHD=10ng/ml (normal 30-100). He began ergocalciferol 50,000 IU/week. The laboratory lost the baseline serum 11-deoxycortisol sample.

On 5/22/2012 at follow-up he began liraglutide,1.2mg SC/day as his recent HbA1c was still above target at 8.8%; serum 11-deoxycortisol=79ng/dl (< 42ng/dl) with serum 25OHD level=41ng/ml. On 8/6/2012 his HbA1c=5.8%, serum 11- deoxycortisol level=70ng/dl, and serum 25OHD level=61ng/dl, so on 8/15/2012 liraglutide was increased to 1.8mg/day. On 11/8/2012 his serum 11-deoxycortisol level =49 ng/dl and HbA1c=5.5%, and on 2/13/13 serum 11-deoxycortisol level was normal at 34 ng/dl, with a serum 25OHD level=62 ng/ml; Table 1.

These data suggest that vitamin D replacement +a GLP-1 receptor agonist may ameliorate non-classic 11-hydroxylase deficiency by lowering IR via reductions in inappropriate glucagon secretion, glucose toxicity, and weight (when it occurs), and by a direct vitamin D effect on IR.

Dono et al. previously reported that weight loss was associated with amelioration of non-classic aldosterone synthase deficiency and that vitamin D replacement in people with classic or non-classic 11-hydroxylase deficiency and hypovitaminosis D apparently normalized their biochemical profiles. In this presentation they reported that weight loss +vitamin D repletion apparently normalized serum 11-deoxycortisol and ameliorated alopecia, and menstrual irregularity in a woman with non-classic 11-hydroxylase deficiency [42-43]. She was 44 years old, presenting with infertility, irregular menses, and androgenic alopecia. Investigation revealed an 0800 serum 11-deoxycortisol concentration=68 ng/dl (<62), which normalized at 0800 after 1 mg dexamethasone taken at 2300 hours the previous night. Serum 25OHD=14

Date	A1c	25OHD	11-deoxycortisol
03/20/2012	11.4%	10 ng/ml	Lost by lab
05/22/2012	8.8%	41 ng/ml	79 ng/dl
08/06/2012	5.8%	61 ng/ml	70 ng/dl
11/08/2012	5.5%	Lost by lab	49 ng/dl
02/13/2013		62 n/ml	34 ng/dl

Table 1. Relationship of Serum 11-deoxycortisol with vitamin D repletion & addition/titration of liraglutide in a man with non-classic 11-hydroxylase deficiency.

	25OHD	11-deoxycortisol	BMI	Weight
Baseline	14 ng/ml	68 ng/dl	22.50 kg/m ²	63.5 kg
After 7 months on ergocalciferol	28 ng/ml	19 ng/dl	21.68 kg/m ²	61.2 kg

Table 2: Relationship between serum 25OHD & serum 11-deoxycortisol in a woman with non-classic 11-hydroxylase deficiency.

ng/ml (30-100). She weighed 63.5 kg; BMI=22.5 kg/m². Treatment began with ergocalciferol 50,000 IU/week. Seven months later her weight fell to 61.2 kg, BMI to 21.68 kg/m², and serum 11-deoxycortisol to 19 ng/dl; serum 25OHD rose to 28 ng/ml (Table 2).

Androgenic alopecia resolved and menses normalized. Weight loss may be effective in treating non-classic 11-hydroxylase deficiency, as it is in non-classic aldosterone synthase deficiency, by decreasing IR (hyperinsulinemia). Ergocalciferol may work similarly and, in addition, the abundance of vitamin D receptors in the adrenal cortex suggests a possible direct vitamin D effect on adrenal steroidogenesis [44]. The ovaries are also rich in vitamin D receptors and a regulatory role for vitamin D in ovarian steroidogenesis, follicular maturation, serum antimüllerian hormone and its receptor gene expression, and soluble receptor for advanced glycation end-products (sRAGE) has been suggested [45].

Fenteany et al. reported normalization of serum 17-OH-progesterone (17OHP) with vitamin D repletion in a man with T2DM, non-classic 21-hydroxylase deficiency, foot infection, and vitamin D insufficiency [46]. They noted that IR is associated with several disorders, e.g., non-classic 21-hydroxylase deficiency and allied disorders and that vitamin D is typically low in insulin resistant people. IR-associated disorders are sometimes mitigated during vitamin D repletion. Serum 25OHD rose by 32% while serum 17OHP fell by 87% over the course of 4 weeks receiving 50,000 IU ergocalciferol orally/week. Vitamin D repletion restored normal serum 25OHD levels with concurrent normalization of serum 17OHP. They suggested that serum 25OHD levels be determined before commencing steroids for treatment of non-classic adrenal hyperplasia (NCAH) and that levels of relevant steroid intermediates should be re-measured when vitamin D levels are replete to determine if steroid replacement is necessary.

Date	25OHD	17-OHP	Total Testosterone	Free Testosterone	LH	Prolactin
05/05/2015	24.7 ng/ml	460 ng/dl	203.6 ng/dl	4.5 pg/ml	3.71mIU/ml	21.03 ng/ml
05/12/2015	29.2 ng/ml	58 ng/dl	217.5 ng/dl	5.7 pg/ml		
06/04/2015	32.6 ng/ml	69 ng/dl	346.8 ng/dl	9.2 pg/ml		

Table 3: Relationship between serum 17OHP, total & free testosterone, & 25OHD in a man with non-classic 21-hydroxylase deficiency.

They reviewed literature reporting that Vitamin D deficiency and glucose intolerance are associated in humans and causally related in some species; although the efficacy of vitamin D repletion/supplementation for diabetes is not yet established [47-48].

The patient is a 59-year-old man admitted for foot infection/gangrene, who was screened for NCAH because he had T2DM and for hypogonadism due to erectile dysfunction (ED). On 5/5/2015 baseline 0800 (unstimulated) serum 17OHP was impressively elevated at 460 ng/dl (27-199), serum total and free testosterone=203.6 ng/dl (348.0-1197.0), and 4.5 pg/ml (7.2-24.0) respectively, serum 25OHD =24.7 ng/ml (30.0-100.0), LH=3.71 mIU/ml (1.5-9.3), and serum prolactin =21.03 ng/ml (2.1-17.7). He began ergocalciferol 50,000 IU/week orally. On 5/12/2015 serum 17OHP=58 ng/dl, total testosterone=217.5 ng/dl, free testosterone=5.7 pg/ml, serum 25OHD=29.2 ng/ml. On 6/4/2015 his 17OHP=69 ng/dl, total testosterone =346.8 ng/dl, free testosterone=9.2 pg/ml, and 25OHD=32.6 ng/ml (Table 3).

They concluded that vitamin D repletion in this man was accompanied by biochemical amelioration of both non-classic 21-hydroxylase deficiency and low testosterone. ED resolved concurrently, consistent with the reported association between low VDS and ED in men with T2DM [49]. Although he took atorvastatin and the similar drug, simvastatin, was reported to ameliorate non-classic 21-hydroxylase deficiency in hypercholesterolemic women, he was taking the same dose of atorvastatin long before hospitalization, so it is unlikely that it played any further role in reducing serum 17OHP. Krysiak et al. attributed the benefit of simvastatin in 4 women with non-classic 21-hydroxylase deficiency to lowering of serum insulin levels-a typical effect of interventions that reduce IR [50]. The mildly diabetogenic effect of statins is due more to reduced insulin secretion via beta cell dysfunction and apoptosis than to increased IR [51].

Since vitamin D repletion may reduce IR, the data of Fenteany et al. may support a pivotal epigenetic role of IR in CAH expression.

The abundance of vitamin D receptors in the adrenal cortex suggests that vitamin D or a downstream molecule may be a transcription factor for steroidogenic adrenal enzymes. In addition, testicular vitamin D receptors are abundant and vitamin D was recently reported to play a major role in testicular steroidogenesis [52]. Pilz et al. reported that vitamin D repletion is associated with increasing serum testosterone levels in men [53]. While there is no published data in males, in premenopausal women high prolactin/macroprolactin levels are reported to be associated with low VDS and repletion with a decrease in prolactin/macroprolactin levels (as possibly occurred in this man), and normalized testosterone levels [54]. Further, Seoane and Perez-Fernandez reported that activation of pituitary vitamin D receptors inhibits the prolactin gene transcription factor Pit-1 [55].

Not only was vitamin D repletion associated with clinical/biochemical amelioration of several CAH types in people with baseline hypovitaminosis D, but the corollary of these interventions was reported in a 58-year-old man with non-classic 11-hydroxylase deficiency and vitamin D insufficiency who underwent partial bowel resection for rectosigmoid carcinoma followed by prolonged total parenteral nutrition (which does not include vitamin D) without an ultraviolet light source [56]. On 07/21/2017 his baseline serum 25OHD concentration=24.4 ng/ml (30-100). Simultaneous serum adrenal steroid metabolites were collected because he had T2DM, which was reported to be frequently associated with NCAH [57]. Unstimulated serum 11-deoxycortisol concentration was elevated at 62 ng/dl (<42). Other adrenal steroid metabolites were all within reference range. On 08/10/2017 his serum 25OHD was in the deficient range, 10.3 ng/ml, and his 11-deoxycortisol rose about 4x to 246 ng/dl. With continued vitamin D deprivation on 08/25/2017 25OHD level remained very low at 12.7 ng/ml while 11-deoxycortisol rose almost 24x from baseline to 1468 ng/dl (Table 4)!

Date	25OHD	11-deoxycortisol
07/21/2017	24.4 ng/ml	62 ng/dl
08/10/2017	10.3 ng/ml	246 ng/dl
09/25/2017	12.7 ng/ml	1468 ng/dl

Table 4. Association of serum 11-deoxycortisol with worsening & prolonged hypovitaminosis D in a man with non-classic 11-hydroxylase deficiency.

Thus, not only may vitamin D repletion ameliorate some forms of CAH, but severe, prolonged deprivation may exacerbate an initially mild form of the disorder.

Role of the Gut Microbiome in Interactions Between Vitamin D, Insulin Resistance, PCOS, and CAH

Jiang and colleagues recently published a comprehensive review of research linking alterations of the gut bacterial biome with IR-associated disorders [58]. They summarized reports of bacterial biome alterations in pre-diabetes, T2DM, non-alcoholic fatty liver disease, and PCOS. A variety of bile acids and other metabolites produced by gut bacteria may affect IR, lipid metabolism, and nutrient absorption (which could include vitamin D). While the details of these biota interactions are beyond the space allowances and scope of our article, suffice it to say that mostly plant-based diets e.g., the Mediterranean diet, are associated with less IR and its associated disorders and a greater diversity of gut bacterial species. The opposite is true of “typical” western diets. Interestingly, a number of interventions used to treat T2DM, pre-diabetes, and obesity e.g., metformin, GLP-1RAs, and bariatric surgery are known to affect the gut biome favorably in terms of insulin sensitivity.

In a 2013 review Barendolts concluded that the combined use of prebiotics and vitamin D was associated with optimization of gut microflora and more normal glucose metabolism in people with either prediabetes or diabetes, particularly if initiated early in the course of the disorder [59].

Kado and colleagues reported that increased diversity of the gut bacterial biota was significantly associated with increased 1-alpha hydroxylation of 25OHD to its active form [60].

A systematic review by Waterhouse et al. lends support to the concept that vitamin D affects the gut bacterial biome, although the specifics of the alteration vary from study to study [61].

Interestingly, gut bacteria conduct steroidogenesis and steroid metabolism, which could potentially exacerbate disorders characterized by hyperandrogenism and hyperestrogenism, e.g., PCOS and CAH [62].

Sacerdote and Bahtiyar reported a patient who had cysticercosis-induced PCOS [37]. Treatment with the selective estrogen receptor antagonist, raloxifene, was associated with remission of PCOS and a marked reduction in cysticercosis burden [63]. In addition, they reported that she had an elevated serum 1,25(OH)₂-vitamin D₃ level which normalized in parallel with the reduction in parasite burden. This indicates that the parasites were directly converting vitamin D into its active form or producing a paracrine secretion inducing surrounding macrophages to do so, as occurs in several granulomatous disorders. This also demonstrated that the biome can manipulate the

hormonal milieu to its advantage and that manipulation of the hormonal milieu can manipulate the biome to the host's advantage.

While we have learned much about the bacterial gut biome from next generation sequencing, it is important to remember that bacteria are only one component of the gut biome, which includes viruses, protozoa, and sometimes macroparasites e.g., *Taenia sp.*, and prions. We have barely scratched the surface in understanding what roles these other organisms may play vis a vis vitamin D and insulin sensitivity.

Learning Points

Concerning T2DM- The essential points about vitamin D were made in the Introduction; a few should be reemphasized:

- Establishing causality of low VDS in terms of incident T2DM risk in humans remains elusive for several reasons: e.g., differences in vitamin D preparations and dosages used, treatment duration, where subjects lie in the spectrum of baseline T2DM risk and VDS, and polymorphisms in VDBP and vitamin D receptors.
- However, a recent reanalysis of data from the D2d study by the study authors using a Cox proportional hazards model showed that there was an interaction of study assignment with intra-study serum 25OHD concentration in forecasting diabetes risk (interaction $P = 0.018$) (The hazard ratio (HR) for diabetes for an increment of 25 nmol/L in intra-study 25OHD concentration was 0.75 (95% CI 0.68-0.82) in people assigned to vitamin D and 0.90 (0.80-1.02) in people assigned to placebo. The HRs for diabetes in people treated with vitamin D who maintained intra-study 25OHD concentrations of 100-124 and ≥ 125 nmol/L were 0.48 (0.29-0.80) and 0.29 (0.17-0.50), respectively, contrasted with people who maintained a concentration of 50-74 nmol/L. In contrast with their original conclusion that vitamin D administration was ineffective in preventing T2DM in people with prediabetes, they now concluded that daily vitamin D intake adequate to achieve and maintain a serum 25OHD level ≥ 100 nmol/L is a promising intervention to lower the risk of T2DM in adults with prediabetes [64].
- Vitamin D analogues +RAAS-inhibitors ameliorate diabetic kidney disease.
- In addition to vitamin D, pro-and pre-biotics combined with a mostly plant-based diet results in a gut bacterial biome associated with a reduction in risk for T2DM and pre-diabetes.

Concerning PCOS-Most published studies report significantly lower serum 25OHD levels in women with PCOS vs controls. Notable exceptions to this trend include the Kim study involving Korean women in whom those with PCOS and controls had similar low VDS.

- Most interventional RCTs reported therapeutic benefits with vitamin D administration in women with PCOS: e.g., improved follicular maturation, menstrual regularity, hyperandrogenemia, and cardiometabolic markers as well as in live birth rates in women undergoing ovarian stimulation. Rashidi et al .reported an at least additive effect of vitamin D +metformin.
- In my clinical experience vitamin D repletion in women with PCOS and low baseline VDS has apparently improved androgen levels and clinical features e.g., acne, alopecia, hirsutism, menstrual irregularity, and conception rates when repletion was achieved and maintained. I have not prescribed vitamin D to women with normal baseline VDS.
- The abundance of vitamin D receptors in the anterior pituitary and ovaries suggests a regulatory role for vitamin D on the hypothalamic-pituitary-ovarian axis.
- The reported lowering of serum prolactin levels with vitamin D administration suggests an additional benefit in the subset of women with both PCOS and sustained or intermittent hyperprolactinemia/macroprolactinemia [54]. It is controversial whether there is a true association between PCOS and hyperprolactinemia, however, dopamine agonist treatment was reported to benefit even normoprolactinemic women with PCOS [65-66]. This may be due to the central IR-reducing effect of dopamine agonists or to suppression of intermittent (undetected) hyperprolactinemia.
- The dietary and vitamin D alterations affecting the gut bacterial biome that help in preventing T2DM are also helpful in PCOS prevention.

Concerning congenital adrenal hyperplasia-

- The presence of IR independently of steroid treatment in people with CAH is well established, but underappreciated.
- Even among those who reported the IR-CAH association, the possibility of treating CAH with IR-reducing interventions, e.g., vitamin D, as in PCOS, is largely unrecognized.
- While there is a dearth of prospective interventional RCTs, every case report and small case series published to date has found clinical and biochemical benefit

associated with IR-reducing interventions (including vitamin D repletion), allowing for successful treatment, free of steroid side effects.

- The demonstration of biochemical worsening of CAH when hypovitaminosis D worsened and was prolonged suggests an epigenetic role for low VDS in CAH expression.
- Normalization of serum 17OHP in 4 women with non-classic 21-hydroxylase deficiency with simvastatin, despite the fact that the statins are associated with a significantly increased risk for incident T2DM, suggests that it is actually the reduction in insulin concentration and inflammation rather than the reduction in IR per se, that ameliorates CAH.

General-There is a signal that vitamin D is more likely beneficial as replacement rather than supplementation.

Disclosures

The author affirms that he has nothing to disclose.

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