RESEARCH ARTICLE

Update on the Role of Adequate Vitamin D Provision for Avoiding Insulin Resistance and its Sequelae [Type 2 Diabetes and Cardiovascular Disease]

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ABSTRACT
Type 2 diabetes prevalence is increasing, reaching ‘pandemic’ proportions globally, and associated with increasing obesity rates. Concomitantly, vitamin D deficiency persists worldwide and is worsened by obesity because it reduces hepatic 25-hydroxylation of vitamin D, which reduces circulating 25(OH)D availability to target tissues; these include islet beta cells, since vitamin D is essential for adequate insulin responses to hyperglycemia. Increased insulin resistance increases type-2 diabetes risks and precedes its development by decades, reflecting changes in hepatic and muscle function that are corrected experimentally by activated hormonal vitamin D [calcitriol]; similarly, abnormal insulin resistance can be corrected in humans by correcting vitamin D deficiency using oral supplementation. Since vitamin D deficiency and inadequacy persist worldwide despite various guidelines on vitamin D intake, the possibility that correcting deficiency would contribute to reducing T2DM risks through beneficial effects on pancreatic islet beta cells and on the metabolic disorders contributing to insulin resistance through vitamin D inadequacy warrants consideration. If this is the case, then ensuring vitamin D adequacy in populations at high risk of Type-2 diabetes would be a valuable adjunct to other measures being taken to reduce that risk such as increased exercise and weight reduction. It would also reduce cardiovascular disease risks, well known to increase with insulin resistance, with or without concomitant Type-2 diabetes. Cardiovascular disease risks themselves can be reduced by adequately correcting deficiency and are lower with higher lifetime circulating 25-hydroxyvitamin D in deficient subjects from Mendelian randomization analysis. This report, therefore, reviews the evidence for increased insulin resistance as a risk factor for Type-2 diabetes, the beneficial effects of correcting vitamin deficiency on insulin resistance, Type-2 diabetes and cardiovascular risks, some basic mechanisms accounting for those benefits, the reasons for the persistence of vitamin D inadequacy globally and how best that problem could be corrected.
1. Background

1.1 vitamin D inadequacy, roles in increasing type 2 diabetes risks.

Vitamin D has been known to be essential for normal insulin secretory responses to glucose for over 40 years, both experimentally and in humans, as has the phenomenon of hormone resistance.1-4 Circulating insulin concentrations increase as insulin sensitivity falls, followed by progressive islet beta cell failure, leading to fasting hyperglycaemia, impaired glucose tolerance and then to type 2 diabetes mellitus (T2DM). Vitamin D repletion is now comparatively rare and T2DM prevalence has increased rapidly, even in the young, becoming a ‘global pandemic’ with ~463 million cases diagnosed by 2019 though undiagnosed cases are also very common.5,6,7

1.2 The discovery of insulin insensitivity [resistance].

Once newly available insulin entered clinical practice from the 1920s it was recognised that insulin was life-saving in those acutely ill while in many patients insulin treatment was neither essential for life nor especially effective for reducing glycaemia. These different responses to insulin treatment of diabetes were described as insulin sensitive or insulin insensitive by Harold Himsworth in the 1930s, a concept taking decades to be accepted. Later classifications used were insulin dependent [IDDM or Type-1DM ] or non-insulin dependent [NIDDM or Type-2DM].8,9,10

1.3. Increasing insulin resistance as a precipitator of T2DM.

Increased insulin resistance is now accepted as a precipitating cause of T2DM, and can be present at least 40 years before T2DM becomes overt while hyperglycaemia can be demonstrated 10-20 years before T2DM can be diagnosed.11,12,13 Rare genetic syndromes that include severe insulin resistance commonly include diabetes, with high CVD risks, but are excluded from this report as no reports linking them to vitamin D were found [as of 7th March 2023]. However, polycystic ovary syndrome [PCOS] includes insulin resistance, often leading to T2DM, is not rare and correcting deficiency of vitamin D in PCOS is reported as reducing insulin resistance and to improve fertility.14

1.4 Might avoiding vitamin D deficiency reduce T2DM risks?

The pertinent question, therefore, is whether ensuring vitamin D repletion across populations could reduce T2DM rates; in turn reducing the massive costs of diabetes to sufferers, and to health services, of the high rates of cardiovascular disease, renal failure, neuropathy, gangrenous amputations and visual loss caused by T2DM.15

2. insulin actions and insulin resistance

2.1 Assessment of insulin resistance

Insulin resistance is assessed variously, by ‘gold standard’ euglycaemic glucose clamp studies, by raised fasting insulin and, most commonly, by Homeostatic model analysis [HOMA] estimation of insulin resistance [HOMA-IR] from fasting and 30-minute blood glucose and insulin values during glucose tolerance tests.16,17

2.2. Insulin efficacy in insulin resistance

Normally, islet beta cell insulin secretion regulates hepatic gluconeogenesis and increases energy provision to tissues like liver, brain, muscle and heart by increasing glucose uptake and regulating hepatic glucose production and glycolysis which contribute to glucose homeostasis.18 In insulin resistance both hepatic glucose and fat synthesis and output increase. However, activated vitamin D [calcitriol] added optimally to hepatocyte cultures, and correcting deficiency in intact animals under insulin resistant conditions, corrects those abnormalities. Calcitriol also reverses evidence of islet beta cell damage in experimental IR [e.g., reducing raised tissue UCP2 content and reactive oxygen species formation].19,20 Replacing vitamin D in deficiency in IR humans, however, takes time to reduce IR. For example, supplementation of vitamin D deficient but normoglycaemic south Asian women took ~6 months and 25(OH)D concentrations that reached at least 80 nmol/l for IR correction.21 In muscle, vitamin D reduces IR by reducing over-production of FOXO1 and through activation of vitamin D receptor driven insulin signaling pathways; for example, through enhancement of IRS-1 and VDR production in muscle tissue 22,23 IR is also well recognised as a risk factor for cardiovascular disease, probably aggravated through metabolic disorders associated with IR and T2DM development.

3. Vitamin D biology

A brief account of the mechanisms by which vitamin D protects against insulin resistance, and hence Type 2 diabetes, and of why so many people are deficient in vitamin D, follows. This is to make the reasons for aiming to reduce vitamin D deficiency rates at the population level clear, because public health measures for avoiding vitamin D deficiency will only improve if those responsible for such measures fully appreciate the need for long-term ViD repletion amongst the measures designed to
reduce T2DM and CVD risks. Vitamin D₃ (cholecalciferol; VitD₃) evolved ~500 million years ago in early unicellular organisms, being protective against damage from high solar irradiation by absorbing damaging UVB.²⁴ Present in most animals, VitD₃ is provided along food chains and often synthesized in skin where it is protective against UVB damage and prevents excessive vitamin D₃ formation.²⁵ Fungi synthesize vitamin D₂ (ergocalciferol) similarly and D₂ is found in small amounts in animals and humans when their diet contains fungal material, for example, it is found naturally in dark chocolate.²⁶ Vitamin D₃ is generally considered more effective than vitamin D₂ in humans and D₂ is not considered specifically in this report, ‘Vitamin D’ implying vitamin D₃ throughout.

Humans obtain D₃ most efficiently from skin synthesis under UVB irradiation of wavelengths around 295-315 nm, from summer and equatorial sunshine.²⁵ Such UVB is only present in sunlight from spring to late summer in temperate climates. Furthermore, increasingly indoor lifestyles, sun avoidance and sunscreen use are reducing skin D₃ synthesis globally. Thus, inadequate D₃ provision is common.²⁷ This situation is aggravated by the low VitD content of most foods.²⁵ Some D₃ is found naturally in dairy products, meat, eggs and in many wild, but not farmed, oily fish but is not enough to meet human needs unless foods are fortified with D₃ and/or adequate VitD supplements are taken regularly.²⁵

### 3.1 Vitamin D activation

Intact D₃ is inactive but activated through two hydroxylations. Firstly, VitD₃ is hydroxylated in the liver to form 25(OH)D, which circulates bound to DBinding proteins and albumen, though small amounts remain unbound.²⁸ Overall circulating 25(OH)D half-life is ~2-3 weeks. 25(OH)D is further 1-alpha-hydroxylated to form 1,25-dihydroxyvitamin D [Calcitriol] in the kidneys to provide the circulating [hormonal] calcitriol that acts to protect bone health. It is also activated, similarly, to form calcitriol in the other target tissues where it has many paracrine, apocrine and intracrine effects relevant to non-skeletal health.²⁹,³⁰

### 3.2 Assessment of vitamin D provision ['status']

25(OH)D having a relatively long circulating half-life, assays measuring serum 25(OH)D are accepted as reflecting VitD 'stores'.²⁵ VitD measurements were firstly made by slow and costly bioassays but Berson & Yalows' 1959 competitive protein binding assays [immunoassays],³¹ allowed measurement of the low concentrations of many circulating hormones and they are widely used to assess serum 25(OH)D concentrations, facilitating studies of disease risks with vitamin D provision [serum 25(OH)D, 'status']. Currently, high-pressure liquid chromatography following by tandem mass spectrometric methodology [HPLC-TMS] assays are thought the most reliable and used as a ‘gold standard’ for laboratory 25(OH)D assay validation, together with international quality control [QC] schemes that improve 25(OH)D assay reliability and reproducibility.³²,³³

### 3.3 How vitamin D acts

The multiple actions of VitD are induced through 3 main mechanisms. Firstly, genetic effects following calcitriol binding to VitD receptors [VDR] that commonly complex with retinol X receptors before binding to vitamin D response elements [VDREs] in the promoter regions of target genes in cell nuclei, of which there are many thousand.³⁴,³⁵ Secondly, RXR:VDR complexes bind to various cell wall receptors and can induce rapid non-genomic effects by opening calcium channels and increasing intracellular calcium which has different effects in different tissues.³⁶ In islet beta cells, calcium activates intracellular endopeptidases, releasing insulin from storage granules, [phase 1 secretion in response to hyperglycaemia]. Phase 2 insulin secretion follows by 20-30 minutes, reflecting slower genetic effects. Thirdly, VitD modulates many epigenetic effects that regulate gene activity without altering their basic DNA structure [through effects on DNA methylation, chromatin histone structure and non-coding RNAs]. These epigenetic effects are important in utero and throughout development.³⁷,³⁸

### 4. Vitamin D deficiency and its avoidance

Vitamin D deficiency [VitDD] is accepted as causal for rickets and osteomalacia, even though one trial has reported that giving large bolus doses in severe nutritional deficiency failed to prevent rickets.³⁹ The serum 25(OH)D values at which risk of rickets and osteomalacia appear have been used to diagnose deficiency in terms of bone health, e.g., <25 nmol/l by the UK Specialist Advisory Committee on Nutrition [SACN], <50 nmol/l by the American Institute of Medicine [IOM] and the European Food Safety Agency [EFSA], though the American Endocrine Society advises >75 nmol/l for optimal bone health.⁴⁰,⁴¹,⁴² Much effort has gone into identifying minimal adult VitD intakes necessary for avoiding ‘deficiency’. Recommendations range from 400 IU/day in the UK to 600 IU/day by the IOM and 400-1000 IU/day by the EFSA.⁴⁰,⁴¹,⁴² IOM calculations of intake aimed to achieve 75 nmol/l in 95% of the population but were made for
achieving 75 nmol/l as a population mean and 6000 IU, not 600 IU, daily would be needed to achieve the stated target 25(OH)D value in 95% of the population.\textsuperscript{43} This miscalculation is well recognised, but IOM advice has not been changed. Since deficiency remains common and 25(OH)D thresholds above 25 nmol/l are needed to achieve various non-skeletal health benefits,\textsuperscript{21,44,45} most intake advice for adult populations needs revision. Furthermore, since VitDD at <25 nmol/l remains common globally despite existing guidelines, such advice must be accompanied by programmes ensuring that advised intakes are met. Intakes up to 4000 IU/day are safe, as is usually mentioned in public health guidance, e.g., from the SACN in the UK.\textsuperscript{40} 10,000 IU/day is also reported as safe. 20,000 IU/day or more of vitamin D is produced by moderate, but safe, sun exposure. Indeed, serum 25(OH)D values of at least 120 nmol/l are recommended by many vitamin D workers since such values are seen in people with outdoor lifestyles providing large sun exposures.\textsuperscript{45} Thus, advice suggesting total adult intakes of up to 6000 IU/day in high-risk individuals should prove generally acceptable.

### 4.1 Problems with very large bolus doses of vitamin D

There is a trend to increased use of large bolus doses of D\textsubscript{3} which raise serum 25(OH)D\textsubscript{3}s rapidly. However, very large bolus doses reduce VitD activation by reducing hepatic 25(OH)D\textsubscript{3} formation and increasing fibroblast growth factor23 [FGF23] secretion which reduces calcitriol synthesis by deactivating the vitamin D-activating 1-alpha-hydroxylase enzyme. Those effects matter since large bolus doses have failed to prevent rickets in a trial in severe deficiency.\textsuperscript{39} Moderate daily doses of D\textsubscript{3} are also more effective than large interval doses for reducing respiratory infection rates.\textsuperscript{46} Thus, public health measures for avoiding VitDD should ensure adequate daily intakes rather than rely on interval bolus supplementation. Fortunately, when correcting deficiency is urgent, calcifediol [25(OH)D\textsubscript{3}] preparations are now available which are fast-acting and do not induce the self-regulatory effects seen with large D\textsubscript{3} boluses.\textsuperscript{47}

### 5. Mechanisms through which vitamin D induces non-skeletal health benefits.

Many mechanisms by which adequate VitD status reduces non-skeletal health risks are well understood, e.g., the reduction of IR and T2DM risks mentioned above. For risk reductions relating to obesity, CVD and hence overall mortality, these mechanisms include reducing inflammation including the remote inflammatory effects of obesity that increase atherosclerotic damage,\textsuperscript{48} along with the well-known reductions in inflammatory processes induced by vitamin D,\textsuperscript{49,50} which are supported by the lower CRP values found with genetically determined increases in D status in insufficiency on non-linear Mendelian randomization analysis.\textsuperscript{51} VitD inhibits matrix-metalloproteinase [MMP]-2/9 secretion in many tissues and macrophages infiltrating arterial plaque secretes MMP2/9 which increases arterial plaque instability.\textsuperscript{52,53} Correcting deficiency would, therefore, be expected to reduce acute thrombotic event risks resulting from plaque disruption, contributing to the reductions in overall and CVD mortality reported from RCTs of supplementation. Reductions in CVD risk are now reported with supplementation and with higher VitD status; that increased vitamin D status, as genetically determined, reduces CVD risks in deficient subjects [from non-linear Mendelian randomization analysis [MRA]], supports the validity and significance of this effect.\textsuperscript{54,55} Cancer risks increase with T2DM and obesity.\textsuperscript{56} Obesity reduces VitD status,\textsuperscript{57} and serum 25(OH)D responses to VitD intake,\textsuperscript{57,58,59} Increases in VitD rates contribute independently to cancer risks, as do increases in T2DM rates, since VitD inhibits many carcinogenic processes and reduces metastatic risks.\textsuperscript{50,61} Such processes will have contributed to the reductions in overall cancer mortality seen with supplementation in the VITAL trial.\textsuperscript{62} However, cancer incidence was only found to be reduced in non-obese subjects - probably because VitD status increases more in slim than obese subjects on comparable supplementation, due to the reduced hepatic 25-hydroxylation seen in obesity.\textsuperscript{57,58,59}

### 6. Assessment of prevalence of vitamin D inadequacy.

Past VitDD prevalence must have been high when rickets was rampant, but only became assessable once 25(OH)D assays were widely available. Since then, it has continued to be common, at 48.6% of boys and 51.4% of girls respectively in a middle eastern country recently, and, when defined by a 25(OH)D < 50 nmol/l, deficiency was present in 30%-99% of adults in the US, India and Iran. Deficiency was found in 48.8% and 51.4% of boys and girls respectively in another middle eastern country.\textsuperscript{63,64} The representative UK Biobank cohort [n ~440,000] showed deficiency in people of White European, Black African and Asian ancestry at 5.9%, 30.8 and 50.8% in spring/summer respectively, and in autumn/winter at 17.5%, 38.5% and 57.2% respectively.\textsuperscript{55}
6.1 Risk factors for adult vitamin D deficiency. The risk factors for adult VitD deficiency [VitDD] include the generally poor dietary provision of VitD and increasing age as outdoor activity falls and skin synthesis and gut absorption become less efficient. Modern lifestyles with increasing indoor work, exercise and leisure activity also increase deficiency risks. Obesity reduces serum 25(OH)D causally [by bi-directional MRA].\textsuperscript{25,26} This is because obesity reduces hepatic 25-hydroxylation, and vitD and 25(OH)D fall with their distribution into the increased fat masses.\textsuperscript{47,48,49} Furthermore, sun avoidance is common in both hot and temperate countries and increasing sunscreen use for skin protection blocks VitD synthesis totally when applied optimally.\textsuperscript{68} Dark skin is a major risk factor since melanin is a natural sunblock, increasing the UVB dosages needed to match VitD production from pale skin. Those on shift work, housebound or living in residential homes, vegans and vegetarians are also well known to be at high-risk. UVB triggering VitD synthesis falls with distance from the equator and none is present between autumn and early summer in temperate climates, making latitude a risk factor.\textsuperscript{25} Overall, chronic deficiency remains common in high-risk groups, globally, except in northern Scandinavian countries that are encouraging supplement usage or where there is an effective food fortification programme, as in Finland.\textsuperscript{69,70}

6.2 Avoidance of vitamin D deficiency. Individuals eating ordinary food can only avoid deficiency if they regularly eat oily sea-fish and have above average summer sun exposure or take adequate VitD supplements and VitDD in adults in most countries is unlikely to be corrected by nationally advised VitD intakes,\textsuperscript{71,40,41,42} a concept supported by the obvious persistence of VitDD despite such guidelines. Public health efforts to avoid VitDD have often failed; for example, the UK ‘Sure Start’ scheme, designed to provide pregnant women on benefits with access to vitD, had very low uptakes until better publicity and increased scheme availability were introduced when maternal vitamin D status increased more than the uptake of the scheme increased.\textsuperscript{72} The UK supplemented fatty spreads from early in world war 2 [WW2] for over ~5 decades, by statute, to match the modest vitamin D content of butter but that statute was abolished ~ten years ago.\textsuperscript{73} UK pregnant and nursing mothers and children under 5 years were supplied with ‘5 welfare foods’ [extra milk, meat, eggs, orange juice and cod-liver-oil] from early in WW2 until 1964, which provided much increased VitD intakes.\textsuperscript{74} Thus schemes designed to provide better provision of vitamin D can be effective.

6.3 Food fortification with vitamin D. Finland’s diet has been improved since the early Karelia ‘experiment’ reduced fat intakes and subsequently reduced CVD rates.\textsuperscript{27} VitDD being common in Finland, a voluntary dairy food fortification programme was started in 2003. Auditing population 25(OH)D concentrations showed inadequate improvement, especially in high-risk groups, after food-fortification was begun and the level of fortification was doubled in 2010 together with the provision of supplementation for high-risk groups, virtually abolishing VitDD in Finland, other than in recent immigrant groups.\textsuperscript{70} Audit of that programme continues and public health records are being kept of the many health problems linked to VitDD.\textsuperscript{75} Hopefully some reductions in non-skeletal disorders linked to VitDD may appear following the 10+ years of adequate VitD provision. However, whether enough of the Finnish population has achieved 25(OH)D levels high enough for this to happen remains to be seen, since, for example, 25(OH)Ds of ≥100 nmol/l were needed to reduce T2DM risks in the D2d trial.\textsuperscript{77} Flour fortification is a cost-effective approach to food fortification suggested for the UK, since flour is a general food-staple.\textsuperscript{76} For multi-ethnic societies this would have to cover all flours and to include gluten free preparations.

7. Potential health benefits of ensuring adequate vitamin D status for reducing rates of type-2 diabetes and cardiovascular disease. Potential health benefits at the population level from ensuring vitamin D adequacy in adults with deficiency can be judged from the data for correcting deficiency in relevant disorders and knowing the prevalence rates of deficiency. For example, calculated risk ratios [RR; 95% CIs] for T2DM risk with supplementation achieving a 25(OH)D of ≥100 nmol/l during years 1-4 of the D2d trial significantly reduced T2DM risks with a RR = 0.48 [95% CI; 0.29-0.8] for achieved 25(OH)Ds of 100-124 nmol/l and a RR = 0.20 [95% CI;0.17-0.5] for achieved 25(OH)Ds of 125 nmol/l or above.\textsuperscript{77} UK-biobank data revealed increased T2DM risks in south Asians and Europeans with vitamin D deficiency but no effect of T2DM on vitamin D status on bi-directional MRA which supports the causality of VitDD for T2DM.\textsuperscript{79} The RR for all-cause mortality over 14 years in UK-Biobank subjects was increased in those with 25(OH)Ds of 25 nmol/l as compared to those with values of 50 nmol/l, RR = 1.25 [95%CI;1.16-1.55] in White
Where deficiency \[25(OH)D < 25 \text{ nmol/l}\] is present at 20%, the overall % reductions in T2DM could, potentially, reach between 10-16%, depending on the prevalence of deficiency. For all-cause mortality, the expected reductions if population 25(OH)Ds could be brought up to at least 40 nmol/l could, potentially, reach 25% in those with proven deficiency. Estimated dose-response relationships for vitamin D with CVD events and all-cause mortality using a combination of observational and MRA data has suggested overall population-wide reductions of \(~4.4\%\) in those disorders if serum 25(OH)D concentrations in deficiency were to be raised to 40-50 nmol/l.\(^8\)

Additionally, in all those disorders, in the UK at least, such risk reductions would be expected to be greatest in dark-skinned minority groups because their deficiency rates are highest but vitamin D intakes would need to be 2-3 times as large in overweight and obese people than in those who are slim.\(^{57,58}\)

### 8. Conclusions

Available evidence from studies of the effects of correction of vitamin D status on insulin resistance suggest that avoiding vitamin D deficiency at the population level over time should reduce T2DM, CVD and all-cause mortality rates significantly, and provide a useful adjunct to measures already used to reduce T2DM risks such as weight control and increased physical activity. Ensuring vitamin D repletion through population level measures such as food fortification should prove highly cost-effective. The potential benefits of avoiding deficiency may become demonstrable in Finland where deficiency was virtually abolished over ten years ago which may be long enough for the benefits of long-term reductions in IR to become apparent. However, this postulate depends on Finnish audits of vitamin D status showing that enough of the 25(OH)D values achieved in their adult population are reaching the levels needed for reductions in T2DM rates to be likely.
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