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Can Vitamin D Supplementation Reduce Insulin Resistance and Hence the Risks of Type 2 Diabetes?

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The question of whether or not correction of vitamin D deficiency might reduce the risks of later type 2 diabetes mellitus (T2DM) has been under debate for many decades. The necessity of vitamin D for normal insulin secretion was first identified experimentally in the 1980s [1,2]. In view of the long run-in period during which increased insulin resistance develops, eventually becoming associated with the development of many or all of the features of the metabolic syndrome, it is not surprising that once all the features of the metabolic syndrome were seen to be associated with vitamin D deficiency/insufficiency [3] reports began to appear looking for suggestive associations and later for reduction in T2DM risks with vitamin D supplementation since vitamin D deficiency and insufficiency remain so common, globally [4,5].

Several prospective studies have shown lower baseline vitamin D status to predict higher T2DM risks, dose-wise, in various population groups. For example, serum 25(OH) D concentrations >30 ng/ml (>75 nmol/l) at baseline in normoglycemic subjects were associated 12 years later with a HR of 0.31(0.14-0.70) vs. the risks of pre-diabetes or T2DM in subjects with baseline 25(OH)D values <30 ng/ml (<75 nmol/l) [6] with similar findings for reductions in the risks associated with both the metabolic syndrome and T2DM after ten years of follow-up in other cohorts [7,8]. Increases in insulin resistance also predict increased risks of both T2DM and of cardiovascular disease and usually before any increases in glycaemia, as is further discussed below and as is also seen when beta cell failure develops rapidly in younger subjects with T2DM [9,10].

The finding that baseline vitamin D status can predict health risks developing up to ten years later may be regarded as surprising since vitamin D status varies with season and with many lifestyle factors [11]. However, a study of measurements of serum 25(OH)D values made at baseline and again 14 years later showed that the baseline values were predictive of 50% of the 14-year values [12]. This data suggests a reasonable degree of consistency in lifestyle factors affecting vitamin D status in individuals over the years; in addition, the predictive link between baseline and follow-up values would likely be greater after ten than after 14 years.

A huge step forward in the understanding of what causes T2DM, as compared to T1DM, came from Harold Himsworth who in 1939 gave the Goulstonian lectures on 'The mechanism of Diabetes Mellitus' at the Royal College of Physicians (London) in London, proposing that T2DM reflected "*a diminished ability of the tissue to utilize glucose*" due to an "*insensitivity to insulin*" and not just from a lack of insulin, "*though both factors may operate together*" [13-16]. This appreciation of the pathophysiology of T2DM was repeated in another formal presentation to the RCP(Lond) in 1949 but only accepted as the underlying problem in T2DM by UK national bodies in 1979, 40 years after his original insight-full observations had been made known [17,18]. The combination of increased insulin resistance with increased risks of later cardiovascular disease, of T2DM or both, as well as with abnormalities in each of the variables used to diagnose metabolic syndrome which first became known as the 'Insulin resistance Syndrome' or, as termed by Reaven, 'Syndrome X'. However, since the 1980s it has been best known as the 'Metabolic Syndrome' [19,20].

Reductions in abnormally increased insulin resistance

(IR) with correction of vitamin D deficiency have been reported in normo-glycaemic south Asians with vitamin D deficiency [21], but only once serum 25(OH)D values had reached 80 nmol/l or above, not after three, but after six months of supplementation at 4000 IU/day. IR was also reduced once serum 25(OH)D values had been raised to ~75 nmol/l in a trial of weight loss ± vitamin D supplementation in obesity, while no change in IR was found in the placebo supplemented arm of the trial, despite the weight loss in the controls [22]. Mechanisms of this beneficial effect may include the reductions of hepatic lipid synthesis and in hepatic glucose output induced by activated hormonal vitamin D (calcitriol) in hepatocyte cultures and in intact liver, *ex-vivo*, under insulin resistant conditions experimentally and from the effects of calcitriol on liver and skeletal muscle [23-26].

Supplementation has been reported in a meta-analysis of 28 earlier trials to have no overall benefits for T2DM risk reduction, insulin resistance or fasting glycemia, but subgroup analyses using stratified data revealed that there were significant reductions in fasting blood glucose in subjects with a BMI <25 or whose 25(OH)D had been <30 ng/ml at baseline; there was also significant reduction in insulin resistance in subjects achieving a 25(OH)D of >30 ng/ml (>75 nmol/l). Subgroup analysis also revealed that T2DM risk was significantly reduced by 16%-18% with doses of vitamin D >2000 IU/day when vitamin D was given without calcium, in pre-diabetics and in overweight (but not obese) subjects [27]. In supplementation of those with T2DM a meta-analysis of 19 RCTs showed significant reductions in insulin resistance, and also in HbA1c, following vitamin D supplementation [HR -0.75(-0.97-0.53)] [28].

These earlier findings are further supported by data from the recent report of Niroomand et al. [29] of a trial of vitamin D supplementation that showed reduced insulin resistance (HOMA-IR) and a 25% reduced risk of overt T2DM after 6 months supplementation, though without overall reductions in fasting or 2-hour OGTT glycaemia. These findings mean that only some subjects can have benefitted from supplementation by reduction in their risk of T2DM. That lack of overall benefit was unlikely to have been due to failure of serum 25(OH)D to increase to levels regarded as 'adequate' as currently advised for bone health, that is to 25(OH)D concentrations of at least 50 nmol/l (20 ng/ml), as defined by the US Institute of Medicine [30], since mean 25(OH)D rose with supplementation to 36 ng/ml (98 nmol/l) vs. 16 ng/ml (40 nmoll/l) in the controls. Thus, there must be additional reasons for this finding. The period of increased insulin resistance preceding overt T2DM may be as long as 10-20 years and overt T2DM is well known to develop only with the progressive reductions in insulin secretory capacity that develop over time. Thus, populations with pre-diabetes studied over periods as short as six months must have contained subjects at different stages of progression of the severity of insulin resistance and of damaging changes in beta cells, whether due to their postulated de-differentiation or to progressive beta cell loss [31,32]. Thus, a six-month period of supplementation would only be likely to be maximally beneficial for those in the relatively early stages of beta cell damage. This view is supported by an observational Japanese study reporting on 27,000 subjects whose average age at baseline was 49 years old, followed between 2005 to 2016, that showed that even minor (though statistically significant) increases in baseline glycemia were clearly associated with increased risks of incident pre-diabetes or overt T2DM up to 20 years later. For example, significant increases in fasting blood glucose were seen (mean 101.5 mg/dL vs 94.5 mg/dL) ten years before T2DM diagnosis and an increase to a mean of 110 mg/dL vs 94 mg/dL was seen in subjects progressing to overt T2DM one year later. Thus, significant increases in glycemia were present more than ten years before T2DM developed and this abnormality progressed over time [33].

The Whitehall occupational health study of South Asian and White individuals set up in 1985 in subjects recruited at the ages of 35-55 years old has reported on the trajectories of glycaemia, insulin sensitivity and insulin secretion over the 12 years from 1991 to 2013 in 8815 subjects with OGTT data over that period. These subjects were screened 5 yearly and the date analysed for best-fit models of the trajectories of the variables measured. It was found in this study that insulin sensitivity was already falling in both ethnic groups ten years before T2DM diagnosis and that it fell more steeply in the South Asian sub group than in Whites; increases in glycaemia, however, only began later, from about 6-8 years before T2DM diagnosis [34].

Trials of vitamin D supplementation in those with increased insulin resistance and vitamin D deficiency should, therefore, show maximum benefit if they are begun before glucose intolerance develops and continued over 5-10 years, though such long studies are rarely feasible. In support of this view, the risk of T2DM in adulthood was found to be inversely associated with baseline vitamin D status 31 years before T2DM diagnosis in 2300 participants who had been 3-18 years old at baseline [35]. Higher status at baseline and larger increases in serum 25(OH)D values at follow-up were followed by reduced risks of T2DM, the HR(95% CI) values found being 0.73(0.57-0.95) and 0.63(0.51-0.84) respectively for each SD increment in the baseline and achieved 25(OH) values. There were also dose-dependent negative associations of risk with increasing quartiles of baseline 25(OH)D values in young people [35].

Clearly, 20-30-year long RCTs will never be performed,

for ethical reasons as well as because of the inherent problems of cost, compliance and feasibility. It will be of great interest, therefore, to see whether the reported plateau in the incidence of childhood T1DM in Finland that began three years after the virtual abolition of deficiency population-wide by their programme of voluntary vitamin D food fortification [36] will be followed by reductions in the risk of overt T2DM at the population level, which can be expected to be picked up in the planned long-term surveillance of chronic health problems in Finland [37]. Any such reductions could be expected to begin between the years 2020-2030 which will be between ten and twenty years after the virtual abolition of vitamin D deficiency in Finland was achieved by their programme of food fortification where manufacturers have been adding vitamin D3 voluntarily to milks and to fatty spreads since 2003, with a doubling of the amounts of vitamin D3 added to those foods from 2010, after which vitamin D deficiency was virtually abolished, as was shown on audit. Furthermore, this improvement was shown to have been achieved in a representative sample of the 60% of the population that were not using personal vitamin D supplementation [38].

In addition, since comparatively large increases in vitamin D status have been found necessary, raising serum 25(OH)D concentrations up to between 80-120 nmol/l for up to 6 months, before reductions in insulin resistance were demonstrable in humans [21,22] the data from RCTs should be examined for T2DM incidence rates in initially normo-glycaemic subjects who had increased insulin resistance at baseline in association with baseline vitamin D deficiency and where deficiency is adequately corrected by supplementation for at least 6 months and ideally for 5-10 years. Any such study that could be done and that produced beneficial outcomes would support the view that the general introduction of vitamin D food fortification, plus the encouragement of self-supplementation (especially by people in high risk groups as is done in Finland) should reduce the incidence of increased insulin resistance and its sequelae with the reductions in vitamin D deficiency. Furthermore, the reductions in the risks of increased insulin resistance [39] should reduce the increases in mortality rates seen with these problems [40], through reductions in cardiovascular disease as already mentioned, and should also lead to reductions in the incidence rates of the debilitating and life-changing complications that are recognised as being associated with overt T2DM [41].

It is encouraging to note that adequate supplementation to correct deficiency could also be expected to lead to reductions in the health risks associated with obesity. The severity of obesity is commonly associated inversely with vitamin D status as assessed by serum 25(OH)D concentration, whether due to dilution of 25(OH)D into the excess fat or to the suppression of the vitamin D 25(OH) ase by obesity, as recently reported experimentally, or both [42,43]; an effect that could well aggravate the many and serious health risks that are well known to be associated with obesity such as increases in early cardiovascular disease, type 2 diabetes and of many types of cancer [44].

Non-alcoholic fatty liver disease (NAFLD), now considered part of the metabolic syndrome, is also reported to be associated with reduced vitamin D status [45]. This lowering in serum 25(OH)D content, even if not aggravating the severity of NAFLD itself, may aggravate the associated health risks of the commonly associated obesity and might also increase the risks of the serious complications of NAFLD. This association may well be due to reverse confounding since the liver is the main site of 25-hydroxylation of intact vitamin, but, whether or not this is the case, the reduced 25(OH)D availability could aggravate the liver damage, providing a potential vicious circle worsening the liver disease. It might also increase the risks of the complications of both the NAFDL and of the commonly associated obesity.

Correction of vitamin D deficiency reduces many of the health risks known to be increased in obesity, as is being shown in current RCT analyses using 'individual participant data' (IPD) as discussed below. However, the dosages needed to achieve repletion in obesity are thought to be 2-3 times higher than in those who are not obese and, since RCTs in obesity have not provided such increased doses this inference has not yet been confirmed directly [42,46].

Supplementation of populations or RCT 'treatment' arms may not reduce health risks significantly overall since many people, in many populations, especially in wealthier countries will not be deficient [47,48]. However, the provision of vitamin D in populations where deficiency remains common, and in amounts adequate to reduce deficiency rates, can now be expected to reduce many health risks. This is because of the increasing acceptance of the fact that findings for analysis of health outcomes in initially deficient subjects can often reveal striking health benefits of vitamin D supplementation. This methodology was first used by Martineau et al. in 2017 in a reanalysis of data from a meta-analysis of 25 RCTs for reduction of upper respiratory tract infection rates which had shown no meaningful benefits [49]. This approach revealed that URTI rates were significantly reduced by 70% [HR=0.30(95% CIs 0.17-0.53] when the data were re-examined for this outcome in the subjects confirmed as having been deficient at baseline following retrieval of individual participant data, including baseline serum 25(OH)D values, in almost 11,000 subjects. This method of ensuring that health outcomes are assessed specifically in those subjects who were deficient at baseline [49] is now being widely used and has already demonstrated reductions in other health

risks, including reductions in blood pressure and in type 2 diabetes risks, [29,50].

Though mortality risks have been found to be reduced overall in several meta-analysis of trials of supplementation, the findings have not been regarded as conclusive, for example in the report from Rejnmark et al. in 2017. It was noted, however, that the trial data used in such meta-analyses "*cannot be expected to prove potential effects of supplementation with vitamin D, if the trials forming the basis for the MAs have not been performed in populations with low 25OHD levels*", a view also held by others [51-53]. Now that this aspect of RCT design is being better appreciated it is encouraging to note that sub-group analyses from RCT data previously thought not to provide any support for health benefits of vitamin D supplementation are now revealing significant benefits in deficient subjects. However, insulin resistance, which has a higher serum 25(OH)D threshold for benefit (>/-80 nmol/l) than that for bone health (>50 nmol/l), is an exception to this view since it has also been reduced by supplementation of subjects with baseline 25(OH)D values >30 ng/ml (>75 nmol/l) in a further review and meta-analysis [SMD for HOMA-IR = -0.49(-0.90 to -0.07)] [27].

The problems reducing the ability of RCTs of vitamin D supplementation to detect any reductions in T2DM risks and also their ability to provide definitive answers on the problems of causation continue to include major confounding from the fact that few RCTs in this, or indeed in any other area, have as yet specifically recruited people with inadequate vitamin D status, so that many of the subjects studied will have been replete. As an example, 56.8% of those sampled at baseline in the VITAL study were replete by IOM standards. Since being replete reduces, and can abolish, biological responses to any nutrient, as already discussed, the presence of a large proportion of replete subjects in any RCT of vitamin D will reduce the chances of finding significant benefits from supplementation overall. Similarly, if the supplemental doses given are too small to raise the serum 25(OH)D onto the steep part of the standard sigmoid dose response curves seen for any nutrient, then another tranche of the subjects studied cannot be expected to benefit from supplementation either [54-56]. These problems reduce the value of many RCTs of vitamin D but there are many other factors in the design of trials of supplemental vitamin D that also reduce their ability to assess health outcomes, explaining why the use of IPD for analyses of health outcomes in subjects with initial deficiency is proving so valuable. These factors include unknown variations in intakes of dietary or supplemental vitamin D, in compliance with supplementation, in genetic factors affecting the vitamin D axis, in the intakes of interacting nutrients and, importantly, in the thresholds of serum 25(OH)D necessary for achieving different health benefits [49,57-60]. These further confounders of RCTs of vitamin D would probably have been operative in the study by Niroomand et al. [29]. However, the fact that the population group studied by those authors is known to have an unusually high prevalence of vitamin D deficiency/insufficiency will have increased the proportion of subjects likely to demonstrate biological responses to the supplementation given and this may must have outweighed such potential confounding [61]. Indeed, the fact that the response was so good for insulin resistance, and that IR has also been reduced in those with established T2DM and is itself considered to be an important risk factor in the pathogenesis of cardiovascular disease [62], suggests that that increased insulin resistance is more responsive to restoration of vitamin D status than is islet beta cell dysfunction and might be more important in reduction in T2DM risks than are the effects reducing islet beta cell damage.

The evidence already discussed suggests that correction of vitamin D deficiency can reduce abnormally raised insulin resistance, both before and during the development of overt dysglycaemia or T2DM itself and which should also reduce the increased cardiovascular risks seen with these disorders as well as that of cardiovascular disease without dysglycaemia. The reductions in IR by vitamin D_3 appear to be induced through modulation of abnormal cellular function in liver, muscle and beta cells. Taken together with the protective effects reported for calcitriol on beta cell function, the benefits of life-long vitamin D repletion for reduction of insulin resistance and its sequelae should be considerable. Thus, the correction of deficiency at the population level by appropriate food fortification could be expected to improve the public health, while also contributing to bone health, whatever its benefits for other non-skeletal disorders may, or may not, prove to be.

Food fortification clearly ensures improved daily intakes which is the optimal way to take supplements and avoids the potential dangers of long-interval supplementation with large doses which can worsen bone health and increase fracture rates, possibly through excessive suppression of parathyroid hormone secretion [63,64]. Furthermore, food fortification provides moderate increases in daily intakes at the individual level and has not been reported to be associated with any evidence of increased risk of any of adverse effects of vitamin D such as hypercalcemia, renal stones or increased fracture rates in Finland [38]. Of interest here is the previously mentioned report showing that by 3 years after the Finnish food fortification programme had been shown to be very effective the relentlessly increasing incidence rates of childhood type 1 diabetes that had reported over many decades had plateaued, a finding in line with the natural history of T1DM development [36,65].

A recent study of various approaches for avoidance of

vitamin D deficiency at the population level in the UK has reported that vitamin D fortification of flour plus free supplementation for those in especially high-risk groups would be a cost-effective approach to the abolition of vitamin D deficiency. It is to be hoped that similar approaches to dealing with vitamin D inadequacy can be developed in many countries where vitamin D inadequacy is endemic [66].

Summary

Re-assessments of RCT data for health benefits of vitamin D supplementation in deficiency, often using 'individual participant data' retrieved from earlier studies, are now demonstrating health benefits in many areas, including reductions in insulin resistance throughout the years of dysglycaemia that precede the development of overt T2DM and in T2DM itself as well as in blood pressure and mortality and these findings are supported by mechanistic evidence. Such evidence suggests that the abolition of deficiency by modest increases in daily vitamin D intakes (as could be provided safely by cost-effective food fortification) can be expected to reduce the health risks associated with increased insulin resistance, including those of atherosclerotic vascular disease, of T2DM and its sequelae, and of some common types of cancer.

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