# Vitamin D Supplementation, Insulin Resistance, and Cardiovascular Risk Factors: Who are Likely to Benefit the Most?

Varshney *et al.* in their double-blinded randomized controlled trial (RCT) suggested that "high-dose vitamin D supplementation" in vitamin D deficient obese children and adolescents and young adults over 12 months was not associated with meaningful changes in insulin resistance, inflammatory cytokines, and other surrogate measures of cardiovascular risk.[1] However, the treatment protocol used for correcting vitamin D deficiency in that study is not commonly used in clinical practice (as per recommendations by different international guidelines like that from the Indian

Academy of Pediatrics), and is definitely not "high-dose".[2] This is because the authors have used cholecalciferol at dose of 60,000 IU fortnightly (120,000 IU/month) for treating severe vitamin D deficiency (8.36 ± 5.45 ng/mL) which is lower than the standard recommendations of 60,000 IU cholecalciferol weekly for at least 6 weeks, and thereafter a maintenance dose of 60,000 IU monthly for preventing recurrence of vitamin D deficiency.[2] Hence, it is not surprising that vitamin D sufficiency was not obtained in the treatment group at the end of the study (26.89 ± 12.23 ng/mL).[1] Only 41.2% of children in the intervention group had serum 25OHD >30 ng/mL at the end of the study.[1] Vitamin D is a fat-soluble vitamin, sequestrated in the adipose tissue, hence vitamin D deficiency is more common and more severe in obese individuals, who also require higher doses for optimal correction of vitamin D deficiency.[3-5]

Studies have consistently demonstrated that the non-bone mineral effects of vitamin D (pleiotropic benefits on cardiovascular system, glucose metabolism, nervous system, immune system, and cancers) are apparent at higher serum 25-hydroxy-vitamin D (25OHD) levels >30 ng/mL in contrast to >20 ng/mL which is considered to be sufficient to prevent adverse bone mineral outcomes.[6-8] Hence, it is likely that the authors did not document any meaningful impact of vitamin D supplementation on insulin resistance and CV risk factors, cause the majority of the children in the treatment group never attained vitamin D sufficiency (25OHD > 30 ng/mL) at the end of the study.

The D2d study, the largest blinded RCT published till date on impact of vitamin D on insulin resistance and prevention of prediabetes to diabetes progression showed that although there were no overall benefits after 2.5 years of vitamin D supplementation in people living with prediabetes who had a mean serum levels of vitamin D of 27 ng/mL at the start of the study.[9] However, subgroup analysis revealed that in a small cohort of 103 prediabetes individuals who had the most severe vitamin D deficiency (25OHD <12 ng/mL), vitamin D supplementation, and ensuring vitamin D sufficiency (25OHD >30 ng/mL) significantly reduced the hazard ratios of prediabetes progression to diabetes to 0.32 (95% CI 0.81–0.80) which is much better than the overall study rates of 0.92 (95% CI 0.78–1.08).[9] Dutta *et al*. demonstrated that vitamin D supplementation resulting in correction of vitamin D deficiency (25OHD levels improved from 17.04 ± 7.66 ng/mL to 35.47 ± 10.1 ng/mL) resulted in decreased prediabetes progression to diabetes and its increased reversal to normoglycemia, along with beneficial impact on insulin resistance and inflammatory cytokines, in a cohort of individuals from eastern India.[10] Another study from Kashmir showed similar results of the beneficial impact of vitamin D supplementation on reducing progression of prediabetes to diabetes with a reduction in fasting glucose, 2-hour plasma glucose, and HbA1c over a period of 1-year follow-up.[11]

The problem is that with rampant, unmonitored vitamin D supplementation (nutraceuticals; without medical supervision) both in India and the western world, which is, unfortunately, increasing the occurrence of vitamin D intoxication; the prevalence of severe vitamin D deficiency in the general population has gone down over the last few decades.[12]

It is very likely that these people who are living with the most severe form of vitamin D deficiency, are expected to get the maximal bone mineral and pleiotropic benefits of vitamin D supplementation once we ensure vitamin D sufficiency (25OHD >30 ng/mL). Therefore, further RCTs evaluating the pleiotropic benefits of vitamin D should primarily focus on them. Vitamin D is definitely not a panacea, and unmonitored prolonged vitamin D supplementation using supraphysiologic doses, especially parental, should be strongly discouraged.

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## Conflicts of interest

There are no conflicts of interest.

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