VITAMIN D
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Circulating levels of vitamin D and risk of developing type 2 diabetes mellitus: is there a link?

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Diabetes mellitus affects more than 500 million people worldwide and its prevalence, especially type 2 diabetes, has been steadily increasing in recent decades (with an estimated global increase of around 50 per cent in 2045). Globally, deaths due to diabetes and its chronic complications in 2019 are estimated to be around 6 million [1]. Impaired fasting blood glucose and impaired glucose tolerance describe prediabetic conditions. These two conditions, both individually and in combination, are also very frequent worldwide (affecting approximately 7-10% of the global population) and represent not only risk factors for the development of type 2 diabetes mellitus, but also risk factors associated with the development of long-term vascular and kidney function complications [1]. In the absence of effective therapeutic strategies (which are mainly based on lifestyle changes), approximately 5-10% of the population with prediabetes progresses to type 2 diabetes each year.

Vitamin D deficiency/insufficiency has been associated with the coexistence of multiple extra-skeletal chronic diseases (including obesity, cardiovascular disease, certain forms of neoplasia, diabetes and nonalcoholic fatty liver disease (NAFLD)), suggesting the possibility that vitamin D may have multiple beneficial pleiotropic effects at the extra-skeletal level due to the ubiquitous distribution of its specific receptor [2-4]. Vitamin D, in fact, has intranuclear receptors that are expressed on many cells and tissues, including pancreatic beta cells, and thus appears to play a role in glucose homeostasis [2,5,6]. Observational studies have shown an association between low serum vitamin D levels and the presence of type 2 diabetes. Although some intervention studies have suggested that vitamin D supplementation may exert a potential beneficial effect on blood sugar control and the degree of insulin resistance, large-scale works and some meta-analyses of randomised clinical trials have reported conflicting data [7]. For instance, in the randomised client trial D2d, which enrolled approximately 2,400 adult subjects with prediabetes, regardless of their basal vitamin status, oral supplementation with vitamin D_3 for 24 months did not reduce the risk of developing diabetes compared to placebo [8]. In contrast, a recent meta-analysis of 4.190 participants, which included individual data from three large randomised clinical trials (including the D2d trial), showed that vitamin D supplementation in subjects with prediabetes (in particular, in subjects who maintained circulating 25(OH)D values ≥ 125 nmol/L [≥ 50 ng/ mL] during the trial compared to those with 25(OH)D values between 50 and 74 nmol/L) was effective in reducing the risk of developing type 2 diabetes by approximately 15% over ~3 years of treatment [9]. However, this observation is not necessarily translatable to the general adult population with normal fasting blood sugar. In particular, there are currently few epidemiological studies in the literature conducted in the general adult population that have assessed the risk of developing type 2 diabetes mellitus within the entire spectrum of carbohydrate tolerance (i.e. in the presence of normal blood sugar levels and forms of prediabetes, which include impaired fasting blood sugar levels and reduced carbohydrate tolerance). Furthermore, it is still not entirely clear whether genetic variants of the vitamin D receptor (VDR), which is expressed in multiple tissues, are able to modulate the association between vitamin D status and long-term risk of developing diabetes.

A recent prospective cohort study, which was published in April 2024 in the *Journal of Clinical Endocrinology & Metabolism* by Fu et al. [10], tried to answer these questions. To do this, the authors used data from a

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Conflict of interest
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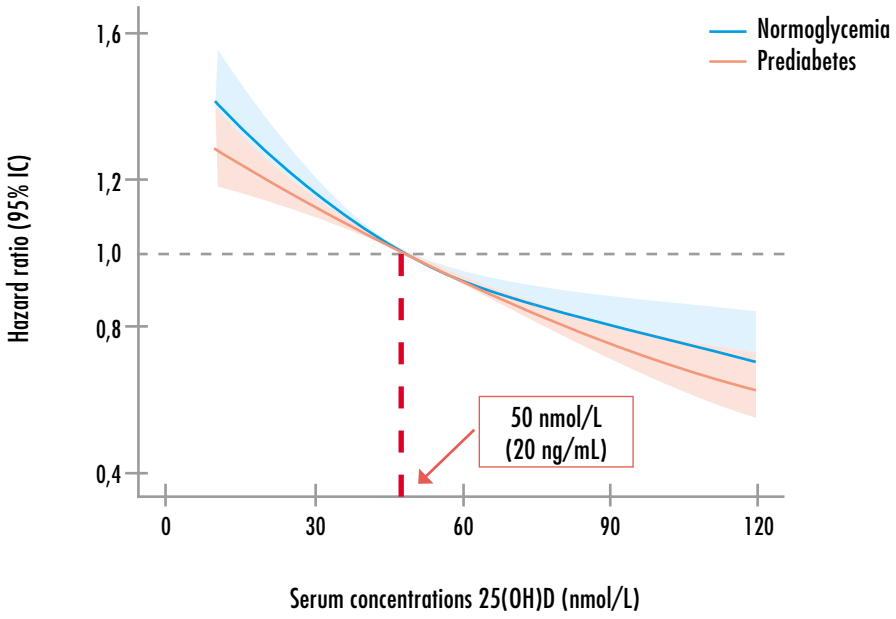

FIGURE 1.
Dose-response type relationship between circulating 25(OH)D levels and risk of developing type 2 diabetes mellitus during follow-up (median of approximately 14 years) in subjects with normal glucose tolerance and subjects with prediabetes at baseline. In both subject groups, the risk of diabetes was progressively reduced in subjects who had 25(OH)D values ≥ 50 nmol/L (≥ 20 ng/mL) at baseline. On the y-axis, data are expressed as hazard ratios and 95% confidence intervals (95% CI, represented as shaded areas in blue and red) after statistical adjustment for possible confounding variables (taken from Fu et al., 2024, mod.) [10].

large observational cohort study, the *UK Biobank database*, which recruited over 500,000 British adult subjects aged 40-69 years between 2006 and 2010. Subjects who had diabetes at baseline (based on their clinical history and/or HbA1c levels) and those without serum 25(OH)D dosage and measurement of four specific VDR genetic polymorphisms (rs7975232 *ApaI*; rs1544410 *BsmI*; rs2228570 *FokI*; rs731236 *TaqI*) were excluded from the study. Information regarding the diagnosis of diabetes during the follow-up period was obtained from the analysis of hospital admission records and death records.
In the study by Fu et. [10] Thus, a total of 379,699 adult individuals without diabetes at baseline (average age 56 years, 54% women) were included; 86% of these subjects had normal glucose tolerance (defined as HbA1c < 5.7%), while the remaining 14% (n = 53,886) had prediabetes at baseline (defined as HbA1c between 5.7% and 6.5%). Participants with normal glucose tolerance at baseline had a mean of 25(OH)D of 48 nmol/L (IQR: 33.5-63.4 nmol/L), while those with pre-diabetes had a mean of 25(OH)D of 45 nmol/L (IQR: 30.9-60.3 nmol/L). Overall, in the entire study cohort 53.4% of the subjects had circulating 25(OH)D values < 50 nmol/L. During the follow-up of the study (median 14 years), 6,315 (1.9%) normal blood sugar level subjects and 9,085 (16.9%) subjects with prediabetes developed type 2 diabetes mellitus.
When study participants were divided according to their circulating 25(OH)D values at baseline in accordance with the cutoffs proposed by the *Endocrine Society* [25(OH)D < 25, 25-49.9, 50-74.9 and ≥ 75 nmol/L], the authors observed a significant association between higher circulating levels of 25(OH)D and reduced risk of developing type 2 diabetes. In particular, compared to subjects who had 25(OH)D levels < 25 nmol/L, subjects with normal blood sugar levels and 25(OH)D values ≥ 75 nmol/L at baseline had a significantly reduced risk of developing type 2 diabetes (hazard ratio: 0.62, 95% CI: 0.56-0.70); similarly, compared with subjects who had 25(OH)D levels < 25 nmol/L, subjects with prediabetes and 25(OH)D values ≥ 75 nmol/L at baseline had a significantly reduced risk of developing diabetes (hazard ratio: 0.64, 95% CI: 0.58-0.70). These data remained significant even after statistical adjustment for gender, age, race, obesity, physical activity, economic status, use of medication for dyslipidemia and hypertension, use of vitamin D supplements, and multiple other possible confounding factors. The results remained significant even when cases of diabetes occurring in the first two years of follow-up of the study were excluded from the statistical analysis. The authors observed that there was a reverse, linear relationship between levels of 25(OH)D and risk of developing diabetes in subjects with prediabetes, whereas this relationship was significant but not linear (but inverse polynomial) in subjects with normal HbA_{1c} values at baseline. For each increment of 10 nmol/L in the circulating values of 25(OH)D at baseline, there was a 7% decrease in the risk of developing diabetes. Furthermore, both in subjects with normal glucose tolerance and in those with prediabetes at baseline the risk of developing diabetes during follow-up was progressively reduced in subjects who had 25(OH)D values ≥ 50 nmol/L (Fig. 1). The authors also reported a statistically significant interaction between 25(OH)D levels and the presence of genetic polymorphisms of the VDR in subjects with prediabetes (but not in those with normal blood sugar levels at baseline); in these subjects, the protective effect of elevated 25(OH)D levels on the risk of developing diabetes was greater in subjects carrying the T allele (rs1544410) of the *BsmI* gene (TT allele carriers: hazard ratio: 0.53, 95% CI: 0.38-0.73; CT alleles: hazard ratio: 0.65, 95% CI 0.55-0.77; CC alleles: hazard ratio: 0.75, 95% CI: 0.61-0.91). Finally, in a statistical mediation analysis, the authors also demonstrated that plasma lipids, in particular plasma triglyceride levels, mediate a significant part of the association between 25(OH)D levels and risk of incident diabetes, both in subjects with normal glucose tolerance (26 per cent) and in those with prediabetes (34 %) at baseline. In particular, if an individual had both low 25(OH)D levels and high circulating levels of triglycerides, his risk of developing di-

abetes during follow-up was much higher than in subjects who only had an isolated alteration [10].

The main strengths of this cohort study are its prospective design, the large number of samples examined (about 380,000 subjects), the length of follow-up (about 14 years), the statistical adjustment for common risk factors and multiple confounding factors. The main limitations of the study include the observational design of the study (in fact, it should be remembered that this is not a study of supplementation/pharmacological intervention with vitamin D and, therefore, the presence of a significant association between 25(OH)D and the risk of diabetes does not automatically mean that there is causality!), the lack of measurement of circulating 25(OH)D levels, the inclusion of British subjects aged between 40 and 69 years and predominantly Caucasian, the lack of measurement of fasting blood glucose at baseline (having available only the HbA1C values) and the fact that the diagnosis of incident diabetes during the follow-up period was based on the analysis of medical records of hospital admissions and death records [10].

Therefore, the results of this British population study (with subjects aged between 40 and 69 years) document that high circulating 25(OH)D levels at baseline are significantly associated with a reduced risk of developing type 2 diabetes over an average follow-up period of approximately 14 years, both in subjects with normal glucose tolerance and in those with prediabetes at baseline. In this cohort of subjects, the serum vitamin D level where possible protective effects on the risk of developing type 2 diabetes began to be observed was ≥ 50 nmol/L (≥ 20 ng/mL). In subjects with prediabetes, the association between high 25(OH)D levels and reduced risk of diabetes was also modified by the presence of genetic variants of the VDR (rs1544410) of the *BsmI* gene. From the data of this study, it can finally be hypothesised that the improvement of the lipid profile (in particular the reduction of plasma triglyceride levels) may help to explain at least part of the protective effect of 25(OH)D levels on the risk of developing type 2 diabetes mellitus [10].

In conclusion, the results of this large prospective cohort study (using the *UK Biobank database*) provide further significant support for the possibility that adequate circulating levels of vitamin D may have beneficial effects on the risk of developing type 2 diabetes mellitus in the general adult population.

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