Vitamin D supplementation improves insulin resistance in type 2 diabetes subjects in Lagos, Nigeria

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Abstract

Type 2 diabetes is a disease caused by both insulin resistance and an insulin secretory defect. Reports suggest that vitamin D_3 supplementation improves insulin resistance and pancreatic beta-cell function, but there is paucity of data on vitamin D and glycaemia in type 2 diabetes in Nigeria. We have therefore performed a single blind prospective randomised placebo-controlled trial, involving type 2 diabetes participants in Lagos, Nigeria. The participants consisted of 42 type 2 diabetes patients with vitamin D deficiency. These participants were randomised into two equal groups of treatment and a placebo arm. Vitamin D_3 (3000 IU daily) was given to the participants in the treatment arm. Insulin resistance (HOMA-IR) and pancreatic beta-cell (HOMA-B) function were determined at baseline and after 12 weeks of vitamin D_3 supplementation, or placebo treatment. There was a reduction from baseline in the mean insulin resistance level in both the treatment and placebo groups. However, this reduction was only statistically significant in the treatment group ($p < 0.01$). The proportion of subjects with improvement in insulin resistance status (homeostatic model assessment insulin resistance score (HOMA-IR)<2.0) was significantly higher in the treatment arm ($p<0.05$). There was a reduction in the mean insulin secretory capacity in the treatment group while it increased in the placebo group, though this difference was not statistically significant. We conclude that vitamin D_3 supplementation results in a reduction in insulin resistance, but has no effect on pancreatic beta-cell function in type 2 diabetes.

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Introduction

Type 2 diabetes is a disease caused by both insulin resistance and an insulin secretory defect.[1] The effect of vitamin D on beta-cell function and insulin sensitivity has been observed in both animal and human studies.[2] Dietary vitamin D_3 supplementation has been shown to improve glycaemic control and insulin sensitivity in people with diabetes and in normal populations.[3]

Vitamin D is required for and improves the production of insulin; and also improves insulin sensitivity.[4] Insulin secretion is impaired in the vitamin D-deficient pancreas, and it is improved by dietary vitamin D_3 supplementation.[2] Vitamin D has been shown to facilitate the biosynthetic capacity of pancreatic beta-cells and also accelerates the conversion of pro-insulin to insulin.[5] One study has shown a significant correlation between changes in vitamin D levels and first- phase insulin secretion, with a decrease in insulin resistance after one month of vitamin D_3 supplementation.[6]

Reports suggest that vitamin D_3 supplementation improves insulin resistance and pancreatic beta-cell function. However, there is paucity of data on the relationship between vitamin D and glycaemia in type 2 diabetes in Nigeria. The objective of this study was therefore to determine the effect of vitamin D_3 supplementation on insulin resistance and pancreatic beta-cell function in vitamin D-deficient type 2 diabetes subjects.

Patients and methods

This study was carried out at the Diabetes Clinic of the Lagos University Teaching Hospital (LUTH). It was a single blind prospective randomised placebo-controlled trial, involving type 2 diabetes participants. The study subjects were 42 type 2 diabetes participants with vitamin D deficiency selected following a prior cross-sectional study on 114 type 2 diabetes patients for determination of vitamin D status. The participants were randomised into two equal groups for the treatment and placebo arms of the study.

Laboratory tests carried out include analysis for: fasting glucose, HbA1c, calcium, albumin, phosphate, serum insulin, creatine, and alanine transaminase. Vitamin D

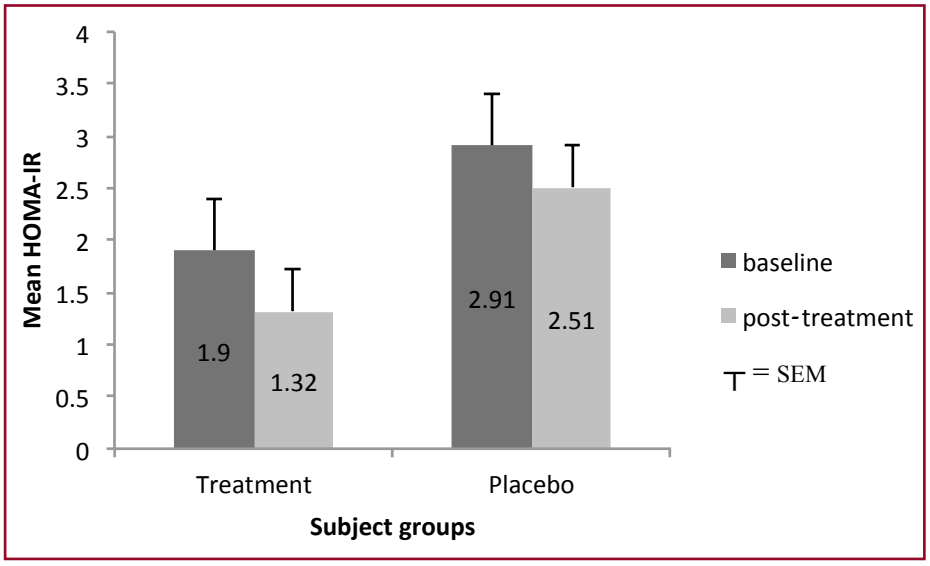

Figure 1: Effect of vitamin D3 on insulin resistance after 12 weeks of treatment. There was a significant reduction in the baseline mean HOMA-IR after 12 weeks of vitamin D3 supplementation in the treatment group. The reduction in mean HOMA-IR in the control group was not statistically significant.

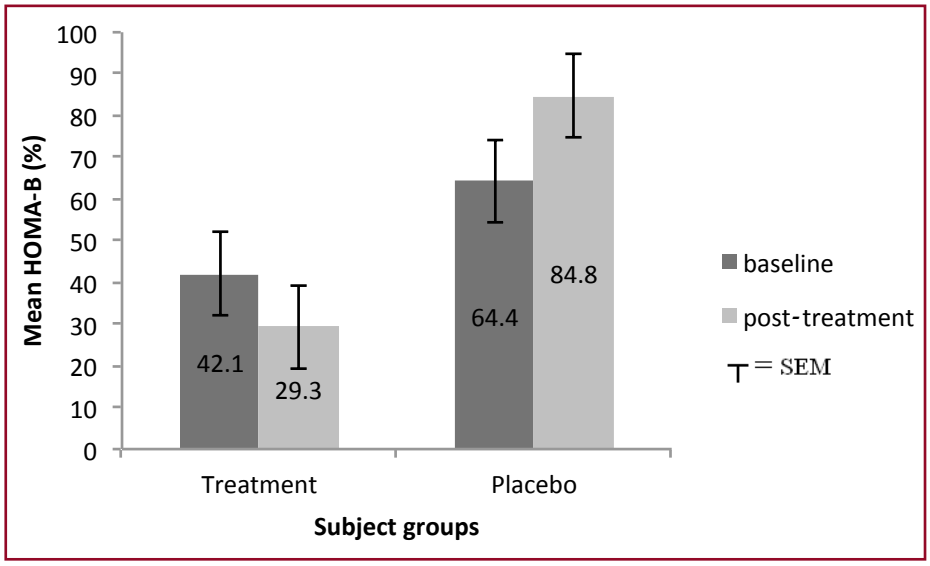

Figure 2: Effect of vitamin D3 on pancreatic beta-cell function

levels were determined using high-performance liquid chromatography (HPLC). Vitamin D_3 supplements (3000 IU daily for 12 weeks) were given to the participants in the treatment arm, and a placebo (50 mg of corn starch) was given to the placebo arm. The doses of participants' oral anti-diabetic medications were kept constant during the study period. Insulin resistance and pancreatic beta-cell function were determined at baseline and after 12 weeks of follow-up. Insulin resistance and beta-cell function were estimated with the homeostasis model assessment (HOMA-IR),[7] defined as the product of fasting serum insulin (μU/ml) and fasting blood glucose (FBG mmol/L) divided by 22.5. A score of ≥2.0 defined IR.[8] Insulin secretion function (IS or HOMA-B) was defined as the product of 20 and fasting insulin (μU/ml) divided by FBG (mmol/l) minus 3.5. A score of <100 defined reduced IS (beta-cell function).[8]

Participants were aged 35–65 years with type 2 diabetes and on oral antidiabetic medication. They gave informed consent, and had previously documented vitamin D deficiency. Patients excluded from the study included those with type 1 diabetes on insulin, pregnant women, and those with chronic diseases including renal insufficiency (glomerular filtration rate (GFR)<30ml/min), chronic liver disease or alanine transaminase (ALT) >5 times the upper reference limit, tuberculosis, diarrhoea, or malabsorption states.

The sample size was calculated using the formula described by Whitley and Ball.[9] Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 20. Results were expressed as means (±SD) and percentages. Comparisons between treatment groups were made using Wilcoxon, Chi square and Z-tests. A p value<0.05 was considered statistically significant.

Results

Patients' adherence was assessed by tablet counts at each visit. There was an overall adherence of 62% and 60% in the treatment and placebo groups respectively.

The mean age of the participants was 52±2 years in the treatment group and 51±2 years in the placebo group (p value not significant (pNS)). There were 10 (59%) females and seven (41%) males in the treatment group, and nine (56%) females and seven (44%) males in the placebo group (pNS). The mean (±SD) body mass index (BMI) was 28.4±4.0 vs 26.5±0.9 in the treatment and placebo arms respectively (pNS).

Figure 1 shows a reduction from baseline in the mean insulin resistance (HOMA-IR) level in both the treatment and placebo groups. The mean baseline values (95% CI) were 1.9 (1.0–2.8) and 2.9 (1.1–4.7) respectively; and the post-treatment values were 1.3 (0.8–1.9) and 2.5 (1.5–3.5) respectively. However, this reduction was only statistically significant in the treatment group (p<0.01).

The proportion of subjects with improvement in insulin resistance status (HOMA-IR<2.0) was significantly higher

in the treatment arm , 80% (4 out of 5) compared with the placebo arm, 12% (1 out of 8).

Figure 2 shows the effect of vitamin D_3 supplementation on pancreatic beta-cell function (HOMA-B) in both groups. There was a reduction in the mean HOMA-B (insulin secretory capacity) in the treatment group (p=0.29) while it increased in the placebo group (p=0.18). These differences were, however, not statistically significant.

There was an appropriate reduction in the mean HOMA-B in the treatment group while it increased in the placebo group.

Out of the 16 subjects with impaired pancreatic beta-cell function, one subject improved in the treatment group; whereas there was no change in the HOMA-B status in the placebo group.

Discussion

Vitamin D deficiency is a global healthcare concern. A growing number of studies have reported widespread vitamin D deficiency and insufficiency in both apparently healthy populations and patients with various pathologies including diabetes.[10] It has been estimated that one billion people worldwide are affected by various degrees of vitamin D deficiency.[11] Since the first report on the influence of vitamin D on insulin secretion,[12] evidence has suggested a role for vitamin D in both the occurrence[13] and treatment of type 2 diabetes.[14,15] There is now convincing evidence that vitamin D has some role in both pancreatic insulin secretion and insulin sensitivity, and thereby affects the pathogenesis of the disease.[14,15]

Vitamin D receptors (VDRs) are found throughout the body including in pancreatic beta-cells.[16] Vitamin D appears to play a role in the regulation of insulin release in response to glucose intake.[16,17] Direct effects may be mediated by binding of the active form 1,25 (OH)D to beta-cell VDRs.[18] Vitamin D may indirectly affect insulin secretion via regulation of calcium-mediated insulin release by regulating calcium influx through the cell membrane.[16] Vitamin D may also enhance insulin responsiveness for glucose transport by directly stimulating the insulin receptor.[16,17] It may indirectly influence insulin action via regulation of calcium influx through the cellular membrane, thereby ensuring normal calcium-mediated insulin release.[16,17]

Vitamin D may promote beta-cell survival by modulating the effects of inflammatory cytokines and decreasing beta-cell destruction.[17] Vitamin D may prevent generation of cytokines by interfering with the promoter gene for transcription factors and up-regulation of cytokine binding proteins.[16,17]

The finding of an improvement in insulin resistance after vitamin D_3 supplementation in this study is consistent with findings from previous studies.[19,20] A randomised, placebo-controlled trial concluded that improving vitamin D status in insulin-resistant women resulted in improved insulin resistance and sensitivity, but no change in insulin secretion.[20] We found no significant effect of vitamin D_3 supplementation on pancreatic beta-cell function (HOMA-B) in individuals with type 2 diabetes compared with controls. This finding is similar to that reported by von Hurst et al.[20] In Caucasian patients with impaired fasting glucose, oral supplementation with vitamin D and calcium reduced the progression of insulin resistance and increased insulin sensitivity.[21]

It is somewhat surprising that the pancreatic beta-cell function (insulin secretory capacity) reduced after supplementation in the treatment group compared with the placebo group. This is probably due to the improvement in insulin sensitivity noted in the treatment group. Interpretation of the beta-cell function should not be done in isolation as one might conclude erroneously that the participants in the treatment arm had failing beta cells as opposed to appropriately low secretion.[22]

Our study does have some limitations. Participants were assumed to have kept their doses of anti-diabetic medication constant during the intervention period. They were also assumed not to be taking vitamin D-containing complementary medicines during the intervention period. Also, HOMA, an indirect index of beta-cell function, was used to assess insulin resistance instead of the euglycaemic clamp (due to cost and unavailability). Finally, changes in lifestyle, diet, or physical activity may have occurred among study participants during the period of vitamin D_3 supplementation, but this was difficult to account for as a confounder.

In conclusion, this study revealed a significant improvement in the insulin resistance status of vitamin D-deficient type 2 diabetes subjects following vitamin D_3 supplementation. However, supplementation of vitamin D did not improve pancreatic beta-cell function. Reports of improvement in glycaemic control in persons with type 2 diabetes after administration of vitamin D may stem from this beneficial effect of vitamin D on insulin resistance.

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Author declaration

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Any ethical issues involving humans or animals: none.
Was informed consent required: yes - documentation on file.

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