Improvement in glucose tolerance and beta-cell function in a patient with vitamin D deficiency during treatment with vitamin D

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Summary: Glucose metabolism was studied in a patient with vitamin D deficiency during its treatment with small doses of vitamin D. A continuous infusion of glucose test was performed to assess glucose tolerance and insulin sensitivity and beta-cell function were derived by mathematical modelling. Fasting glucose was 5.6 mmol/l and achieved glucose after the infusion was 10.4 mmol/l confirming diabetes.

The test was repeated 0.5, 1, 3 and 5 months after starting treatment. Serum calcium increased glucose intolerance from 1.76 to 2.0, 2.08, 1.96 and 2.0 mmol/l, respectively; vitamin D reached supraphysiological levels initially and returned to normal levels, and parathyroid hormone levels were normalized. Her weight did not change during treatment. Glucose tolerance improved during treatment and achieved glucose was 9.4, 8.6, 9.2 and 9.0 mmol/l at 0.5, 1, 3 and 5 months, respectively; insulin sensitivity did not change. Beta-cell function improved from 101% at diagnosis to 126%, 147%, 173% and 198% at 0.5, 1, 3 and 5 months, respectively.

Improvement in beta-cell function and consequently in glucose tolerance is likely to have been due to correction of hypocalcaemia, vitamin D deficiency and secondary hyperparathyroidism.

Introduction

The vitamin D endocrine system is important for the regulation of insulin secretion from the pancreatic islet beta cells.[1] The presence of vitamin D receptors and vitamin D-dependent calcium-binding proteins on pancreatic beta-cells suggests a physiological role for 1,25 dihydroxyvitamin D $(1,25(OH)_2D)$ in the regulation of beta-cell secretion.[1] Deficiency of both calcium and $1,25(OH)_2D$ deficiency leads to impaired insulin secretion[2] and $1,25(OH)_2D$ has been shown to affect insulin sensitivity in studies *in vitro*[3] and in rats with vitamin D deficiency.[4]

We report a patient with osteomalacia and vitamin deficiency in whom glucose metabolism was assessed in detail during treatment with native vitamin D. During treatment with vitamin D, causing a rise in $1,25(OH)_2D$, improvement in glucose tolerance was observed which appears to have been mainly due to an improvement in insulin secretory capacity.

Case report

The patient, a 65 year old Nepalese woman who had been in England for 4 years was found to have hypocalcaemia (1.76 mmol/l) during investigation in a general medical clinic for generalized aches and weakness. Two years previously, she had received triple therapy for 9 months for pulmonary tuberculosis. She had slight proximal muscle weakness with difficulty standing from a squatting position and bone tenderness. X-rays of her hips showed osteopaenia but no pseudo-fractures, and dual-energy X-ray absorptiometry confirmed reduced bone mass and a clinical diagnosis of vitamin D deficiency was made.

She was a vegetarian and dietary assessment revealed a daily calcium intake of 1,593 mg and vitamin D intake of 0.2 µg/day; she had a history of avoiding sunlight. The recommended requirement for dietary vitamin D in the absence of sunlight exposure is 10 µg/day.[5] Vitamin D deficiency was treated with daily oral doses of vitamin D 2,000 IU (50 µg) and within one month of treatment there was subjective improvement of symptoms.

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Methods

Glucose metabolism was assessed before treatment and 15 days, and 1, 3 and 5 months after commencing treatment. She remained on her usual unrestricted diet with at least 50% calories derived from carbohydrate for 3 days before each test. On each occasion, she was studied recumbent after a minimum fast of 12 hours. A continuous infusion of glucose test was performed.[6] Glucose was infused at a low dose (5 mg/kg ideal body weight/minute) and blood samples were taken at -10, -5, 0 minutes and at 50, 55 and 60 minutes after commencing the glucose infusion. Glucose, insulin and C-peptide were measured in samples taken before and during the infusion.[7] An achieved plasma glucose of 9.3 mmol/l or greater at the end of the glucose infusion was considered diagnostic of impaired glucose tolerance.[8] Glucose, insulin, parathyroid hormone (PTH), calcium and vitamin D metabolites were assayed as described previously[9] at the end of the study. Measures of insulin sensitivity and beta-cell function were derived from the glucose and insulin data by using the CIGMA (continuous infusion of glucose with model assessment) mathematical model.[6] Beta-cell function and insulin sensitivity are expressed as a percentage of those in a reference lean healthy population for whom the model has been calibrated at 100% for insulin sensitivity and beta-cell function. The study of glucose metabolism was approved by the local ethics committee and informed consent was obtained.

Results

Correction of abnormalities of calcium metabolism was associated with improvement in glucose tolerance; the initial assessment revealed glucose intolerance but during treatment glucose tolerance improved progressively (Table I and Figure 1). There was no change in weight. During treatment with vitamin D, 1,25(OH)$_2$D levels became supraphysiological at first before normalizing and secondary hyperparathyroidism was corrected. The glucose and insulin profile before and 5 months after treatment are shown in Figure 1. Chi-squared test for trend showed that the changes in glucose tolerance and beta-cell function were statistically significant. The above results did not become available until she had completed the study and therefore she had not received any specific dietary advice with respect to diabetes.
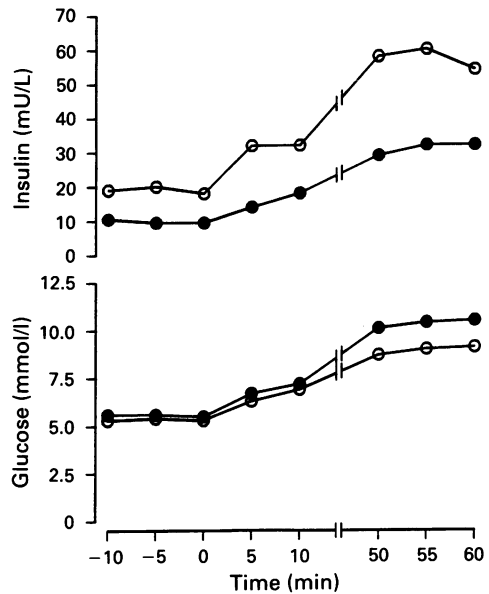

Figure 1 Glucose and insulin profiles during the continuous infusion of glucose test before (●) and 5 months after (○) treatment are shown.

Table I Changes in the parameters of calcium and glucose metabolism during treatment of vitamin D deficiency

	At diagnosis	15 days	1 month	3 months	5 months
Body mass index (kg/m²)	26.24	26.36	26.52	26.64	26.32
Calcium (corr.) (2.3–2.7 mmol/l)	1.65	2.0	2.08	1.96	2.0
PTH (normal: 20–60 pg/ml)	115	80	59	44	44
1,25(OH)$_2$D (normal: 20–50 pg/ml)	12	97	65	41	47
25(OH)D (normal: 4.3–25.4 ng/ml)	2.7	13	17.6	33	21.4
Alkaline phosphatase (70–330 U/l)	501	469	361	304	288
Fasting glucose (normal: 2.5–4.5 mmol/l)	5.6	4.4	4.6	5.3	5.6
Achieved glucose (mmol/l)*	10.4	9.4	8.6	9.2	9.0
Achieved insulin (mU/l)*	32	34	33	52	60
Beta-cell function (%)*	101.4	126.3	146.5	173.4	198.3
Insulin sensitivity (%)	36.6	39	44.8	27.9	25.4

*Chi-squared for trend, $P < 0.05$.

Discussion

Improvement in glucose tolerance was observed in this patient during correction of vitamin D deficiency with low doses of vitamin D. This appears to have been mainly due to improvement in beta-cell insulin secretory capacity rather than to any change in peripheral insulin sensitivity. During the previous 2 years her plasma glucose concentrations were between 3.6 and 6.5 (all random), whereas she was found to be glucose intolerant when vitamin D deficient and hypocalcaemic. A series of assessments of glucose metabolism was performed in this patient during treatment in view of the possibility that the initial results would tend to 'regress to the mean' during further tests. However, this would appear to be unlikely in this case, both due to the magnitude of the change observed and as the improvement observed in glucose tolerance was associated with a continual improvement in beta-cell function during treatment. Thus, this report illustrates the importance of the vitamin D endocrine system on the regulation of insulin secretion.

Serum calcium concentrations did not return to within the normal range in this patient during the period of study. This is probably because she had osteomalacia which takes longer to heal and because there is a continuing net movement of calcium into the bones, continuing hypocalcaemia is seen in spite of normal or supraphysiological serum concentrations of the vitamin D metabolites.[10] There were no features to suggest other possible causes of osteomalacia such as those associated with malabsorption (pancreatic disease, giardiasis, coeliac disease).

The main effect of $1,25(OH)_2D$ on glucose metabolism is thought to be on the regulation of insulin secretion.[2,11-13] Thus, reduced insulin secretion is seen in vitamin D-deficient rats compared to $1,25(OH)_2D$ replete rats and $1,25(OH)_2D$ stimulation of insulin secretion was confirmed in rats and in human subjects.[12,14] It has been suggested that $1,25(OH)_2D$ maximizes glucose-induced insulin release by stimulation of islet cell Ca^{2+} uptake.[15] A more recent report suggests that in an experimental rat model, acute insulin release in response to GTT

is primarily determined by calcium rather than vitamin D.[16] However, the vitamin D endocrine system is important not only for the release of insulin but it may also be important for the synthesis of insulin, as vitamin D deficiency is accompanied by decreased pancreatic preproinsulin mRNA which is reversible by $1,25(OH)_2D$ treatment.[17] In this patient the fact that improvement in insulin secretory capacity occurred despite the fact that her calcium levels were subnormal suggests that $1,25(OH)_2D$ is more likely to be the active agent.

It has also been suggested that $1,25(OH)_2D$ may improve insulin sensitivity.[4] In an *in vitro* model, calcium increased insulin binding and insulin sensitivity *in vitro*.[3] No change in insulin sensitivity was observed during vitamin D deficiency and its subsequent treatment with $1,25(OH)_2D$ in the same study. Insulin insensitivity is a feature of both primary and secondary hyperparathyroidism[9,18] and correction of primary hyperparathyroidism is associated with improvement in insulin sensitivity.[19] In our patient, despite the administration of vitamin D and correction of secondary hyperparathyroidism, we did not observe any change in insulin sensitivity. This patient was, however, quite insulin resistant which may be related to her ethnic origin. Therefore despite seemingly 'normal' insulin concentrations, this degree of insulin secretion was inadequate to maintain normoglycaemia, prior to treatment with vitamin D. The correction of vitamin D deficiency may have allowed her to secrete an amount of insulin that is appropriate to her degree of insulin resistance and maintain normoglycaemia.

The changes in this vitamin D-deficient patient's glucose tolerance and beta-cell function during vitamin D treatment suggest that the main clinically relevant effect of $1,25(OH)_2D$ deficiency is reduced beta-cell function which can be corrected by the treatment.

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