Effect of Short-Term Vitamin D Supplementation On Glycemic Control In Newly-Diagnosed Type 2 Diabetics

Ali, A.M., Awad, T.G. and Ali, O.M.

1Department of Pharmacology & Toxicology. Faculty of Pharmacy, October 6 University, October 6 Governate, Egypt.  
2General Organization of Health Insurance, Cairo, Egypt.  
3Department of Clinical Chemistry, Saridar Laboratories, Cairo, Egypt.

Abstract: This study aimed at assessing the effect of vitamin D supplementation on glycemic control in newly-diagnosed type 2 diabetics started on glimepiride therapy. In a 12-week, open-label clinical study, 30 newly diagnosed type 2 diabetics with poor glycemic control (Glycosylated hemoglobin [HbA1c] 7.5-11 % and fasting blood glucose [FBG] ≥ 130 mg/dl) were randomized to either glimepiride or glimepiride plus oral active vitamin D for 12 weeks. Mean HbA1c decrease from baseline was significantly more pronounced (-1.95 vs. -1.43 %, P < 0.05) and more patients reached target HbA1c < 7.0% (53.5 vs. 33.3 %, P < 0.05) with glimepiride plus vitamin D than with glimepiride alone. Similarly, mean FBG decrease was greater with glimepiride plus vitamin D than glimepiride alone (-59 vs. -39 mg/dl, P < 0.05), and more patients reached target FBG < 110 mg% with glimepiride plus vitamin D than with glimepiride alone (46.6 vs. 26.7 %, P < 0.05). We conclude that addition of oral active vitamin D to glimepiride therapy achieves better glycemic control than single glimepiride therapy in newly-diagnosed type 2 diabetics.

Key words: Vitamin D- glimepiride- type 2 diabetes-Glycemic control- HbA1c.

INTRODUCTION

Glycated hemoglobin (HbA1c) is a form of hemoglobin used primarily to identify the average plasma glucose concentration over a prolonged period of time. It is formed in a non-enzymatic pathway by hemoglobin's normal exposure to high plasma levels of glucose. Glycation of hemoglobin has been associated with cardiovascular disease, nephropathy, neuropathy and retinopathy in diabetes mellitus (Larsen, et al., 1990). The association between poor glycemic control and the occurrence of micro- and macrovascular complications has been demonstrated in patients with type 1 and type 2 diabetes (UK Prospective Diabetes Study, 1998, Ohkubo, et al., 1995, The Diabetes Control and Complications Trial, 1996); however achieving glycemic control preferably with HbA1c values < 7 mg % can markedly reduce the risk of such complications (Stratton, et al., 2000) and is now recommended clinical practice (American Diabetes Association, 2002). Vitamin D is a group of fat-soluble steroids, the two major physiologically relevant forms of which are vitamin D₃ (ergocalciferol) and cholecalciferol or vitamin D₉ (Adams and Hewison, 2010). Food sources such as fatty fish, eggs, and meat are rich in vitamin D and are often recommended for consumption to those suffering vitamin D deficiency (Joshi, et al., 2010). Recent studies indicate that persons with diabetes have lower serum concentrations of vitamin D. In addition, persons at risk for diabetes or metabolic syndrome have inadequate serum concentrations of vitamin D (Penckofer, et al., 2008 and Takiishi, et al., 2010).

The aim of this study is to evaluate the effect of short-term vitamin D supplementation on glycemic control in newly diagnosed type 2 diabetics with normal serum calcium levels.

MATERIALS AND METHODS

Study Design and Patients:

Thirty newly-diagnosed type 2 male diabetics, aged 38-56 years and with normal serum calcium levels were enrolled in this randomized open-label efficacy study. Patients have poor glycemic control manifested as fasting blood glucose (FBG) ≥ 130 mg/dl and HbA1c ranging from 7.5 to 11 %. All patients were subjected to detailed history taking and clinical examination (stressing the onset and duration of diabetes) and routine laboratory investigations. The study subjects were diagnosed according to the criteria of the American Diabetes Association. Patients were randomized to either glimepiride (1-3 mg once daily) or glimepiride (1-3 mg once daily) plus oral alphacalcidiol (1 µg once weekly). Alphacalcidiol is converted in the liver to vitamin D₃. All treatments were continued for 12 weeks. HbA1c levels were measured at diagnosis (baseline) and again after
12 weeks of continued therapy (end-point). HbA1c were measured by immunoassay with a reference range of 4.5–9%. FBG levels were measured at baseline and subsequently self-monitored and recorded on a daily basis for 12 weeks using glucometers (AccuCheck Sensor, Roche Diagnostics). Serum 25-Hydroxycholecalciferol [25(OH)D₃] was determined at baseline using ELISA kits (Immundiagnostik AG, Germany). The study patients have hydroxycholecalciferol values in the range of 25-36 ng/ml which is described according to recent studies as "low, borderline or suboptimal". Serum calcium levels were measured initially and at 4-week intervals throughout the study.

Setting:
Out-patient treatment at Health insurance Clinics, Cairo, Egypt.

Inclusion Criteria:
BMI < 35 kg/m², HbA1c > 7.5%, and FBG levels ≥ 126 mg/dl.

Exclusion Criteria:
Previous use of any blood glucose-lowering agents, diabetic complications and history of ketoacidosis.

Study Drugs:
Glimepiride 1, 2 and 3 mg (Amaryl®; Aventis-Sanofi ; Egypt), alphacalcidiol 1 mg (One-alpha®, Leo Pharmaceutical Co.).

Efficacy Measures:
The primary efficacy measure was the mean change in HbA1c from baseline to end-point. Secondary efficacy measures were mean FBG level, proportion of patients with HbA1c < 7% and proportion of patients with FBG < 110 mg/dl.

Data Analysis:
Data were expressed as mean ± standard deviation. Statistical testing was performed at a significance level of p < 0.05. ANCOVAs were performed to compare changes in HbA1c and secondary variables between treatment groups at baseline and end-point. Statistical analyses were performed using SAS software (version 8.2).

RESULTS AND DISCUSSION
A total of 30 newly diagnosed patients with type 2 diabetes were enrolled in the study. There were 15 patients randomly assigned to glimepiride and 15 to glimepiride plus vitamin D. Baseline characteristics were similar between groups (Table 1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glimepiride</th>
<th>Glimepiride plus vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.8±6.7</td>
<td>45.2±7.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.1±3.8</td>
<td>29.8±3.4</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.23±0.36</td>
<td>9.25±0.45</td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>175±37</td>
<td>176±41</td>
</tr>
<tr>
<td>Serum 25(OH)D₃ (ng/ml)</td>
<td>31±5.2</td>
<td>29±4.5</td>
</tr>
<tr>
<td>Serum Calcium (mg/dl)</td>
<td>9.4±0.35</td>
<td>9.3±0.44</td>
</tr>
</tbody>
</table>

Data are means ± SD unless otherwise indicated.

Glycemic Control Efficacy Measures:
Over the 12-week treatment period, mean HbA1c levels decreased from to 9.25 ± 0.45 to 7.3 ± 0.33 % with glimepiride plus vitamin D and from to 9.23 to 7.8 ± 0.41 % with glimepiride monotherapy (Table 2 and Fig. 1). Improvement in HbA1c was significantly better with glimepiride plus vitamin D compared with glimepiride monotherapy (-1.95 vs. -1.43 %, P ≤ 0.05).

Significantly more patients (Table 2 and Fig. 2) on glimepiride plus vitamin D than on glimepiride alone reached a target HbA1c of 7% (53.3% vs. 33.3%, P < 0.05).

FBG levels decreased from 176 ± 41 to 117 ± 14 mg/dl with glimepiride plus vitamin D and from 175 ± 37 to136 ± 17 with glimepiride monotherapy (Table 2 and Fig. 3). Improvement in FBG was significantly better with glimepiride plus vitamin D compared with glimepiride monotherapy (adjusted mean between-treatment difference -20 mg/dl).

As shown in Table 2 and Figure 4, a significantly greater proportion of patients reached a target FBG level < 110 mg/dl with glimepiride plus vitamin D than with glimepiride alone (46.6% vs. 26.7%, P < 0.5).

Discussion:
Accumulating epidemiological evidence suggests that Vitamin D deficiency may be associated with a
greater risk of type 2 diabetes mellitus and related metabolic risks (Sebherwal, et al., 2010). The results of our study demonstrated that in patients with type 2 diabetes, adding short-term oral vitamin D to glimepiride can provide more effective glycemic control than glimepiride monotherapy. The vitamin D plus glimepiride regimen enabled 53.5% of patients to reach a target HbA1c ≤ 7% compared to 33.3% on glimepiride monotherapy. Also, significantly more patients (46.6%) on vitamin D plus glimepiride regimen reached a target FBG < 110 mg/dl compared to those (26.7%) on glimepiride monotherapy. Studies looking at the effect of vitamin D replacement on glycemic control in type 2 diabetics are few and conflicting. Evidence from observational studies and clinical trials indicates that vitamin D supplementation may be important in the prevention of diabetes (type 1 and 2), particularly for those with glucose intolerance (Pittas, et al., 2007 and Zipitis and Akobeng, 2008). In the Nurse Health Study (Pittas, et al., 2006) and the Mini-Finland Health Study (Matilla, et al., 2007), higher incidence of type 2 diabetes was associated with low serum 25(OH) D concentrations in subjects with no history of diabetes at baseline. According to the Medical Research Council Ely Prospective Study (Forouhi, et al., 2008), an inverse association has been found between baseline serum 25(OH) D and future glycaemia and insulin resistance. Nagpal et al., (2009), reported that vitamin D, supplementation improves postprandial insulin sensitivity in non-diabetic, middle-aged centrally obese men. Chiu and colleagues, (2004) studied a group of healthy glucose-tolerant subjects who were assessed for insulin sensitivity and beta-cell function. They reported that 25(OH) D levels were positively associated with insulin sensitivity and negatively with first and second phase of insulin response. A negative association has been also found between 25(OH) D concentrations and glucose concentrations at fasting and 60, 90 and 120 minutes during the glucose tolerance test. Borissova et al., (2003) reported that vitamin D deficiency contributes to impaired insulin secretion and probably insulin action in type 2 diabetics. Patients with type 2 diabetes were given 1332 IU daily of vitamin D (cholecalciferol) for 1 month. They reported a 21.4% decrease in insulin resistance after 1 month. They also reported that both the first phase insulin secretion, as well as the second phase insulin secretion, decreased by 34% and 20%, respectively. This study suggested that vitamin D supplementation may have positive metabolic effects for Patients with type 2 diabetes. Sabherwal et al.,(2010) demonstrated that vitamin D and calcium replacement therapy causes a significant decrease in both HbA1c and weight in South Asian patients with type 2 diabetes. Suzuki et al., (2006) reported on the microvascular complications associated with type 2 diabetes.

**Fig. 1:** Mean change in FBG Conc.(mg/dl) from baseline in type 2 diabetics treated with glimepiride monotherapy or glimepiride plus vitamin D. Significantly different from baseline(*) and glimepiride monotherapy (@), p ≤ 0.05.

**Table 2:** End-point results of 12-week therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Glimepiride</th>
<th>Glimepiride plus vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>7.8</td>
<td>7.3</td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>136 ± 17</td>
<td>117 ± 14</td>
</tr>
<tr>
<td>% Patients with HbA1c ≤ 7%</td>
<td>33.3</td>
<td>53.5</td>
</tr>
<tr>
<td>% Patients with FBG &lt; 110</td>
<td>26.7</td>
<td>46.6</td>
</tr>
</tbody>
</table>

Data are means ± SD unless otherwise indicated.

**Fig. 2:** Percentage (%) of of diabetic patients achieving HbA1c target (≤ 7 %) in both glimepiride and glimepiride plus vitamin D groups.
in the presence of hypovitaminosis D. In this observational study of Japanese patients with type 2 diabetes and controls, the mean level of 25 (OH) D was inversely related to HbA1c as well as the number of diabetes complications. A recently published randomized controlled study concluded that high-dose vitamin D therapy does not improve insulin resistance or HbA1c in patients with type 2 diabetes (Witham, et al., 2010). The mechanisms whereby vitamin D may impact on the development and management of diabetes are important areas of research. The mechanisms whereby vitamin D may impact on the development and management of diabetes are important areas of research. It has been reported that insulin secretion is dependent upon vitamin D in animals and isolated islets (Boucher, 1998). It has also been reported that vitamin D deficiency reduces insulin secretion (Boucher, 1998 and Borissova, et al., 2003). In addition, recent data has demonstrated the presence of vitamin D receptors on the beta cells of the islets of Langerhans, and the ability of the islets to express 1-alpha hydroxylase thereby activating 25 (OH) D. An indirect effect of vitamin D on beta cell insulin secretion is also postulated by means of increased intracellular calcium in the islet (Pittas, et al., 2007 and Peechakara and Pittas, 2008). Vitamin D receptors have also been identified in cells of the immune system. In studies of nonobese diabetic mice, high doses of 1 alpha 25-dihydroxyvitamin D, (active form of vitamin D) have been shown to delay the onset of diabetes by means of immune modulation (Mathieu, et al., 2005). This active form has been shown to protect beta cell against destruction caused by inflammatory cytokines including IL-6 and TNF-alpha (Flores, 2005). IL-6 has been noted to inhibit insulin receptor signal transduction, and administration of this cytokine has been associated with hyperglycemia and hyperinsulinemia (Flores, 2005). Recent evidence has demonstrated that persons with type 2 diabetes who have hypovitaminosis D are more likely to have increased HbA1c, C-reactive protein (CRP) and fibrinogen concentrations compared with those persons with diabetes who do not (Cigolini, et al., 2006). Therefore, understanding the role that vitamin D receptors play in immune function for the development and progression of diabetes will be an important area of future research.

**Conclusion:**

This study demonstrated that in newly-diagnosed patients with type 2 diabetes, adding short-term oral vitamin D to glimepiride can provide more effective glycemic control than starting with glimepiride monotherapy. We recommend adding low-dose vitamin D supplementation to commercially available edible vegetable oils to minimize future risk of diabetes.

**REFERENCES**


