

Effect of Initial Intensive Insulin Therapy Followed by Sitagliptin on β Cell Function in Patients with New Onset Type 2 Diabetes

Hua Xu^{1#}, Huan Zhou^{1#}, Xiangyu Teng¹, Tzuchun Lin¹, Rilun Feng¹, Qianjing Liu¹, Huiying Qiu¹, Chris K Rayner^{2,3}, Jing Ma^{1*} and Wei Liu^{1*}

¹Division of Endocrinology and Metabolism, Department of Internal Medicine, Renji Hospital affiliated to Shanghai Jiaotong University, Shanghai, China

²Discipline of Medicine, University of Adelaide, Adelaide, Australia

³Centre of Research Excellence in Translating Nutritional Science to Good Health, University of Adelaide, Adelaide, Australia

*Corresponding author: Dr. Jing Ma and Dr. Wei Liu, Division of Endocrinology and Metabolism, Department of Internal Medicine, Renji Hospital affiliated to Shanghai Jiaotong University, No.160 Pujian Road, Pudong New Area Shanghai, China, Tel: +86-21-68383073; Fax: +86-21-58394262; E-mail: majing3436@163.com; sue_liuwei@163.com

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#Contributed equally to this work.

Abstract

Objective: It is established that early insulin therapy can improve both β cell function and glycaemic control in newly diagnosed type 2 diabetic patients. The dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin, can preserve or even increase the number of β cells in animal models of diabetes. Therefore, we aimed to determine whether treatment with sitagliptin after initial intensive insulin therapy would further reduce glycaemia and preserve β cell function in new-onset type 2 diabetes.

Methods: 48 Chinese patients with newly diagnosed type 2 diabetes (fasting blood glucose concentration 13.42 ± 0.38 mmol/L; HbA1c: $11.8 \pm 0.2\%$) were recruited. All received insulin pump therapy for two weeks, followed by sitagliptin (100mg orally once daily) for three months. Arginine tests were performed at baseline, after two-weeks' insulin pump therapy, and after 3 months' sitagliptin therapy. Blood samples were collected at baseline, before and after the treatment with sitagliptin for measurement of blood glucose, plasma insulin and lipids profiles. β cell function was evaluated by HOMA- β and the insulin response to arginine.

Results: Fasting blood glucose concentrations were substantially decreased after two weeks' insulin therapy ($P < 0.01$), and were further reduced after 3 months' treatment with sitagliptin ($P < 0.01$). HOMA- β and HOMA-IR were improved ($P < 0.01$) after two weeks' treatment with insulin, while HOMA- β was further improved after 3 months' sitagliptin ($P < 0.01$). However, the insulin response to arginine did not increase after two weeks' insulin therapy, but did improve after sitagliptin ($P < 0.05$).

Conclusions: Intensive insulin therapy improved both glycaemic control and β cell function in newly diagnosed Chinese type 2 diabetes, and the improvements in β cell function was preserved after 3 months of sitagliptin.

Keywords: Type 2 diabetes; Initial intensive insulin therapy; Dipeptidyl peptidase-4

Introduction

There is a worldwide epidemic of diabetes, with the prevalence in China estimated at almost 12% in 2013 [1]. Impaired β -cell function outweighs insulin resistance in the development of type 2 diabetes in Asian populations [2]. American Association of Clinical Endocrinologists (AACE) recommended that treatment for newly diagnosed type 2 patients should be determined by glycated hemoglobin (HbA1C) [3]. For example, patients with HbA1C $> 9.0\%$ would benefit more from insulin therapy, which can rapidly eliminate gluco-toxicity and reduce the excessive stimulation of β cells [4]. It has been reported that two weeks' intensive insulin therapy can achieve better long-term glycaemic control than oral antidiabetic medications in patients with new-onset type 2 diabetes [5], associated with restoration of first-phase insulin secretion [5].

Intensive insulin therapy can be administered either by continuous subcutaneous insulin infusion (CSII) or by multiple daily insulin injections, although glycaemic goals are achieved more rapidly with CSII [6]. CSII also achieves more stable blood glucose concentrations when compared to multiple daily insulin injections, and therefore holds greater potential to maintain the acute insulin response at one year in newly diagnosed type 2 diabetes [7]. Among the antidiabetic medications, dipeptidyl peptidase-4 (DPP-4) inhibitors, sitagliptin, increases endogenous glucagon like peptide-1 (GLP-1), and improves β -cell function to lower the blood glucose levels without occurrence of hypoglycaemic events [8]. It is widely used in the type 2 diabetic patients, even in those with high cardiovascular risk [9]. However, there were no studies about the effects of insulin therapy and sitagliptin on β -cell function and glycaemic control in newly diagnosed type 2 diabetes.

Therefore, we aimed to assess the effects of combination of CSII and sitagliptin on glycaemic control, β -cell function and lipid profiles in patients with newly diagnosed type 2 diabetes.

Methods

Subjects

All patients presenting to our institution between 1 Jan 2012 and 30 July 2014 with newly diagnosed type 2 diabetes according to World Health Organization criteria were included in this retrospective study (43 males/13 females; age (mean \pm SE) 46.5 ± 1.6 years, BMI 25.5 ± 0.5 kg/m², HbA1c $11.80 \pm 0.2\%$) were diagnosed. None had diabetic ketoacidosis, hyperosmolar status or chronic complications of diabetes. Patients with liver, renal and heart dysfunction, those positive for glutamic acid decarboxylase antibody, and those with a history of gastrointestinal symptoms or gastrointestinal surgery during the preceding three months were excluded. All patients provided written informed consent.

Study protocol

A total of 56 Chinese patients with type 2 diabetes were hospitalized in the Department of Endocrinology and Metabolism of Shanghai Renji Hospital. The protocol was approved by the Human Research Ethics Committee of the Shanghai Renji Hospital, and was conducted in accordance with the Declaration of Helsinki. Each subject provided written informed consent. All had fasting hyperglycaemia (13.42 ± 0.38 mmol/L) at admission, and were treated with rapid-acting insulin (Insulin Aspart Injection, Novo Nordisk) delivered by insulin pump (Paradigm 712 pump, Medtronic, Northridge, CA) for two weeks. The daily insulin dose was initially 0.4-0.5 IU per kg, divided into 40% basal and 60% bolus administration with subsequent adjustment of doses to achieve fasting blood glucose of 6 mmol/L and 2h postprandial glucose of 8mmol/L. During the two weeks of insulin therapy, all meals were prepared by dietitians (total energy intake 20-25 kcal/kg, 50-60% from carbohydrate, 15-20% from protein, and 20-25% from fat). Additional food was provided only in the event of hypoglycemia. After two weeks, insulin therapy was discontinued and patients commenced oral sitagliptin (100mg, once daily) which was continued for three months.

At baseline, after two weeks' insulin therapy, and after three months sitagliptin therapy, blood was sampled after overnight fasting for blood glucose, insulin and lipid assays. HbA1c and body weight were also measured at baseline and after 3 months' sitagliptin. Arginine was then administered intravenously (5 g arginine iv) and blood samples collected at 0, 2, 4, 6, and 8 min to measure insulin concentrations.

Measurements

Blood glucose concentrations were measured by the hexokinase method (Roche Diagnostics GmbH, Mannheim, Germany). Plasma insulin was assayed by radioimmunoassay kit (Beijing Atom HighTech Co., Ltd; Beijing; China). HbA1c was measured by High Performance Liquid Chromatography. Lipid profiles were determined using a clinical chemistry analyzer (Roche Original Reagents; Stockholm, Sweden).

Statistical Analysis

β cell function was evaluated using HOMA- β . HOMA β was calculated as $20 \times \text{fasting insulin} / (\text{fasting plasma glucose} - 3.5)$. The insulin response to arginine was calculated as the incremental area under the curve (iAUC) over 8 minutes, using the trapezoidal rule. Insulin resistance was evaluated by HOMA-IR, calculated as fasting

plasma glucose \times fasting insulin/22.5. Data are shown as mean \pm SE. Paired t tests were used to compare outcome measures before and after each phase of treatment, using statistical software (SPSS 20.0). Comparison of variables between two groups was performed by using repeated measures ANOVA. P values <0.05 were considered significant.

Results

48 patients completed the study. One discontinued due to persisting hyperglycaemia, during the sitagliptin therapy. 7 patients were lost to follow-up due to moving to another city or overseas. The mean maximum daily doses were 0.63 IU/kg (± 0.02). During the insulin intervention period, all patients reached glycaemic goals in 6.9 days (± 0.22). During the intensive insulin intervention, hypoglycemia (defined as a blood glucose level is lower than 3.9 mmol/L) occurred in 11 patients. There were no severe hypoglycaemic events, defined as requirement of assistant to relief symptom.

Fasting blood glucose concentrations (Figure 1).

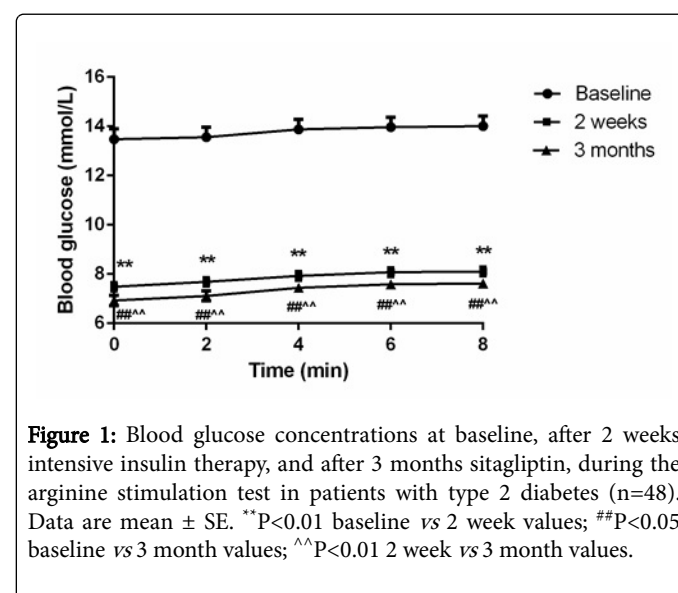


Figure 1: Blood glucose concentrations at baseline, after 2 weeks intensive insulin therapy, and after 3 months sitagliptin, during the arginine stimulation test in patients with type 2 diabetes (n=48). Data are mean \pm SE. **P<0.01 baseline vs 2 week values; ##P<0.05 baseline vs 3 month values; ^^P<0.01 2 week vs 3 month values.

Fasting blood glucose was decreased after insulin therapy compared to baseline values (7.56 ± 0.17 mmol/L vs 13.42 ± 0.38 mmol/L, $P<0.01$). Fasting blood glucose decreased further after 3 months' treatment with sitagliptin (6.93 ± 0.21 mmol/L, $P<0.01$).

Plasma insulin concentrations (Figure 2).

There were no differences in fasting plasma insulin concentrations after 2 weeks insulin treatment compared to baseline values (13.3 ± 0.8 uIU/mL vs 18.5 ± 4.1 uIU/mL). However, fasting plasma insulin increased after 3 months treatment with sitagliptin (16.4 ± 1.2 uIU/mL, $P<0.05$). The insulin response to arginine was reduced after insulin treatment at t=4 min and 6 min, but insulin secretion was significantly increased after 3 month treatment of sitagliptin at t=0 min, 2 min, 4 min, 6 min and 8 min ($P<0.05$). iAUC insulin concentrations did not differ statistically between baseline and after 2 weeks insulin treatment (iAUC 179.19 ± 16.41 uIU/mL.min vs 150.23 ± 14.67 uIU/mL.min).

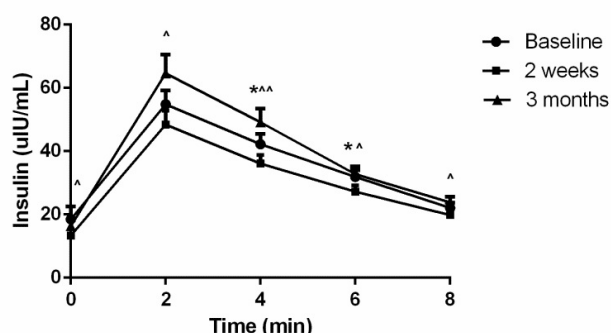


Figure 2: Plasma insulin concentrations at baseline, after 2 weeks intensive insulin therapy, and after 3 months sitagliptin, during the arginine stimulation test in patients with type 2 diabetes (n=48). Data are mean \pm SE. *P<0.05 and **P<0.01 baseline vs 2 week values; #P<0.05 and ##P<0.01 baseline vs 3 month values; ^P<0.05 and ^^P<0.01 2 week vs 3 month values.

However, iAUC insulin levels increased after 3 months treatment with sitagliptin (iAUC 205.48 ± 21.32 uIU/mL.min, P<0.05). HOMA-IR decreased markedly after 2 weeks insulin therapy (4.99 ± 0.39 vs 12.12 ± 3.40 , P<0.01), but did not change further after 3 months sitagliptin treatment (4.44 ± 0.28). HOMA- β increased after two weeks insulin treatment when compared to baseline (73.0 ± 5.6 vs 40.2 ± 7.1 , P<0.01), and increased further after 3 months oral sitagliptin (114.76 ± 11.06 , P<0.01).

HbA1c (Figure 3).

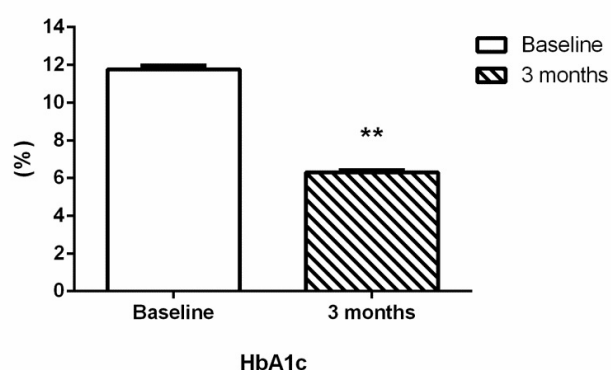


Figure 3: HbA1c at baseline, and after 3 months sitagliptin treatment following initial intensive insulin therapy, in patients with type 2 diabetes (n=48). Data are mean \pm SE. *P<0.05 and **P<0.01 baseline vs 3 month values.

HbA1c decreased markedly after 3 months sitagliptin when compared to baseline (6.3 ± 0.1 %, vs 11.8 ± 0.2 %, P<0.01).

Serum lipids (Figure 4).

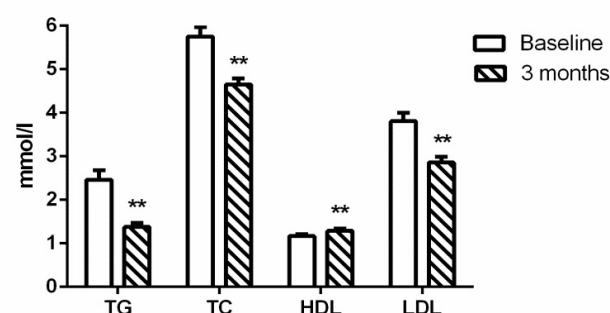


Figure 4: Lipid profile at baseline, and after 3 months sitagliptin treatment following initial intensive insulin therapy, in patients with type 2 diabetes (n=48). *P<0.05 and **P<0.01 baseline vs 3 month values.

When compared to baseline, there were reductions after 3 months sitagliptin therapy in TC (4.7 ± 0.1 mmol/L vs 5.8 ± 0.2 mmol/L, P<0.01), TG (1.4 ± 0.1 mmol/L vs 2.5 ± 0.2 mmol/L, P<0.01), and LDL (2.9 ± 0.1 mmol/L vs 3.8 ± 0.2 mmol/L, P<0.01). In contrast, HDL at the end of treatment increased when compared to baseline (1.29 ± 0.05 mmol/L vs 1.17 ± 0.04 mmol/L, P<0.01).

Body weight

Body weight at the end of treatment did not differ from baseline (72.3 ± 0.3 kg vs 72.1 ± 0.2 kg).

Discussion

We have shown, in Chinese patients with newly diagnosed type 2 diabetes and poor glycaemic control, that initial intensive insulin therapy followed by oral sitagliptin not only preserved but even improved beta-cell function over 3 months, with concomitant reductions in fasting blood glucose concentrations, HbA1C, and serum lipids.

Impaired insulin release, particularly for the first phase of secretion, plays a pathogenic role in newly diagnosed patients with type 2 diabetes mellitus. Early intensive insulin treatment can eliminate hyperglycaemic toxicity and thereby improve β -cell function, with improved glycaemic control over 12 months when compared to less intensive initial therapy with oral agents [10,11]. We enrolled newly diagnosed patients with marked fasting hyperglycemia (mean fasting blood glucose >13 mmol/L) and even worse overall glycaemic control than those reported previously (mean HbA1C >11% compared to <10%) [11]. Fasting blood glucose predominates over postprandial glycaemia as a determinant of HbA1c at such high levels [12], and even more modest elevation of fasting glycaemia (>7 mmol/L) can impair first phase insulin secretion [13]. We chose to evaluate beta cell function with the arginine stimulation test in addition to HOMA- β , given that it is less susceptible to being affected by glucotoxicity when compared to the intravenous glucose test or meal tolerance tests. Similar to the previous study, blood glucose levels were reduced and HOMA- β and HOMA-IR were improved after two weeks insulin pump therapy, but the insulin response to arginine was not enhanced.

The “incretin” hormones, glucose-dependent insulintropic polypeptide (GIP) and GLP-1, are responsible for 50-70% of the insulin response to meals in healthy humans [14]. Although the insulintropic effects of GIP are diminished, those of GLP-1 are relatively preserved in patients with type 2 diabetes. DPP-IV inhibitors, such as sitagliptin, increase concentrations of the active form of GLP-1 to lower blood glucose levels in glucose-dependent manner, and tend to reduce HbA1c by 0.5–1.0% [15]. It has been reported that the DPP-IV inhibitors are more effective in Asian patients than in caucasian due to the differences of insulin sensitivity [16]. In our study, HbA1C was decreased by 4.5% after treatment of insulin and sitagliptin. Following the two week CSII, sitagliptin further idealized glycaemic control which was related to further improvement of β cell function. Both the acute insulin release and HOMA- β was increased after sitagliptin dosage in newly diagnosed type 2 diabetes. The data is different from the previous study which concludes sitagliptin might not be associated with improvement of beta-cell function [17]. However, the population was small in Retnakaran's study. The study design was also different. It included patients with 2-8 years duration of type 2 diabetes and they were on 0-2 oral diabetic medications.

In addition to glucotoxicity, β -cell damage and impaired insulin secretion in patients with poor glycaemic control have been linked to lipotoxicity [18]. Consistent with previous studies [19,20], we observed an improvement in the lipid profile with 3 months sitagliptin treatment in our patients. As in previous studies involving DPP-IV inhibitors, sitagliptin was not associated with weight loss [21,22], suggesting that DPP-4 inhibitors may improve lipid oxidation rate rather than storage in adipose tissue [23].

There are some limitations in our study. Firstly, our study was observational, without a comparator group during either the intensive insulin phase or the sitagliptin phase. However, the benefits of initial intensive insulin therapy on β cell function have already been established in comparison to an active control [11], and we believe that these gains in newly diagnosed type 2 patients are preserved and further enhanced after 3 months treatment with sitagliptin is an important one in our observation. Secondly, we did not measure plasma glucagon concentrations, but the emphasis of our study was on beta cell rather than α cell function. Finally, the duration of our observations was relatively short, and more prolonged observation during sitagliptin treatment, after a similar initial intensive insulin regimen, would be of interest.

In summary, we demonstrated that after 2 weeks of initial intensive insulin therapy, β cell function and glycaemic control were improved in patients with newly diagnosed type 2 diabetes. Moreover, β cell function was preserved and further enhanced after three months treatment with sitagliptin. The capacity for DPP-IV inhibitors to preserve beta cell function over the longer term in patients in this context, when compared to other therapies, should be examined in subsequent clinical trials.

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Disclosure

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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