Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Effects of saxagliptin on glucose homeostasis and body composition of obese patients with newly diagnosed pre-diabetes

Zixuan Wang [a,1], Dengcheng Xu [a,b,1], Lanhui Huang [a], Tiantian Zhang [a,c], Junqiao Wang [a], Qing Chen [a], Lei Kong [a], Xinli Zhou [a,*]

[a] Department of Endocrinology, Shandong Provincial Hospital Affiliated to Shandong University, Shandong Clinical Medical Center of Endocrinology and Metabolism, Institute of Endocrinology and Metabolism, Shandong Academy of Clinical Medicine, 324 Jing 5 Road, Jinan, Shandong, China

[b] Department of Endocrinology, The People's Hospital of Rizhao, Rizhao, Shandong, China

[c] Department of Hematology, The First Affiliated Hospital, Chinese PLA General Hospital, Beijing, China

ARTICLE INFO

Article history:
Received 28 December 2016
Received in revised form
21 April 2017
Accepted 8 May 2017
Available online 12 May 2017

Keywords:
Saxagliptin
Pre-diabetes
Obesity
Islet function
Monotherapy
Metformin

ABSTRACT

Aims: To assess the effect of saxagliptin monotherapy on blood glucose and islet β-cell function in obese patients with newly diagnosed pre-diabetes and abnormal fat metabolism.

Methods: A 24-week, randomized controlled trial was conducted involving 25 obese subjects with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) (mean age 45 years) to receive lifestyle intervention only (control group) or combined with saxagliptin 2.5 mg or 5 mg daily (S2.5 or S5 group), metformin 1500 mg daily (Met group). Anthropometrics, body fat and biochemical parameters were measured before and after 4, 12 and 24 weeks intervention.

Results: S5 group and Met group showed a significant decrease in fasting plasma glucose (FPG) and HbA1c compared with the control group (all $P < 0.05$) after 24-week intervention. However, the decrease in 2 h postprandial plasma glucose levels (2 h PPG) in S5 group were greater compared with control group ($P < 0.01$). Insulin resistance (HOMA-IR) was reduced in S5 group, Met group and control group ($P < 0.05$), and the β-cell function (HOMA-β) was improved in all groups ($P < 0.05$). However, the changes in obesity-related indicators including waist circumference, hip circumference, weight, BMI, body fat, percentage of body fat and waist-to-hip fat ratio were greate in Met group (all $P < 0.05$) compared with other groups ($P > 0.05$).

Conclusions: Saxagliptin monotherapy may prevent or delay the progression of IGT or IFG to type 2 diabetes mellitus in obese patients with newly diagnosed pre-diabetes.

ClinicalTrials.gov: NCT01960205.

* Corresponding author at: Department of Endocrinology, Shandong Provincial Hospital affiliated to Shandong University, 324 Jing 5 Road, Jinan 250021, China.
E-mail address: zhouxinli0301@163.com (X. Zhou).

[1] Zixuan Wang and Dengcheng Xu contributed equally to this study.

http://dx.doi.org/10.1016/j.diabres.2017.05.012
0168-8227/

1. Introduction

Type 2 diabetes mellitus (type 2 DM) is a metabolic disease with high mortality and morbidity [1], characterized by progressive β-cell dysfunction, requiring long-term therapeutic intervention [2]. More than 340 million individuals worldwide are affected and hundreds of millions are at risk of diabetes [3]. The overall prevalence of diabetes and pre-diabetes in the Chinese adult population were estimated to be 11.6% and 50.1% [4] However, people with IGT or IFG are asymptomatic and at high risk of diabetes and vascular disease [5]. Meanwhile, patients with overweight or obesity have a greater risk of diabetes. According to the World Health Organization (WHO) [6] and American Diabetes Association (ADA) [7] diagnostic criteria, IGT or IFG is a stage in the pathophysiology of patients with type 2 DM [8]. However, the incretin function in pre-diabetes is not adversely affected [9]. Meanwhile, epidemiological studies have shown that the risk of complications occurs in the early stage of diabetes. Therefore, early diagnosis and treatment of pre-diabetes reduces or delays the progress of diabetes mellitus, cardiovascular and microvascular disease.

DPP-4 inhibitors such as saxagliptin are the new therapeutic strategy for clinically confirmed type 2 DM. They improve the function of islet cells, promote regeneration of islet β-cells, protect islet function, and potentially slow down or even reverse the progression of type 2 DM [10]. In addition, compared with the traditional hypoglycemic drugs, saxagliptin is associated with higher safety and tolerability [11,12], and low rates of hypoglycemia and other adverse reactions [13–15]. However, prospective randomized controlled studies investigating the role of saxagliptin in pre-diabetes are rarely conducted. Therefore, we investigated the effect of saxagliptin therapy on body fat, blood glucose, and islet β-cell function in obese patients diagnosed with IGT or IFG, or both.

2. Methods

2.1. Study design and patients

This 24-week, prospective, randomized, controlled study was registered under Clinical trial reg. no. NCT01960205, with clinicaltrials.gov, and was conducted at Shandong Provincial Hospital affiliated to Shandong University between June 2013 and April 2016. The study was approved by the ethics committee of Shandong Provincial Hospital affiliated to Shandong University ethics committee. All the subjects provided written informed consent. All the patients were advised lifestyle interventions, including reasonable diet based on the formula for meal distribution in patients with moderate obesity and low physical labor [16]. The daily calorie intake and total nutrient distribution were calculated. Moderate exercise including diet combined with physical exercise was also recommended.

We screened men and women aged between 20 and 70 years who had a body-mass index (BMI) of 25 or higher combined with abdominal obesity (male waistline ≥90 cm, female waistline ≥80 cm in Asians), and impaired fasting glucose (IFG:FPG ≥6.1 mmol/L and <7.0 mmol/L and 2 h PPG <7.8 mmol/L after a 75 g glucose load) or impaired glucose tolerance (IGT; FPG <7.0 mmol/L and 2hPG ≥7.8 mmol/L and <11.1 mmol/L after a 75 g glucose load) [6,17,18].

The exclusion criteria were: type 1 diabetes, a history of diabetic ketoacidosis (DKA) or hyperosmolar non-ketonic coma; uncontrolled hypertension, a history of unstable angina or myocardial infarction within the previous 6 months; hemoglobinopathies or pancreatitis; severe gastrointestinal disease; hepatic disease, or elevation in aspartate amino transferase or alanine aminotransferase levels at least twice the maximum limit; a history of renal disease with a plasma creatinine concentration of at least 133 μmol/L (1.5 mg/dL); chronic hypoxic diseases (emphysema or cor pulmonale); hematological diseases; endocrine disorders (hypothyroidism, hyperthyroidism, Cushing's syndrome); mental disorders; acute illness; a history of intestinal surgery; fertile, pregnant or breastfeeding women; and clinical trial participation 3 months prior to enrolment.

Eligible participants were randomly assigned to one of the four groups: standard lifestyle (control group, $n = 5$) [16], standard lifestyle plus saxagliptin at a dose of 5 mg daily group (S5 group: conventional dose of saxagliptin, $n = 7$), standard lifestyle plus metformin 1,500 mg daily (Met group, $n = 6$), and standard lifestyle plus saxagliptin 2.5 mg daily (S2.5: low-dose saxagliptin, $n = 6$). We measured blood pressure (BP), bodyweight, height, waist circumference, hip circumference, body fat composition (Biospace Inbody 720) and laboratory parameters [including blood routine, FPG and 2 h PPG, fasting insulin (FINS), plasma creatinine and lipids total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), renal and liver function] before intervention and 4, 12, and 24 weeks after intervention. The HbA1c levels were measured at 0, 12 and 24 weeks. The 75 g oral glucose tolerance test (OGTT) and insulin release test (OGIRT) were used to evaluate insulin sensitivity or β-cell function based on HOMA index at baseline and 24 weeks later.

2.2. Efficacy and safety

The primary efficacy endpoint was the absolute change from baseline in FPG, 2 h PPG and HbA1c level at week 24. Secondary efficacy endpoints included the HOMA indices HOMA-IR and HOMA-β using the following equation: HOMA-IR = [FPG (mmol/L) * FINS (mIU/L)/22.5]; HOMA-β = 20 * FINS (mIU/L)/[FPG (mmol/L) − 3.5] [19,20]). The latter endpoint entailed assessment of BP, weight, height, waist circumference, hip circumference, BMI and body fat (Biospace Inbody 720). All the assessments were performed at the Laboratory Department or Endocrine Laboratory of the Shandong Provincial Hospital Affiliated to Shandong University with standardized and validated procedures.

All the adverse events (AEs) associated with the study drug were recorded and investigated, and graded as mild, moderate or severe in intensity. Symptoms suggestive of