Journal of Diabetes and Its Complications xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Effect of ketotifen in obese patients with type 2 diabetes mellitus☆

Sahar M. El-Haggar [a], Wael F. Farrag [b], Fedaa A. Kotkata [a,*]

[a] Clinical Pharmacy Department, Faculty of Pharmacy, Tanta University, Egypt
[b] Internal Medicine Department, Faculty of Medicine, Tanta University, Egypt

ARTICLE INFO

Article history:
Received 10 December 2014
Received in revised form 25 January 2015
Accepted 28 January 2015
Available online xxxx

Keywords:
T2DM
Mast cells
Ketotifen
Obesity
Inflammation

ABSTRACT

Aim: Mast cells are found to be an important contributor in obesity induced insulin resistance. We evaluate the effect of ketotifen in obese patient with type 2 diabetes (T2DM) treated with glimepiride.
Method: In a randomized controlled study we recruited forty-eight obese patients with T2DM from Internal Medicine Department at Tanta University Hospital, Egypt. They were classified into three groups: group 1, those who received glimepiride (GL) 3 mg/d alone; group 2, those who received GL 3 mg/d + ketotifen 1 mg once daily; and group 3, those who received GL 3 mg/d + ketotifen 1 mg twice daily. Fasting blood samples were obtained before and 12 weeks after treatment for biochemical analysis of glycemic and inflammatory biomarkers. Data were statistically analyzed by paired Student's t-test and one way analysis of variance; $p < 0.05$ was considered statistically significant.
Results: The obtained data suggested that the addition of ketotifen in twice daily dose has a beneficial effect on all measured parameters except adiponectin. However, glimepiride plus ketotifen once daily only affected the level of inflammatory biomarkers without any significant effect on other parameters.
Conclusions: The co-administration of ketotifen twice daily plus glimepiride improves glycemic and inflammatory process in obese patients with T2DM.

1. Introduction

Obesity is a major risk factor for insulin resistance and type 2 diabetes mellitus (T2DM). Although how obesity promotes insulin resistance is unclear, the inflammatory response is thought to be a potentially important mechanism, which could alter adipose tissue function, thus leading to systemic insulin resistance. The development of insulin resistance is associated with pro-inflammatory cytokines produced by infiltrating leukocytes and resident adipocytes within the adipose tissue in obese subjects (Sismanopoulos et al., 2013). A previous report has demonstrated that mast cells (MCs) are important inflammatory cells that participate in immune responses during allergic reactions. Recent studies, however, suggest that these cells also participate in other inflammatory diseases, such as cancers, inflammatory bowel disease, metabolic bone disease, renal injury, arthritis, atherosclerosis, abdominal aortic aneurysms, obesity, and diabetes (Wang & Shi, 2011). Higher numbers of mast cells were found in Wight adipose tissue from obese subjects compared with that of lean subjects; obese subjects also had significantly higher mast cell tryptase (MCT) concentrations in their serum than did lean individuals. These observations suggest a possible association between mast cells and obesity (Liu et al., 2009).

Ketotifen is a mast cell stabilizer used as anti-allergic drug. The most important finding of recent studies is that mast cell stabilization with cromolyn or ketotifen reduces body weight gain and improves glucose and insulin tolerance in mice without noticeable toxicity (Wang & Shi, 2011). Although the precise roles of mast cell interleukin-6 (IL-6) and interferon gamma (IFN-γ) in obesity and diabetes remain incompletely understood, the absence of these inflammatory cytokines in mast cells reduces body weight gain, glucose tolerance, and serum levels of insulin, and glucose (Wang & Shi, 2011). No clear data on the effect of mast cell stabilizers on human were reported, so the present study was designed to investigate the effect of ketotifen on glycemic parameters (fasting blood glucose (FBG) and hemoglobin A1c (HbA1c)) and some inflammatory biomarkers (IL-6 and leukotriene B4 (LTB4)) in obese patients with T2DM.

2. Patients and methods

2.1. Patients

From January 2013 to April 2014, we recruited forty-eight obese patients with T2DM from internal medicine department at Tanta University Hospital, Egypt. The inclusion criteria were patients who had

Conflict of interest: There are no conflicts of interest.
There is no source of financial support for the research (no fund from any organization).
* Corresponding author at: 31111. Tel.: +20 1017872669; fax: +20 403335466.
E-mail address: Fedaa.eldeep@yahoo.com (F.A. Kotkata).

http://dx.doi.org/10.1016/j.jdiacomp.2015.01.013
1056-8727/

body mass index (BMI) ≥ 30 kg/m^2, had diabetes duration from 5 to 10 years, were treated with glimepiride alone and had ages ranging from 45 to 55 years. The exclusion criteria were patients who had any other inflammatory disease (bone, asthma, etc.), severe hepatic or renal disease, epilepsy and also pregnant or lactating females.

2.2. Study design

A total number of 48 patients who fulfilled the selection criteria were enrolled in the study. The study has been approved by the national research ethics committee (Tanta University ethical committee) and has been performed in accordance with the ethical standards as laid down in the 1964 declaration of Helsinki and its later amendments or comparable ethical standards. An informed written consent was obtained from all patients included in the study. The study design was a parallel randomized controlled study to compare the effect of two different doses (once and twice daily) of ketotifen (Ketoti®, Pharco, Egypt) in addition to glimepiride (GL) (Amaryl®, Sanofi-Aventis, Berlin, Germany). The patients were divided into three groups (each group [$n = 16$]) as follows: group 1, those who received glimepiride (GL) 3 mg/d alone; group 2, those who received GL 3 mg/d plus ketotifen 1 mg once daily; and group 3, those who received GL 3 mg/d plus ketotifen 1 mg twice daily for 12 weeks. Patients were followed up at monthly intervals for assessment of compliance to the study medication and adverse events. All blood samples were obtained after a 10- to 12-hours fasting period. Blood samples were collected in tubes containing EDTA and centrifuged immediately. Plasma was separated, coded and stored at −80 °C until analysis.

2.3. Demographic characters

Patients' medical history was taken to ensure the absence of any interacting or interfering drugs. Demographic data were collected at baseline using questionnaire. Information collected included age, sex, diabetes duration, BMI, FBG and HbA1c (Table 1).

2.4. Anthropometric evaluations

Weights were measured and recorded to the nearest 0.5 kg. Body heights were measured and recorded to the nearest centimeter. Body mass index was calculated which is defined as the weight in kilograms divided by the square of the height in meters; i.e., BMI = weight (kg)/height^2 (m).

Height and weight were measured using Detecto scale (Detecto Company, 203 East Daugherty Sheet, USA).

2.5. Biochemical assays

2.5.1. Blood glucose and hemoglobin A1c

Fasting blood glucose (FBG) levels were assayed using glucose oxidase method (Kaplan, 1984) (Spinreact, Spain). Hemoglobin A1c% (HbA1c %) was assayed by ion exchange method (Bissé & Abraham, 1985) (Biosystems, Spain).

2.5.2. Assay of adiponectin, interleukin-6 (IL-6), leukotriene B4 (LTB4) and mast cell tryptase (MCT)

Enzyme-linked immunosorbent assay (ELISA) using commercial kits was carried out according to the manufacturers' instructions for assay of plasma adiponectin (Assaypro, USA), MCT (Wuhan Elaab Science Company, China), IL-6 Platinum ELISA (eBioscience, San Diego) and LTB4 (R&D Systems, USA).

2.5.3. Lipid panel

Plasma was used for determination of lipid profiles including total cholesterol (TC) which was measured by enzymatic colorimetric method (Watson, 1960), triglycerides (TGs) which was measured by enzymatic-colorimetric method (Fossati & Prencipe, 1982) and high density lipoprotein (HDL-C) which was determined by precipitation method (Warnick & Wood, 1995) using commercial kits (BioMed, Germany). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula (Friedewald, Levy, & Fredrickson, 1972) where LDL-C = [TC − HDL-C − (TGs/5)] provided that TGs level is less than 400 mg/dl (Friedewald et al., 1972).

Table 1
Demographic data of patients at baseline.

Characteristics	Group 1	Group 2	Group 3
Number	16	16	16
Sex (M/F)	3/13	3/13	4/12
Age (years)	51.3 ± 4.5	50.1 ± 4.6	49.1 ± 4.9
Diabetes duration	7.9 ± 2.5	7.1 ± 2.7	8 ± 2.5
BMI (kg/m^2)	37.3 ± 5.4	37.5 ± 6.1	37.8 ± 5.3
FBG (mg/dl)	190.3 ± 50.6	205.9 ± 38.1	183.2 ± 52
(mmol/l)	(10.6 ± 2.8)	(11.4 ± 2.1)	(10.2 ± 2.9)
HbA1c %	7.9 ± 0.96	8 ± 0.76	7.6 ± 0.88
(mmol/mol)	(63 ± 10.5)	(64 ± 8.3)	(60 ± 9.6)

Data presented as mean ± SD. Group 1: obese patients with *type 2 diabetes* treated with glimepiride 3 mg/d alone; Group 2: obese patients with *type 2 diabetes* treated with glimepiride 3 mg/d plus ketotifen 1 mg once daily; Group 3: obese patients with *type 2 diabetes* treated with glimepiride 3 mg/d plus ketotifen 1 mg twice daily; M: male; F: female; BMI: body mass index; FBG: fasting blood glucose; HbA1c: hemoglobin A1c.

2.6. Statistical analysis

Data were analyzed using SPSS statistical package version 22.0, IBM Corporation Software Group, USA. Paired Student's t-test was used to assess any significant difference between each group at baseline and after 12 weeks of treatment course. One way analysis of variance (ANOVA) test followed by Bonferroni or Tamhane tests was used to assess any significant difference among the three groups at baseline and after 12 weeks. Values were presented as mean ± standard deviation (SD). Pearson's correlation test was used to assess the correlation between measured parameters after the effective intervention. Fisher's exact test was used for statistical analysis of the reported side effects. All p values were two-tailed and $p < 0.05$ was considered significant for statistical analysis.

3. Results

3.1. Characteristics of patients

At baseline, there were no significant differences between group 1 treated with glimepiride alone and intervention groups (group 2 and group 3) treated with glimepiride plus ketotifen once and twice daily respectively), in demographic or anthropometric parameters (Table 1).

3.2. Effect of ketotifen on glycemic and metabolic parameters

A summary of the mean ± SD values of variables at baseline and after 12 weeks in all groups is presented in (Table 2). After 12 weeks of co-treatment with glimepiride plus ketotifen 1 mg twice daily (group 3), there were significant decreases in BMI, FBG, HbA1c, TC, TGs and LDL-C. While there was a significant increase in HDL, there was no significant change in plasma adiponectin level. For groups 1 and 2 treated with glimepiride alone or plus ketotifen once daily), there were no significant differences in these outcome variables measured over the intervention period.

The comparison of the three groups before and 12 weeks after treatment revealed that, there were no significant differences in measured parameters between all groups at baseline. After 12 weeks,

Please cite this article as: El-Haggar, S.M., et al., Effect of ketotifen in obese patients with type 2 diabetes mellitus, *Journal of Diabetes and Its Complications* (2015), http://dx.doi.org/10.1016/j.jdiacomp.2015.01.013