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Multifactorial effects of vildagliptin added to ongoing metformin therapy in patients with type 2 diabetes mellitus

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ABSTRACT

Background: To assess the efficacy of a vildagliptin and metformin combination therapy to a metformin monotherapy in type 2 diabetes mellitus patients.
Methods: Sixty-one patients with diabetes inadequately controlled by a metformin monotherapy were randomized to treatment with a combination therapy of vildagliptin 100 mg and a metformin versus metformin monotherapy. This was a 12-week randomized parallel group study. During the study we assessed parameters of glycemic and lipid metabolism as well as the treatment effects on the release of proinflammatory and antiinflammatory cytokines.
Results: Compared with baseline values we observed a significant improvement of glycaemic parameters such as HbA_{1c}, FPG, PPG, FPI, HOMA-IR and HOMA-β index as well as decrease of TCh, TG and LDL and an increase of HDL with the greatest extent of vildagliptin plus a low-dose metformin therapy group. A metformin combination therapy significantly decreased such inflamation parameters as hs-CRP, ox-LDL, TNF-α and IL-1β levels relative to monotherapies. All treatments were well tolerated and there was no incidence of hypoglycaemia.
Conclusions: Vildagliptin added to an ongoing metformin therapy allows to achieve better metabolic control parameters in comparison with a metformin monotherapy and the combination treatment is well tolerated and has a low risk of serious adverse effects.
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Introduction

Type 2 diabetes is one of the most rapidly growing diseases correlated with serious micro- and macrovascular complications that increases morbidity and mortality in worldwide population [1]. Effective treatment of type 2 diabetes is based on adequate glucose control and other risk factors by a lifestyle modification and current pharmacotherapies. Achieving optimal metabolic goals in diabetes is still a difficult aim to obtain and thus, there is still need for further trials in the understanding of pathophysiological mechanisms that contribute to the onset and progression of the disease and permit the development of more effective options for diabetes treatment [2].

Metformin is a well-known drug recommended as the first-line treatment for type 2 diabetes. It is efficient, safe and has beneficial effects on a large number of metabolic parameters leading to a reduction of micro- and macrovascular complication [3]. Vildagliptin, as a new agent, is a long-acting, competitive and reversible inhibitor of the enzyme dipeptidyl peptidase-IV that affects an enteroinsular axis by increasing plasma levels of the intact incretin hormones like GLP-1 and/or GIP. Thus, it improves glucose homeostasis mainly by glucose-dependent β-cell insulin synthesis and suppression of inappropriate α-cell glucagon secretion [4,5].

The aim of this study was to assess the effects of the combination therapy using vildagliptin with metformin compared with metformin monotherapy in type 2 diabetes mellitus patients on glycaemic control as well as the efficacy on a lipid profile, an

Abbreviations: BMI, body mass index; CRP, high-sensitivity C-reactive protein; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HbA_{1c}, glycated hemoglobin; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; hs-oxLDL, oxidized LDL fraction; IL-1, βinterleukin 1β; PAI-1, plasminogen activator inhibitor-1; PPG, postprandial plasma glucose; TNF-α, tumor necrosis factor-α.

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inflammatory state and haemostatic parameters crucial factors in the atherosclerotic process.

Materials and methods

Study population

Our population consists of 40–65 year-old male and female patients with type 2 diabetes and the mean HbA_{1c} 7.5%, who had received a metformin monotherapy for at least 6 months and were on a stable dose of ≥1500 mg daily for over 3 months before visit 1. BMI in the range of 25–35 kg/m^2 was an additional inclusion criterion. The main exclusion criteria contained: the history of type 1 diabetes, diabetes as a result of a pancreatic injury or secondary forms of diabetes, acute metabolic diabetic complications (ketoacidosis, hyperosmolar state), the history of serious cardio-vascular events within the past 6 months (myocardial infarction, unstable angina, coronary artery bypass surgery, percutaneous coronary angioplasty or stroke), congestive heart failure requiring pharmacological treatment, clinically significant cardiac defects or arrhythmias, malignancy including leukemia and lymphoma within the last 5 years, serious liver and renal diseases, endocrine disorders, malabsorption syndromes or surgery on the digestive system and the history of alcohol or active substance abuse within the last 2 years. Patients with contraindications according to the label of metformin, treated in the past with no anti-diabetic agent other than metformin and with clinically significant laboratory abnormalities such as alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 2 times the upper normal limit, serum creatinine ≥ 130 μmol/l or estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73m^2. The most common concomitant disorders were hypertension and hyperlipidemia treated by commonly used antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics and β-adrenolytics), lipid lowering agents (statins) and antiplatelet inhibitors (acetylsalicylic acid).

Study design

It was a 12-week randomized parallel group study conducted at the Department of Internal Medicine and Clinical Pharmacology, Medical University of Silesia. Patients with diabetes inadequately controlled by an ongoing metformin monotherapy attended one screening visit (visit 1) to assess inclusion and exclusion criteria. Eligible sixty-one patients at the baseline (visit 2) were randomized to one of four treatment groups using a computer-generated allocation schedule to receive: vildagliptin 100 mg daily plus metformin 1500 mg daily (low-dose combination), vildagliptin 100 mg daily plus metformin 3000 mg daily (high-dose combination), metformin 1500 mg daily (low-dose monotherapy,) or metformin 3000 mg daily (high-dose monotherapy). Efficacy and tolerability were assessed during the endpoint visit at week 12 of the treatment (visit 3). There were not any additional standard visits within the 12 weeks but patients had possibility to see the researchers at any time during study if necessary.

Study assessments

At the baseline (week 0) and at the end of the endpoint (week 12) we evaluated such parameters as: fasting plasma glucose (FPG), postprandial plasma glucose (PPG), glycated hemoglobin A_{1c} (HbA_{1c}), fasting plasma insulin (FPI), homeostasis model assessment β-cell function index (HOMA-β), homeostasis model assessment insulin resistance index (HOMA-IR), total cholesterol (TCh), triglycerides (TG), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, oxidized low-density lipoprotein (oxLDL) and high-sensitivity C-reactive protein (hs-CRP), proinflammatory cytokines produced by stimulated monocytes: tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β), haemostatic parameters: fibrinogen and plasminogen activator inhibitor-1 (PAI-1), body weight, body mass index (BMI), systolic (SBP) and diastolic blood pressure (DBP) as well as vital signs and 12-lead electrocardiograms. Standard hematology and biochemistry laboratory assessments were also made at both visits. All plasmatic parameters were determined after a 12-h overnight fasting, with the exception of PPG, which was determined 2 h after a standardized meal. Venous blood samples were taken from all patients between 8:00 and 9:00 a.m.

To evaluate the tolerability assessments, all adverse events were recorded. The patients were provided with glucose monitoring devices and supplies, and also instructed on their use. Hypoglycaemia was defined as the presence of symptoms suggestive of hypoglycemia, confirmed by self-monitored glucose <56 mg/dl (3.1 mmol/l). Severe hypoglycemia was defined as an episode requiring assistance of another party.

All laboratory assessments were made by a Pharmacology Department Laboratory in the Medical University of Silesia. Assays were performed with standardized and validated procedures according to good laboratory practice.

Glycated hemoglobin level was measured by a spectrophotomery method (Cormay HbA1c, Poland) with intra- and inter-assay coefficients of variation (CVs) 2.8 and 2.62%, respectively.

Fasting and postprandial plasma glucose was assayed by a spectrophotomery method (Liquick Cor-Glucose, Cormay, Poland) with intra- and inter-assay CVs 1.5 and 1.3%, respectively.

Plasma insulin was assayed with a commercially available immunoenzymatic assay for the measurement of human insulin in serum according to manufacturer's instructions (Human Insulin ELISA kit, Invitrogen, USA). The intra- and inter-assay CVs were 4.8% and 8.1%, respectively. Homeostasis Model Assessment Index (HOMA-β) and an estimate of insulin resistance (HOMA-IR) were calculated as follows:

$$\text{HOMA-}\beta = \frac{20 \times \text{FPI}(\mu\text{U/l})}{\text{FPG}(\text{mg/dl})/18.016 - 3.5}$$

$\text{HOMA} - \text{IR} = [\text{FPI}\,(\mu\text{U/l})] \times [\text{FPG}(\text{mg/dl})/18.016/22.5]$ (normal if <2.5, marker of insulin resistance if ≥2.5).

Fasting lipid profile: total cholesterol, triglycerides, high-density lipoprotein cholesterol were determined using an spectrophotomery assay (Cormay, Poland). The intra-assay coefficient of variation (CV) and inter-assay CV was for total cholesterol 1.4% and 1.55%, respectively, for triglycerides – 1.1% and 1.55%, respectively, and for high-density lipoprotein cholesterol – 1.36% and 0.9%, respectively. Low-density lipoprotein cholesterol was estimated if triglycerides were ≤400 mg/dl and calculated with the Friedewald formula:

$$\text{LDL cholesterol (mg/dl)} = \text{TCh (mg/dl)} - \text{HDL(mg/dl)} - [\text{TG(mg/dl)}/5]$$

Oxidized low-density lipoprotein was determined using a two-site enzyme immunoassay (Mercodia Oxidized LDL ELISA kit, Mercodia, Sweden). Intra-assay CV was 5.5% and inter-assay CV was 6.2%.

High-sensitivity C-reactive protein was measured with the use of a commercially available Immundiagnostik CRP ELISA test according to manufacturer's instructions (CRP ELISA kit; Enzyme Immuno Assay, Immundiagnostik, Germany). The intra- and inter-assay CVs were 6% and 11.6%, respectively.

Cytokine release from blood monocytes was measured as previously described [5,6]. Monocytes were isolated from peripheral blood before and after the treatment. Tumor necrosis factor-α and

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