The differential influence of glimepiride and glibenclamide on insulin resistance and adiponectin levels in patients with type 2 diabetes

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Abstract. Several studies have demonstrated the decreased insulin resistance (IR) in persons with type 2 diabetes mellitus (T2DM) treated with glimepiride. Those suggest this might be associated with observed higher concentrations of adiponectin. We assessed if there is a difference in IR and metabolic syndrome components between glimepiride and glibenclamide treatment as well as adiponectin concentration in T2DM. Our research observed 20 T2DM patients treated with glibenclamide and 20 switched to glimepiride (n = 20) treatment for 24 weeks. Anthropometric measurements and laboratory analysis were performed at the beginning and at the end of treatment while IR was accessed by homeostasis model assessment of insulin resistance (HOMA-IR). The glimepiride group revealed better glycaemic control compared to glibenclamide group. Moreover, the adiponectin concentration increased (23.9 ± 17.3 to 29.1 ± 12.2 ng/mL, p = 0.087) whereas it decreased in the glibenclamide group (34.3 ± 22.6 to 20.3 ± 11.3 ng/mL, p = 0.011) following 24 weeks of treatment. The serum adiponectin and HOMA-IR were inversely correlated within the group of glibenclamide (r = –0.667, p = 0.009). The present study demonstrates that glimepiride might have beneficial effect on IR compared to glibenclamide, as suggested. However, this observation needs further study investigation among other formulations of SU.

Key words: Insulin resistance, Adiponectin, Glimepiride, Glibenclamide

SULFONYLUREAS (SUs) represent a group of glucose lowering agents acting by stimulating insulin release through a direct action on β cells sulfonfylurea receptors 1 (SUR 1). The frequent world wide use of SUs despite new drug generations, due to their cost-effectiveness, and in general “last line” treatment before insulin, remain effective options [1]. Glimepiride is a second generation sulfonfylurea formulation with a wide range of extra pancreatic effects which showed more favorable effects on insulin resistance (IR) compared to other sulfonfylurea agents [2].

Several studies have demonstrated that the decreased IR due to glimepiride might be associated with increased serum adiponectinemia [3, 4].

Insulin resistance is probably the “core” pathophysiological in the course of type 2 diabetes (T2DM) and metabolic syndrome (MS) characterized with central obesity, dyslipidaemia and hypertension according to the 2009 worldwide definition criteria [5].

Adiponectin is a human protein actively secreted by the visceral adipose tissue considered to be an important link between IR, inflammation and atherosclerosis and to have a cardio protective role [6, 7]. It has been demonstrated that adiponectin concentration negatively correlates with the degree of IR, obesity, oxidative stress [8] as well as endothelial dysfunction [6]. It is considered to
be a very useful positive predictive biomarker for cardiovascular risk [9]. It has been demonstrated that glimepiride reduces inflammatory cytokines and oxidative stress such as ox-LDL and 8-iso PGF (2α) [4]. Due to the fact that glimepiride compared to all other SUs might act beneficially on other metabolic changes in T2DM, several studies suggesting that this might be due to adiponectin, i.e. high-molecular adiponectin following glimepiride treatment [10, 11].

Thus, we aimed to assess whether there are differences in plasma adiponectin concentration and its repercussion to IR and MS components in two types of SU regimes in overweight and obese T2DM patients as previously suggested on molecular level.

**Material and Methods**

**Study population**

This was open label, randomized, prospective and convenient sampling study undertaken in the out-patient setting of the Clinic of Endocrinology, University Clinical Center of Kosovo, for a period of 12 months. The protocol comprised 24-weeks of treatment period. From the screened 167 patients, 40 patients met the inclusion criteria with a body mass index (BMI) >25 kg/m² with central obesity and treatment with glibenclamide for more than 3 months before the screening period. 127 patients did not meet the study inclusion criteria.

Non inclusion criteria were: impaired kidney function (creatinine >1.5 mg/dL), anemia (Hb <115 g/L), severe heart valve disease, atrial fibrillation as detected by electrocardiography, symptoms or signs of severe retinopathy, hypertension, impaired liver function (transaminases >40 U/L), severe neuropathy (Neuropathy Disability Score/NDS ≥5) [12], concomitant diseases (arthritis) or conditions that could possibly be associated with an acute-phase reaction (such as estrogen use), infections such as viral rhinitis or suspicious conditions, coronary artery disease as determined by 12 Leads Electrocardiography (ECG) and exercise testing according to the American Heart Association 12 [13], those taking any agents that might significantly impact the glycemic control such as corticosteroids and metformin treatment (in order to determine the pure effect of glimepiride and glibenclamide on insulin resistance in both groups of treatment).

**Study protocol**

Medical history, physical examination, standard ECG record, exercise test and 12-hours fasting laboratory tests were obtained for all participants. Patients were randomly assigned either to glimepiride treatment group either to continue with glibenclamide (n = 20).

The dose adjustment of two agents was based on: glibenclamide 1.25 milligram equivalent to 1 mg of glimepiride [14]. Glibenclamide and glimepiride doses were progressively decreased or increased in order to achieve glycemic control. The frequency of the patients’ visits depended on their glycemic control. Glimepiride doses were ordered from 1 mg, which was the lowest dose, to 7.5 mg, which was the highest dose, whereas glibenclamide dosage ranged from 2.5 mg to 15 mg.

**Laboratory measurements**

The following laboratory parameters were evaluated at the beginning and at the end of the study: fasting venous plasma glucose which was determined by means of an enzymatic method (reference value 3.6–6.4 mmol/L), lipid profile included serum total cholesterol (reference values 3.6–5.7 mmol/L), high density lipoproteins (HDL) cholesterol (reference value 0.78–1.81 mmol/L) and triglycerides (reference value 0.4–1.7 mmol/L) measured by an automated enzymatic methods, whereas low density lipoproteins (LDL) cholesterol (reference values 3.6–5.7 mmol/L) was measured by means of Friedewald equation [15]. Hemoglobin A1C (HbA1C) was determined by standardized automated assays and the results were compared with chromatography spectrophotometric method (reference value 4–6.5%; the difference between the results obtained by these two methods not being statistically significant [p = 0.784]). Insulin was determined by means of CLIA (ChemiluminescentImmunoAssay, IMMULITE 1000, DPC-Siemens) (reference value 6–27 μIU/mL), adiponectin by an enzyme-linkedimmunosorbent assay (ELISA, DIA Source, HumaReaderSungle plus) (range 3–30 μg/mL), and hs-CRP by an enzyme-linkedimmunosorbent assay (ELISA, DIA Source HumaReaderSungle plus) (reference value 1–3 mg/L).

Homeostasis model assessment of insulin resistance (HOMA-IR) [fasting insulin (μIU/mL) × fasting glycemia (mmol/L)/22.5] was used for IR assessment. It has been demonstrated that HOMA-IR correlates well with the “gold standard” clamp-derived values [5].

Eligible subjects signed an informed consent at the study entry after full explanation of the purpose and nature of all procedures. The study protocol was approved by Institutional Ethics Committee of University Clinical Centre of Kosova and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

**Statistical analysis**

Statistical analyses were performed using InStat 3 program. Data are presented as mean ± SD. Statistical significance between the groups was assessed by the Student t-test or Mann-Whitney test for independent samples and paired t-test or Wilcoxon sign-rank test for
dependent samples depending on the data distribution. The $X^2$ statistics was used to assess differences between categorical variables. Target power was 80% for 40 patients included in the study and $p < 0.05$ was considered statistically significant.

**Results**

The study population had mean age 55.43 ± 8.3 years with diabetes duration of 3.73 ± 3.3 years. The baseline characteristics are given in Table 1. Out of total, 34 patients completed the entire study, 3 of the patients we excluded due to the antibiotics needs for infections and 3 of them withdrawn the study for unknown reasons. Serum adiponectin concentration increased in the glimepiride group (from 23.9 ± 17.3 to 29.1 ± 12.2, $p = 0.08$) whereas it decreased in the glibenclamide group (from 34.3 ± 22.6 to 20.3 ± 11.3, $p = 0.011$) (Fig. 1) Similarly, HOMA-IR decreased significantly (from 3.0 ± 1.5 to 1.9 ± 1.4, $p = 0.02$) in the glimepiride group. No significant changes in plasma triglyceride, total cholesterol, LDL-cholesterol, HDL-cholesterol and high sensitive C-reactive protein (hs-CRP) levels were observed (Table 2). In glimepiride waist circumference was reduced significantly (from 108.5 ± 6.7 to 106.2 ± 6.5, $p = 0.0014$), whereas in the group of glibenclamide no significant changes were evident. HbA1c was significantly reduced ($p < 0.0001$) in both groups (Table 2).

It was noticed that changes in serum adiponectin and HOMA-IR were inversely correlated within the group of glibenclamide ($r = -0.667, p = 0.009$) (Fig. 2), whereas in the glimepiride group no correlation was detected in the changes of serum adiponectin and HOMA-IR after the treatment (Fig. 3).

**Discussion**

The general conclusion of our study research is that there is a significantly higher serum concentration of adiponectin in a group of patients treated with glimepiride, lower IR regardless of glycaemic control. This might be due to extra pancreatic effects of glimepiride as suggested [10, 11]: the inhibition of hepatic gluconeogenesis, activation of insulin mediated glycogen synthesis and increase glucose uptake in the peripheral tissue [2, 10, 16]. Inukai et al. [2] demonstrated that glimepiride stimulates adipocyte differentiation via enhancement of peroxisome proliferator-activated receptor gamma (PPAR-gamma) activity by increasing secretion of adiponectin from adipose tissue, thereby reducing IR. We found lower BMI and body weight in the glimepiride group, but only the decreased hip perimeter, while in the group of glibenclamide no changes were obvious after the treatment. In a large surveillance study of type 2 diabetic patients in Germany, body weight was reduced in relation to baseline BMI in all patients after 8 weeks of treatment with glimepiride [17]. All these anthropometric changes are related to the amelioration of insulin resistance.

Different lipid profile in our study were not significant in both groups of treatment. This can also be attributed to the fact that mean disease duration was shorter, which could have delayed the onset of marked dyslipidemia.

In our study, adiponectin concentration increased after glimepiride treatment, although it did not reach the statistical significance. In the group of glibenclamide, the adiponectin levels at the end of treatment were decreased. This might be explained based on that glibenclamide with optimal treatment dose can’t increase adi-

### Table 1  Baseline clinical and laboratory data of the study patients

| Variables | $n = 40$ | Mean ± SD |
|-----------|---------|-----------|
| Age (years) | 55.43 ± 8.3 | |
| Sex (female/male) | 21/19 | |
| Duration of diabetes (years) | 3.73 ± 3.3 | |
| Weight (kg) | 82.77 ± 14.7 | |
| Height (m) | 1.68 ± 0.1 | |
| BMI | 29.2 ± 3.8 | |
| Waist (cm) | 102.8 ± 10 | |
| Hip (cm) | 108.4 ± 8.3 | |
| Waist to hip ratio | 0.95 ± 0.08 | |
| Heart rate (beats/minute) | 69.2 ± 6.4 | |
| Systolic blood pressure (mmHg) | 126 ± 9.3 | |
| Diastolic blood pressure (mmHg) | 81.6 ± 4.3 | |
| Fasting plasma glucose (mmol/L) | 8.97 ± 2.4 | |
| Fasting plasma insulin (ulU/mL) | 7.7 ± 4.7 | |
| HbA1C (%) | 8.9 ± 1.4 | |
| HOMA-IR | 2.9 ± 1.7 | |
| Total cholesterol (mmol/L) | 5.1 ± 1.3 | |
| Triglycerides (mmol/L) | 1.8 ± 1 | |
| HDL (mmol/L) | 1 ± 0.3 | |
| LDL (mmol/L) | 3.36 ± 0.9 | |
| hs-CRP (mg/L) | 6.4 ± 4.8 | |
| Adiponectin (ng/mL) | 27.9 ± 18.8 | |

Normally distributed data expressed as mean ± standard deviation. BMI, body mass index; FBG, fasting blood glucose; HbA1C, Glycosylated hemoglobin; HOMA-IR, Homeostasis model assessment of insulin resistance; HDL, Hight density lipoprotein; LDL, low-density lipoprotein.
Adiponectin levels as in experimental adipocytes via PPARγ partially activation with 10 fold higher doses [18]. Another study reported that hyperglycemia, especially intermittent hyperglycemia, decreased adiponectin production in adipocytes through mitochondrial superoxide overproduction [21]. In a group of obese subjects, plasma concentration of adiponectin was negatively correlated with fasting insulin and 2-hour glucose concentration [19].

Several reports suggest that reduction in plasma adiponectin level may be related to the elevation of insulin resistance [14, 20]. Adiponectin is a specific plasma glycoprotein, contained in adipose tissue, with various homologies to collagen, complement proteins, and hibernation associated proteins. Althogh, in the study of Fukuen et al. [21] it was found that glibenclamide treated adipocytes cell culture media enhanced adiponectin secretion as well as glimepiride. These results suggest that both glimepiride and glibenclamide enhance the production of adiponectin, which is an insulin-sensitizing hormone, via PPARγ partially activation in adipocytes, but these effect is dose dependent and highly different doses treatment than in humans with T2DM [21].

Hence, Li et al. found a significant negative correlation between the increase in the adiponectin levels and changes in the HbA1c after 24 weeks of glimepiride treatment [10].

Whereas, Pfützner et al. [22] found increased serum adiponectin levels caused by PPAR-gamma agonist differs from adiponectin levels induced by glimepiride treatment.

Glimepiride is reported to increase adiponectin gene expression in adipocytes, thus it is considered to play very important role for metabolic changes in diabetic patients [23].

Both study groups demonstrated a significant drop in the HbA1c. This finding is in agreement with the results of a randomized clinical trial with glimepiride and glibenclamide, where no clinically significant differences in mean concentrations of HbA1c have been observed between the treatment groups [24].

However, in the PREVENT-J (Pioglitazone and Sulfonylurea Remission from Type 2 Diabetes Mellitus Development and Anti-Atherosclerosis) multicenter prospective, randomized clinical trial in Japan, it was found a significant increase in serum adiponectin level, and decreases in hs-CRP and HOMA-IR in type 2 diabetic patients treated with pioglitazone group but not in SUs (glimepiride and gliclazide) and life style modification group of treatment [25].

Our study did not reveal any changes in hs-CRP after the treatment in both groups, with glimepiride and glibenclamide. While in a study by Koshiba et al. a significant decrease in HOMA-IR, tumor necrosis factor alpha (TNF-alpha), interleukin-6 (IL-6), and hs-CRP levels were observed, as well as an increase in plasma adiponectin levels.
nectin levels with glimepiride when compared to glibenclamide and insulin after 28 weeks of treatment [14]. This can probably be explained by the fact that, in our study, the duration of treatment for both groups was for 4 weeks shorter.

This study has several limitations that should be pointed out: primarily small number of participants and relatively short period of treatment which does not allow us to generate any general conclusion. In addition, we used HOMA-IR to measure IR, and not euglycaemic hyperinsulinaemic clamp, did not measure inflammatory cytokines and oxidative stress but just hs-CRP and we did not measure HMW-adiponectine but total adiponectine.

The present study demonstrates that glimepiride might have good effect on insulin resistance and metabolic syndrome components, and glibenclamide do not increase adiponectin followed with no impact on insulin resistance; whereas both drugs have same effect on HbA1c levels in overweight type 2 diabetic patients. Glimepiride for these beneficial effect can continues to be the drug of choice when the other modern drugs are not available in clinical practice.

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**Disclosure**

None of the authors have any potential conflicts of interest associated with this research. The study was partially supported by Grant of Ministry of Science and Education of Kosovo.

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### Table 2 Changes in outcome parameters after 24 weeks of treatment

| Clinical characteristics | Glimepiride group (n = 19) | Glibenclamide group (n = 15) |          |
|--------------------------|-----------------------------|-----------------------------|----------|
|                          | Beginning                   | After                       | p-value  | Beginning              | After              | p-value  |
| Weight (kg)              | 82.6 ± 17.0                 | 82.3 ± 15.4                 | 0.515    | 81.5 ± 9               | 80.9 ± 8.7        | 0.423    |
| BMI                      | 29.4 ± 4.0                  | 29.1 ± 3.8                  | 0.257    | 28 ± 2.5               | 28.0 ± 2.8        | 0.289    |
| Waist (cm)               | 102.5 ± 11.7                | 100.8 ± 11.7                | 0.113    | 101.4 ± 8.4            | 99.8 ± 5.6        | 0.384    |
| Hip (cm)                 | 108.5 ± 6.7                 | 106.2 ± 6.5                 | 0.0014** | 107 ± 6.6              | 106.9 ± 5.6       | 0.907    |
| Waist/Hip ratio          | 0.9 ± 0.1                   | 0.9 ± 0.1                   | 0.644    | 0.9 ± 0.1              | 0.9 ± 0.0         | 0.428    |
| Heart rate (beats/minute)| 70.4 ± 6.4                  | 69.2 ± 6.5                  | 0.246    | 67 ± 6.4               | 68.9 ± 4.5        | 0.09     |
| Systolic BP (mmHg)       | 126.8 ± 9.5                 | 125.8 ± 15.7                | 0.742    | 125 ± 8.5              | 129.3 ± 12        | 0.25     |
| Diastolic BP (mmHg)      | 81.3 ± 3.3                  | 81.3 ± 6.0                  | 0.999    | 80.7 ± 2.7             | 82.9 ± 4.7        | 0.25     |
| Fasting plasma glucose (mmol/L) | 8.5 ± 2.4 | 7.4 ± 1.1 | 0.101 | 9.6 ± 2.7 | 8.6 ± 1.5 | 0.170 |
| Fasting plasma insulin (mmol/L) | 8.8 ± 5.2 | 6.1 ± 4.8 | 0.078 | 6 ± 2 | 7.1 ± 3 | 0.145 |
| Total cholesterol (mmol/L) | 4.9 ± 0.9 | 5.0 ± 0.9 | 0.783 | 5.4 ± 1.6 | 5.6 ± 1 | 0.695 |
| hs-CRP (mg/L)            | 5.8 ± 3.8                   | 5.9 ± 4.1                   | 0.999    | 6.4 ± 4                | 8.3 ± 4.5         | 0.183    |
| Triglycerides (mmol/L)   | 1.7 ± 0.7                   | 1.7 ± 0.5                   | 0.744    | 1.9 ± 1.3              | 2.1 ± 1.3         | 0.497    |
| HDL (mmol/L)             | 0.9 ± 0.2                   | 1.0 ± 0.2                   | 0.249    | 1 ± 0.4                | 1.0 ± 0.3         | 0.640    |
| LDL (mmol/L)             | 3.3 ± 0.8                   | 3.3 ± 0.8                   | 0.779    | 3.4 ± 1                | 3.5 ± 1           | 0.593    |
| HbA1c (%)                | 8.9 ± 1.4                   | 8.4 ± 1.2                   | 0.0001** | 8.8 ± 1.4             | 8.3 ± 1           | 0.0002** |
| HOMA-IR                  | 3.0 ± 1.5                   | 1.9 ± 1.4                   | 0.020*   | 2.8 ± 1.5              | 2.6 ± 1           | 0.561    |
| Adiponectin (ng/mL)      | 23.9 ± 17.3                 | 29.1 ± 12.2                 | 0.087    | 34.3 ± 22.6            | 20.3 ± 11.3       | 0.011*   |

Normally distributed data expressed as mean ± standard deviation. BMI, body mass index; FBG, fasting blood glucose; HbA1c, Glycosylated hemoglobin; HOMA-IR, Homeostasis model assessment of insulin resistance; HDL, Hight density lipoprotein; LDL, low-density lipoprotein

* p < 0.05 vs. baseline, ** p < 0.0 vs. baseline
Fig. 2  Correlation between serum adiponectin and HOMA-IR in glibenclamide group
The serum adiponectin showed an inverse correlation with HOMA-IR after the treatment ($r = -0.667, p = 0.009$).

Fig. 3  Correlation of serum adiponectin and HOMA-IR in glimepiride group
No correlation was showed between serum adiponectin and HOMA-IR after the treatment ($r = -0.199, p = 0.413$).

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