

Effects of gliclazide add on metformin on serum omentin-1 levels in patients with type 2 diabetes mellitus

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ABSTRACT

Background: Omentin is a newly identified adipokine that has beneficial influence against cardiovascular disorders. Hence, considering the impact of anti-diabetic drug on omentin levels may provide an adjuvant strategy to protect diabetic patients against valuable clinical hazards. **Aim of the Study:** To investigate the influence of metformin alone or in combination with gliclazide on the level of serum omentin among patients with type 2 diabetes mellitus (T2DM). **Patients and Methods:** A total of 70 newly diagnosed patients with T2DM were enrolled in this randomized, double-blind prospective study, and divided into two equal groups based on treatment regimen in which Group 1 treated with metformin (1000 mg) and Group 2 treated with metformin (1000 mg) plus gliclazide (80 mg). Blood glucose levels, HbA1C, insulin levels, and serum omentin-1 were measured at baseline and after 12 weeks of treatment. **Result:** Use of gliclazide as an add-on therapy to metformin in patients with T2DM result in better glycemic control evidenced by significant reductions in the levels of blood glucose levels and HbA1C and much more improvement in insulin sensitivity evidenced by significant decreased in insulin resistance index, whereas it has adverse impact on serum omentin-1 levels evidenced by significant decrement in omentin-1 level in comparison to their pretreatment levels among Group 2 patients. **Conclusions:** Adding of gliclazide to metformin in treatment of patients with T2DM might extend the therapeutic action of metformin in regarding much better controlling of glycemic indices, but, at the same time, it might attenuate the cardioprotective effects of metformin by its adverse influence on serum omentin-1 levels.

Key words: Diabetes mellitus, gliclazide, metformin, omentin-1

INTRODUCTION

Diabetes mellitus is one of the chronic metabolic diseases characterized by high blood glucose level, due to the absence of insulin and/or defect in insulin action. The chronic elevation of blood glucose level in diabetic patient leads to complications and failure of many organs in the

body such as heart, kidney, and blood vessels.^[1] According to the WHO assessments, diabetes mellitus considered the seven cause of death in the next 20 years in the world.^[2] It is well-known that patients with diabetes are more prone to develop ischemic heart disease due to metabolic derangement that leads to accelerated atherosclerosis.^[3] There are numerous molecules produced from an adipose tissue called adipocytokines can estimate metabolic disturbances. Omentin is an as of late recognized novel adipocytokine secreted by visceral adipose tissue, and

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it falls under the classification of being a benefit adipokine. In which diminished in patients with obesity, insulin resistance (IR), and diabetes that assist in development of the metabolic disorder and other illness conditions such as atherosclerosis and immune system disorders.^[4] Omentin is determined by two isoforms omentin-1 and omentin-2 that predominantly found in visceral omental fat tissue. Omentin-1 has been demonstrated to be the real circling isoform in the human serum.^[5] The reduction in plasma omentin levels encourages the pathogenesis of IR, type 2 diabetes mellitus (T2DM), and cardiovascular disorders in individuals with overweight.^[6] Omentin-1 strengthens the role of insulin in the stimulus of Akt-phosphorylation, glucose uptake, while suppress the cytokine as tumor necrosis factor α that provoked inflammation so this shows that omentin-1 has a protective role as adiponectin. Omentin-1 levels in plasma and epicardial adipose tissue are diminished in patients with T2DM.^[7] Omentin act as multi-events as “anti-inflammatory, anti-atherogenic, anti-cardiovascular disease, and anti-diabetic properties in addition to its action on vascular by inducing vasodilatation of veins and lessens C-receptive protein provoked angiogenesis.^[8]

This study aimed to evaluate the influence of treatment for 12 weeks with 1000 mg metformin drug (insulin sensitizer) in Group 1 or in combination with 80 mg gliclazide drug (insulin secreting agent) in Group 2 on serum omentin-1 level and others biomarkers represented by blood pressure, pulse rate, body mass index, lipid profile, fasting serum glucose (FSG), postprandial blood glucose (PPG), HbA1C, fasting serum insulin, and IR index in patients with newly diagnosed T2DM.

PATIENTS AND METHODS

A total of 70 newly diagnosed patients with T2DM who visited (the specialized Center for Endocrinology and Diabetes, Al-Mustansiriya University – Baghdad) were enrolled in this study from December 2014 to June 2015. Two patients (1 from each group) did not complete the course of the treatment for unknown reasons and considered as default. Sixty-eight patients completed the 12 weeks course of treatment; patients were divided equally into two groups; Group 1 (20 males and 14 females) with mean age 51.35 ± 11.70 years, treated with 1000 mg metformin tablet, and Group 2 (19 males and 15 females) with mean age 51.21 ± 9.63 years, treated with 1000 mg metformin plus 80 mg gliclazide. The patients were considered excluded if they have type 1 diabetes or others conditions that linked with hyperglycemia such as (polycystic ovary syndrome and gestational diabetes), having any persistent diseases

of the heart, kidney, thyroid, lung, and liver and taking corticosteroids.

The blood samples were taken from fasting volunteers (for 8–12 h) through “vein puncture technique” by sterile (10 ml) syringe, at the beginning of the study (before starting metformin for the Group 1 and before starting metformin plus gliclazide for the Group 2) to measure specific parameters included in this study and after 12 weeks of taking the drugs to see the effect of the drugs on these parameters (FSG, PPG, HbA1C, Fasting serum insulin, and serum omentin-1 levels). Serum omentin-1 was determined by utilization of an instant serum omentin-1 ELIZA kit (BioVendor – Laboratorní medicína a.s., Czech Republic) and fasting serum insulin was determined by utilization of an instant insulin ELIZA kit (accubind ELISA Microwells, Monobind Inc., USA) (HumaReader HS, Human, Germany), in addition to determination of HbA1C concentrations by utilizing an instant kit (Clover A1c Analyzer, Infopia Inc., Korea). IR determined from the “homeostasis model assessment of IR (HOMA-IR) = insulin concentration (μ IU/ml) \times fasting glucose concentration (mg/dl)/405.

Analysis of the current data was carried out using SPSS software (version 22.0. 2013, IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean \pm standard deviation. On the other hand, the significance of difference of different means (quantitative data) was tested using Student’s *t*-test for difference between two independent means. Statistical significance was considered whenever the $P \leq 0.05$.

RESULTS

Therapeutic regimen used in this study showed variable influence on the studied parameters. Both of treated groups showed significant reductions in the levels of FSG, PPG, and HbA1C after 12 weeks of treatment regimen, while there were variable influences of treatment regimen on serum insulin levels over 12 weeks of treatment among study groups [Table 1]. It has been found that treatment with metformin alone result in reduction in serum insulin level in comparison to pretreatment values but not reached to the significant levels, whereas using of both of metformin and gliclazide in combination resulted in an increment (but not significant) in this parameter in comparison to their pretreatment levels. Regarding IR index represented by HOMA-IR showed that there was significantly decreased in IR index respect to their pretreatment values after 12 weeks treatment with metformin used in combination with gliclazide among Group 2, while the extent of reduction

Table 1: The effects of 12 weeks treatment with metformin alone (Group 1), or metformin plus gliclazide (Group 2) on glycemic indices and omentin-1

Parameter	Group 1 (n=34)			Group 2 (n=34)		
	Pretreatment	After 12 weeks	P	Pretreatment	After 12 weeks	P
FSG (mg/dl)	180.38±53.27	149.26±30.00*	0.001*	213.44±60.18	158.18±40.79*	0.0001*
PPG (mg/dl)	252.09±83.38	187.03±50.72*	0.0001*	277.32±91.70	173.74±53.80*	0.0001*
HbA1C (%)	8.92±1.86	7.22±1.34*	0.0001*	9.79±2.08	7.25±1.41*	0.0001*
Serum insulin (μIU/ml)	15.04±8.32	14.84±7.88	0.908	14.40±6.63	16.27±8.15	0.075
Insulin resistance index	5.93±4.78	4.76±3.51	0.179	7.19±4.62	4.88±4.28**	0.006
Serum omentin-1 (MIU/dl)	6.75±4.73	9.43±7.87	0.083	8.53±7.77	4.93±3.91**	0.016

Values are presented as mean±SD. *Significantly different compared to pretreatment level (using paired *t*-test), **Significant different between Group 1 and Group 2 (using unpaired *t*-test). n: Number of patients, SD: Standard deviation, FSG: Fasting serum glucose, PPG: Postprandial blood glucose

in IR among Group 1 treated with metformin alone not reached to the significant levels over 12 weeks of treatment. It is nice to mention that there is a significant decreased in IR index ($P = 0.043$) in Group 2 when it compared to Group 1 values after 12 weeks of treatment.

Regarding omentin-1 levels, it has been found that treatment with metformin alone result in clearly increment in omentin-1 level in comparison to pretreatment values among Group 1 but not reached to the significant levels, whereas using of both of metformin and gliclazide in combination for 12 weeks resulted in significant decrement in omentin-1 level in comparison to their pretreatment levels among Group 2. It's nice to mention that there was a significant reduction in this parameter after treatment regimens among patients of Group 2 compared to Group 1 ($P = 0.004$).

DISCUSSION

This study revealed that use of gliclazide as an add-on therapy to metformin in patients with the T2DM result in better glycemic control and much more improvement in insulin sensitivity, whereas it has an adverse impact on serum omentin-1 levels.

In this study, there were significant reduction and improvement in FSG, PPG, and HbA1C levels following treatment with metformin alone or metformin plus gliclazide for 12 weeks among type 2 diabetic patients (Group 1 and Group 2) in which the greatest reduction in these parameters were achieve by metformin plus gliclazide and these results consistent with other previous study.^[9,10]

In type 2 diabetic patients metformin considered the first choice treatment unless there is a contraindication, in which it acts through inhibition of hepatic gluconeogenesis, lower down intestinal absorption of glucose and fasting glycemia and improvement in insulin sensitivity. Combination of metformin with sulfonylureas acts with different mechanisms considered the most common one among combination

therapy in treatment of persistent hyperglycemia in type 2 diabetic patients by increasing insulin secretion and insulin sensitivity so more intensive glycemic controls.^[11,12]

Concerning the influences of treatment regimen on fasting serum insulin the results of current study were showed that serum insulin level changed in a different way when gliclazide was combined to metformin in treatment of patients with DM. Hence, treatment with metformin alone leads to nonsignificant reduction in serum insulin levels whereas adding gliclazide to metformin result in nonsignificant elevation in its. The trend of insulin changing with treatment regimen in this study (although it not reached significance level) is consistent with other previous study.^[13] Metformin treatment acts mainly through inhibition of hepatic glucose production, decrease workload on beta-cells and improved insulin sensitivity as a result in reduction in serum insulin levels, while during treatment with sulfonylurea as a single agent or combined with metformin result in an elevation of serum insulin levels in which gliclazide and metformin acts through different mechanisms as increase insulin secretion through blocked of ATP-sensitive K channels on pancreatic beta-cell and improve insulin sensitivity, respectively resulting an additive effect on glycemic control.^[14]

This study shown that IR lowered by metformin treatment for 12 weeks. This reduction of IR was further lowered and reached the degree of significance when both of gliclazide and metformin used together. Result of this study document the previous reports regarding beneficial influence of gliclazide on IR.^[15,16] The interesting finding in the present study is the synergistic improvement in insulin sensitivity when gliclazide used in combination with metformin in treatment of diabetic patients. It is important to mention that not all members of sulfonylureas have this helpful impact on IR. Gliclazide in contrast to other sulfonylureas drug has the ability to counteract the deteriorating effects of free radicals on insulin sensitivity of peripheral tissue by its anti-oxidant ability.^[17] Hence, the combinations of metformin with gliclazide showed

this clear improvement in insulin sensitivity by reduce IR by more than one mechanism.

The present study revealed that metformin alone behave positively in regard serum omentin-1 levels whereas combination therapy of metformin plus gliclazide are adversely affects omentin-1 level ($P < 0.05$). The influence of metformin toward omentin in the present study approves the finding of many previous studies which stated that treatment with metformin result in an increment in serum omentin levels.^[18,19]

It is nice to mention that to the best of our knowledge there are no published reports describing the combined effects of both of metformin and gliclazide (or any other sulfonylureas) on serum omentin-1 level. The current study highlights an important impact of adding gliclazide on cardioprotective action of metformin. It showed that adding of gliclazide might at least attenuate cardioprotective effects of metformin in term of reversing the positive influence of metformin on serum omentin-1 levels.

In this study, the changing trend of serum omentin-1 in response to treatment course can be attributed to different influence of both treatment regimens on serum insulin levels. It is well-known that serum insulin has negative impact on serum omentin-1 levels. Hence, in the case of treatment with metformin alone, plasma insulin is decreased due to the action of metformin as an insulin sensitizer.^[20] Whereas adding of gliclazide, although it enhances insulin sensitivity to a certain extent, is associated with an increment of plasma insulin levels.^[21]

CONCLUSION

Adding of gliclazide to metformin in treatment of patients with T2DM might extend the therapeutic action of metformin in regarding much better controlling of glycemic indices, insulin sensitivity, and lipid profile. However, at the same time, it might attenuate the cardioprotective effects of metformin by its adverse influence on body weight and serum omentin-1 levels.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Piero MN, Nzaro GM, Njagi JM. Diabetes mellitus – A devastating metabolic disorder. *Asian J Biomed Pharm Sci* 2014;4:1-7.
- Maiese K. mTOR: Driving apoptosis and autophagy for neurocardiac complications of diabetes mellitus. *World J Diabetes* 2015;6:217-24.
- Gastaldelli A. Role of beta-cell dysfunction, ectopic fat accumulation and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2011;93 Suppl 1:S60-5.
- Jaikanth C, Gurumurthy P, Cherian KM, Indhumathi T. Emergence of omentin as a pleiotropic adipocytokine. *Exp Clin Endocrinol Diabetes* 2013;121:377-83.
- Lu Y, Zhou L, Liu L, Feng Y, Lu L, Ren X, *et al.* Serum omentin-1 as a disease activity marker for Crohn's disease. *Dis Markers* 2014;2014:162517.
- Zhou JY, Chan L, Zhou SW. Omentin: Linking metabolic syndrome and cardiovascular disease. *Curr Vasc Pharmacol* 2014;12:136-43.
- Wang C. Obesity, inflammation, and lung injury (OILI): The good. *Mediators Inflamm* 2014;2014:978463.
- Wang H, Ni Y, Yang S, Li H, Li X, Feng B. The effects of gliclazide, metformin, and acarbose on body composition in patients with newly diagnosed type 2 diabetes mellitus. *Curr Ther Res Clin Exp* 2013;75:88-92.
- Hassan MH, Abd-Allah GM. Effects of metformin plus gliclazide versus metformin plus glimepiride on cardiovascular risk factors in patients with type 2 diabetes mellitus. *Pak J Pharm Sci* 2015;28:1723-30.
- Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: Perspectives on the past, present, and future. *Lancet* 2014;383:1068-83.
- Erem C, Ozbas HM, Nuhoglu I, Deger O, Civan N, Ersoz HO. Comparison of effects of gliclazide, metformin and pioglitazone monotherapies on glycemic control and cardiovascular risk factors in patients with newly diagnosed uncontrolled type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2014;122:295-302.
- Singh AK. Deciding oral drugs after metformin in type 2 diabetes: An evidence-based approach. *Indian J Endocrinol Metab* 2014;18:617-23.
- Hissa MR, Cavalcante LL, Guimarães SB, Hissa MN. A 16-week study to compare the effect of vildagliptin versus gliclazide on postprandial lipoprotein concentrations and oxidative stress in patients with type 2 diabetes inadequately controlled with metformin monotherapy. *Diabetol Metab Syndr* 2015;7:62.
- Kalra S, Madhu SV, Bajaj S. Sulfonylureas: Assets in the past, present and future. *Indian J Endocrinol Metab* 2015;19:314-6.
- Schweizer A, Dejager S, Foley JE. Impact of insulin resistance, body mass index, disease duration, and duration of metformin use on the efficacy of vildagliptin. *Diabetes Ther* 2012;3:8.
- Phung OJ, Sood NA, Sill BE, Coleman CI. Oral anti-diabetic drugs for the prevention of type 2 diabetes. *Diabet Med* 2011;28:948-64.
- Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, *et al.* Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: A nationwide study. *Eur Heart J* 2011;32:1900-8.
- Feng WH, Yuan XW, Tong GY, Wang WM, Hu Y, Shen SM, *et al.* Correlated increase of omentin-1 and adiponectin by exenatide, avandamet and dietary change in diet-induced obese rats. *Folia Biol (Praha)* 2013;59:217-24.
- Tan YL, Zheng XL, Tang CK. The protective functions of omentin in cardiovascular diseases. *Clin Chim Acta* 2015;448:98-106.
- Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: An overview. *Clin Sci (Lond)* 2012;122:253-70.
- Raz I. Guideline approach to therapy in patients with newly diagnosed type 2 diabetes. *Diabetes Care* 2013;36 Suppl 2:S139-44.