Effects of Metformin &/or Glimepiride on Resistin Level and Related Biochemical Markers in Type 2 Diabetes Mellitus

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Abstract:

Resistin is a novel adipocyte-secreted hormone proposed to link obesity with diabetes in mice and may play a similar role in human. The aim of our study was to examine the relationship of serum resistin level to insulin resistance, and related parameters. Also to evaluate the effect of metformin &/or glimepiride on resistin level and glycemic control in Type 2 Diabetes Mellitus (T2DM).

This is an open-label, randomized study carried out on 50 newly diagnosed type 2 diabetic patients and 20 healthy subjects. Patients were randomly divided into three groups and assigned for treatment with either metformin or glimepiride or both for 12 weeks. The comparisons were conducted between pre- and post-treatment for fasting serum glucose (FSG), glycocylated hemoglobin (HbA$_{1c}$), fasting serum insulin (FSI), insulin resistance (IR), body mass index (BMI) and serum resistin level.

At week 12, FSG, HbA$_{1c}$ and IR were significantly decreased in all groups. Resistin level decreased only in glimepiride group. Serum insulin levels show no significant change. Metformin significantly decreased while glimepiride significantly increased BMI. In our study serum resistin level did not correlate with markers of adiposity or diabetes. Circulating resistin is unlikely to play a major role in obesity, insulin resistance, or energy homeostasis in human and only glimepiride monotherapy showed an effect on resistin level after 3 months of treatment.

Keywords: Type 2 DM, resistin, metformin, glimepiride.

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تأثير المتفورمين و/أو لغليميبيرايد على مستوى الريزستين والمؤشرات الحيوية ذات العلاقة لمرضى السكري النوع الثاني

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الخلاصة:

الريزستين هرمون يفرز من الخلايا الشحمية تم اكتشافه حديثا، وقد أظهرت دراسات أجريت على نماذج من القوارض أنه يربط السمنة ومقاومة الجسم للانسولين بالسكري من النوع الثاني، ولكن أهميتها بالنسبة للانسان لاتزال مثيرة للجدل وتحتاج إلى توضيح. أظهرت دراسات أخرى ان ناهضات (PPARγ) تمنع تعبير الريزستين في الخلايا الشحمية، وبالتالي مفسرة طرق عمل بعض محفزات الانسولين.

تم تصميم هذه الدراسة لتقييم العلاقة بين مستوى الريزستين ومؤشرات السكري والبدانة لدى مرضى سكري من النوع الثاني تم تشخيصهم حديثا بالمرض. كذلك لمعرفة تأثير العلاج بالميتفورمين والغليميبيرايد على مستوى الريزستين وبقية المؤشرات. أجريت هذه الدراسة على 70 شخص من الذكور، منهم 20 شخصا من الاصحاء و50 مريضا حديثي الاصابه بالمرض تم توزيعهم إلى ثلاث مجموعات، 20 مريضا تمت معالجتهم بعقار الميتفورمين، و10 مرضى تمت معالجتهم بعقار الغليميبيرايد، و20 مريضا تمت معالجتهم بالميتفورمين والغليميبيرايد. تلقى جميع المرضى علاجهم لمدة 3 أشهر، وجمعت عينات الدم منهم قبل البدء بالعلاج وبعد 3 أشهر وذلك بعد صيام لمدة 12 ساعة على الأقل لقياس التغيير

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الحاصل في مستوى كل من سكر الدم، الهيموغلوبين الغليكوزيلاتي، الانسولين ومستوى الريزستين، فضلاً عن قياس وزن الجسم و طوله و مؤشر العلاقة بينهما.

أظهرت النتائج أن العلاج قد خفض نسبة السكر والهيموغلوبين الغليكوزيلاتي في الدم بالاضافة الى تقليل المقاومة للانسولين بشكل معنوي إيجابي في المجموعات الثلاث بالمقارنة مع القراءات الاولية، أما بالنسبة للريزستين فقد أنخفض في مجموعة الغليميبيرايد فقط. أما بالنسبة لمؤشر كتلة الجسم فقد أزدادت بالنسبة للمجموعات التي عولجت بالغليميبيرايد وحده أو مع الميتفورمين بينما انخفض مؤشر كتلة الجسم بشكل معنوي إيجابي في حالة العلاج بالميتفورمين وحده. وقد أظهرالريزستين علاقة غير كبيرة مع نسبة السكر في الدم، ومستوى الأنسولين ومؤشر كتلة الجسم، بينما أظهر علاقة إيجابية هامة مع مؤشر مقاومة الانسولين فقط بعد العلاج بالميتفورمين. إن تأثير الغليميبيرايد على مستوى الريزستين قد يكون نتيجة لقدرته على العمل على مستقبلات (PPARγ) ومستقلة عن تأثيره على مؤشرات السكري أو السمنة، مما أدى الى انخفاض الريزستين وتحسين فاعلية الانسولين في الجسم. اما بالنسبة للميتفورمين فقد حسن مؤشرات السكري والسمنة وفاعلية الانسولين بدون تأثير على مستوى الريزستين.

Introduction:

Type 2 diabetes mellitus is a chronic disease characterized by chronic hyperglycemia resulting either from a deficiency of insulin, or decreased insulin action, or both[1,2]. The proportion of patients with type 2 diabetes has been consistently increasing worldwide; Global estimates for the year 2010 predict a further growth of almost 50%, with the greatest increases in the developing countries of Africa, Asia, and South America[3]. Approximately 80% of persons with type 2 diabetes are overweight[4]. Obese people have increased resistance to the action of insulin and impaired suppression of glucose production by the liver, resulting in both hyperglycemia and hyper-insulinemia.

Adipose tissue excess or obesity, particularly in the visceral compartment, is associated with insulin resistance, hyper- glycemia, dyslipidemia, hyper-tension, and prothrombotic and pro-inflammatory states[5,6]. Recent studies showed that adipose tissue is not only a passive energy store, but also an active endocrine organ that, in addition to regulating fat mass and nutrient homeostasis, releases a large number of bioactive mediators known as (adipokines) influence the function of many systems [7,8].

From these adipokines, resistin a peptide hormone belongs to a family of cystein-rich C-terminal proteins have been discovered by Steppan et al[9]. It was identified as an adipocyte-specific secreted protein whose expression is down-regulated by anti-diabetic drugs targeting the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) which is involved in the regulation of lipid and glucose metabolism[10,11,12]. In cultured adipocytes, resistin reduced insulin-stimulated glucose transport and inhibited adipocyte differentiation[12]. Recent studies suggest that resistin could be a link between adipose tissue, obesity and insulin resistance[13-18].

However, other studies failed to show such an association[19]. This effect is mediated at least in part via increased activity of AMP-activated protein kinase (AMPK) and decreased expression of gluco-neogenic enzymes in the liver. Moreover, resistin has been shown to induce the expression of suppressor of cytokine signaling-3 (SOCS-3), a well-known negative regulator of insulin signaling[20], both in vitro and in vivo[21].

Materials and Methods:

50 male patients with newly diagnosed T2DM were participated in the present study. They were randomly selected and assigned either to metformin, glimepiride or combination treated groups. All subjects were recruited from the National Diabetes Center for Treatment and Research, University of Al-

Mustansiriyah, Baghdad; age (30–69) years, BMI (25-34.9).

All subjects have been treated for 12 weeks. All subjects were diagnosed with T2DM in accordance with the WHO diabetes diagnostic criteria of 1999 and had never been treated before.

After 12 hr overnight fasting, blood samples were analyzed for fasting serum glucose (FSG), HbA_{1c}, fasting serum insulin (FSI) and serum resistin. All subjects were orally administered with either 2–3 mg glimepiride once a day before meal and/or 500 mg metformin twice a day.

After 12 weeks of the treatment, we observed the changes in these parameters. Insulin resistance (IR) was evaluated by the homeostasis model assessment and expressed in HOMA-IR. HOMA-IR score= FSG (mg/dL) $\times$ FSI (mg/dL)/405[22].Serum Resistin and insulin concentrations were measured by enzyme-linked immunosorbent assay (ELISA) (DRG international Inc, USA). FSG measured using enzymatic colorimetric method (Spinreact, Spain) and glycated-hemoglobin levels (HbA_{1c}) were determined by high-performance liquid chromato- graphy (HPLC) (Bio-Rad Variant, Italy).

Statistical Analysis:

Data are expressed as means ± SE. Statistics were performed using SPSS (version 19). Differences from baseline were assessed by the paired Student's *t*-test. A *P*-value of <0.05 was considered significant. Correlations were performed using Pearson's correlation coefficient. Differences between groups were compared by one-way ANOVA.

Results:

Of 50 patients randomized to treatment, 20 in the metformin group, 10 in the glimepiride group and 20 in the glimepiride and metformin group. There were no apparent differences between the three groups with respect to demographic and baseline characteristics (Table -1). Changes from baseline to the end of the study are summarized in Table-2. FSG and HbA_{1c} were progressively decreased in all groups. Combination of metformin and glimepiride was superior in reducing FSG and HbA_{1c} levels than mono- therapy of each one alone; there was no significant difference between metformin or glimepiride mono- therapy with respect to the change in FSG or HbA_{1c}.

Serum insulin showed no significant change from baseline although it apparently slightly decreased in metformin group while slightly increased in glimepiride as monotherapy and combination. HOMA-IR score significantly decreased in all treatment groups; metformin monotherapy was significantly more effective than other groups in reducing IR, glimepiride as monotherapy and as combination were significantly not different with respect to IR. Glimepiride alone significantly reduced serum resistin concentration, while metformin as monotherapy and as combination with glimepiride showed non-significant change from baseline. Metformin significantly lowered BMI, while glimepiride significantly increased BMI and non-significant increase reported by combination treatment.

The present study illustrates the association between serum resistin level and other parameters. We found no correlation for resistin with any markers of adiposity or insulin resistance, including FSG, BMI and IR before treatment, while a positive correlation with body weight before starting treatment with metformin (r=0.498, p=0.030) then switch to non-significant after treatment, figure-1. A positive significant correlation with between resistin and IR achieved after treatment with metformin (r=0.519, p=0.023), figure-2, and negative significant correlation with BMI achieved after treatment with glimepiride (r=-0.677, p=0.032), figure-3.

Table-1: Patient characteristic at baseline.

Characteristic	Metformin (Met)	Glimepiride (Glim)	Met + Glim
n=50	20	10	20
Age; years	52.63± 2.23	48.80± 2.99	47.95± 1.55
Body Weight; kg	96.05 ± 3.03	86.15 ± 1.53	92.45 ± 3.29
BMI; kg/m^2	32.71 ± 0.77	30.22 ± 0.81	29.97 ±1.089
FSG; mg/dl	213.47 ± 13.14	218 ± 13.97	249.05 ± 12.15
HbA$_{1c}$; %	9.47 ± 0.58	8.75 ± 0.36	11.65 ± 0.39
Insulin; μIU/ml	25.57 ± 1.65	27.75 ± 3.15	25.05 ± 1.99
HOMA-IR	13.17 ± 0.87	14.84 ± 1.90	15.19 ± 1.40
Resistin ng/ml	0.44 ± 0.0145	0.45 ± 0.01	0.43 ± 0.015

n=number of patients; Data are given as mean ± SE.

Table 2: Changes from baseline and after 12 weeks

Variable/time point	Metformin (Met)	Glimepiride (Glim)	Met + Glim
FSG (%) Baseline Week 12 Change from baseline	 213.47 ± 13.14 132.95 ± 3.99*[b] -37.72 %	 218 ± 13.97 132.60 ± 1.45*[b] -39.17 %	 249.05 ± 12.15 145.15 ± 3.41*[a] -41.72 %
HbA$_{1c}$ (%) Baseline Week 12 Change from baseline	 9.47 ± 0.58 6.04 ± 0.32*[a] -36.27 %	 8.75 ± 0.36 5.71 ± 0.21*[b] -34.74 %	 11.65 ± 0.39 6.91 ± 0.31*[a] -40.70%
Insulin (%) Baseline Week 12 Change from baseline	 25.57 ± 1.65 23.86 ± 1.65[a] -6.7 %	 27.75 ± 3.15 23.86 ± 1.65[a] 7.93 %	 25.05 ± 1.99 27.23 ± 2.12[b] 8.68 %
HOMA-IR (%) Baseline Week 12 Change from baseline	 13.17 ± 0.87 9.16 ± 0.58[*a] -40.50 %	 14.84 ± 1.90 9.78 ± 0.43[*b] -34.10 %	 15.19 ± 1.40 9.85 ± 0.84[*b] -35.15 %
Resistin (%) Baseline Week 12 Change from baseline	 0.44 ± 0.0145 0.40 ± 0.0147[b] -3.52 %	 0.45 ± 0.01 0.40 ± 0.02*[a] -11.10%	 0.43 ± 0.015 0.40 ± 0.010[b] -8.56 %
BMI (%) Baseline Week 12 Change from baseline	 32.71 ± 0.77 30.57 ± 0.60*[a] -6.54 %	 30.22 ± 0.81 31.51 ± 0.93*[a] 4.27 %	 29.97 ±1.089 30.33 ± 1.099[a] 1.21 %
Weight (%) Baseline Week 12 Change from baseline	 96.05 ± 3.03 90.29 ± 3.26*[a] -6.00 %	 86.15 ± 1.53 88.10 ± 1.43[a] 2.26 %	 92.45 ± 3.29 93.30 ± 3.08[a] 0.92 %

Data are given as mean ± SE; * Significantly different compared to pre-treatment level (*P*<0.05); values with non-identical superscripts (a,b) among different groups are considered significantly different (*P*<0.05).
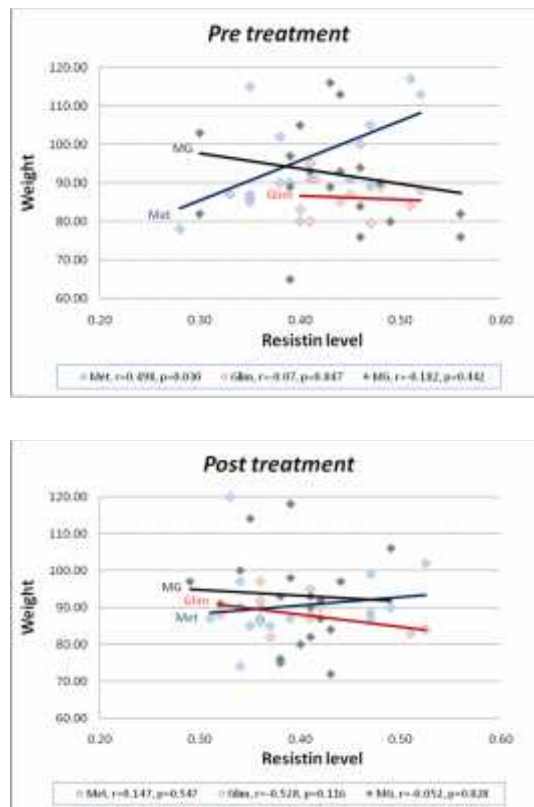
Figure-1:Correlation between serum resistin and body weight pre- and post-treatment with Metformin; Met, Glimepiride; Glim or combination; MG.
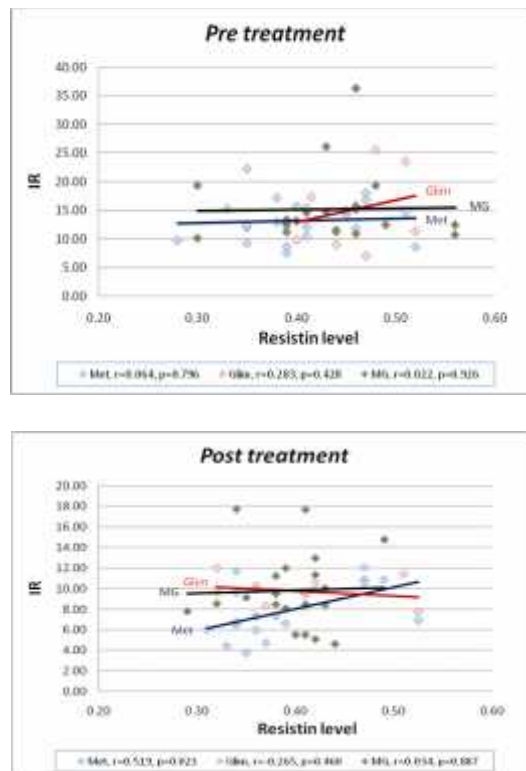

Figure-2: Correlation between serum resistin and insulin resistance (IR) pre- and post-treatment with Metformin; Met, Glimepiride; Glim or combination; MG.
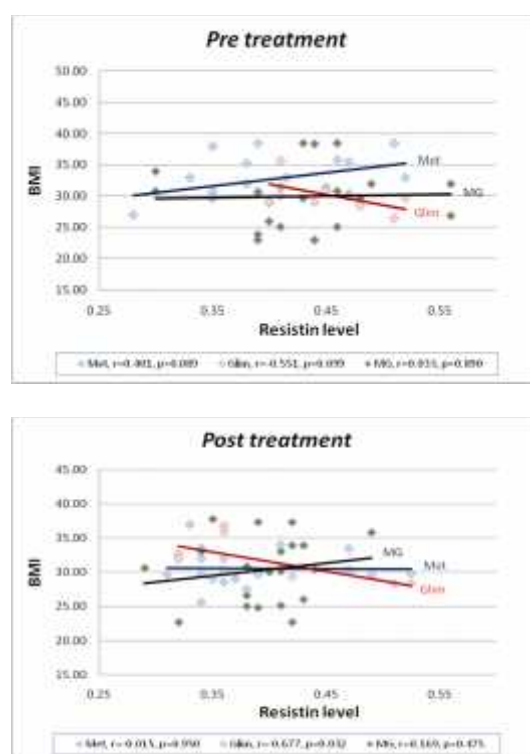
Figure-3: Correlation between serum resistin and body mass index (BMI) pre- and post-treatment with Metformin; Met, Glimepiride; Glim or combination; MG.

Discussion:

Resistin is one of the adipokines that has been implicated in the pathogenesis of obesity-related co-morbidities. Resistin in previous studies showed conflicting results to be a link between obesity IR and diabetes. More than 100 research papers on resistin have been published since its initial description in 2001[23]. The present study found that there was no difference in resistin levels between newly diagnosed T2DM with age and BMI matched healthy control subjects confirming results of other studies; since control subjects involved in the study were overweight and obese, despite a distinct elevation in insulin levels and IR in diabetic group, compared with the control group[24,25].

Moreover, the study used only male subjects and, as previous studies had shown resistin to exhibit sexual dimorphism, with women having approximately 20% higher levels than men, this may explain these findings[26,27].

Glimepiride alone significantly reduced serum resistin concentration after 3 months of treatment consistent with other studies[28,29], which showed that glimepiride directly binds to PPARγ and stimulates the trans- criptional activity of this receptor which decrease resistin expression and then improve insulin sensitivity. While studies on metformin showed controversial effect on adipocytokines and inflammatory markers[30,31]. Our study, consistent with Derosa *et al*. analysis, showed no significant change in serum resistin level after 3 months of treatment with metformin[32].

Glimepiride when combined with metformin showed decrease in serum resistin level less than that reported by glimepiride monotherapy, this may be due to biological variations between the patients or may be partly due to the effect of metformin; since several studies showed increase resistin level with metformin therapy[33,34]. This made the net result of

combination therapy on resistin level less than that produced by glimepiride alone.

The data reported in the present study provide an important view of plasma resistin concentrations in relation to glycemic control (FSG and HbA$_{1c}$), FSI, IR and BMI before and after mono-therapy with either glimepiride or metformin or their combination. Accordingly, the change in serum resistin level after metformin treatment correlated positively with the change in HOMA-IR score in diabetic overweight to obese individuals, while the correlation with FSG, FSI and BMI is not changed. We cannot relate such change in the state to the weight lowering effect of metformin, although a positive correlation with the weight was reported only in metformin group before treatment, since resistin level did not decrease while weight, as well as BMI, significantly reduced. This conclusion supported by the results of glimepiride group, since it reduced the level of resistin while weight, as well as BMI, significantly increased. Accordingly we found negative correlation between resistin and BMI after treatment with glimepiride.

Similarly, we did not find any correlation between decrease in HbA$_{1c}$ and change in resistin level in any group of treatment. Our data suggest that the impact of glimepiride and metformin on resistin is independent on hypoglycemic properties, it is also clearly demonstrated that serum resistin levels did not correlate with any marker of insulin resistance and obesity which remains in accordance with other studies[35,36]. Other study demonstrated that no correlation between resistin gene expression in human adipocytes and insulin resistance[37] or BMI[38], this is in contrast to mice studies[39,40].

All treatment types showed significant decrease in glycemic parameters and HOMA-IR compared with pre-treatment, this consistent with many studies done on metformin, glimepiride and their combination[41,42]. The improvements in glycemic parameters with glimepiride and metformin were similar, while combination produced a lower degree of reduction in FSG and HbA$_{1c}$[43,44]. Improvement in IR was seen in all groups, the maximum effect was found with metformin[45]. While it has been noticed that insulin secretion changed according to treatment type[46].

A previous study approved that glimepiride increases insulin sensitivity at peripheral target sites and improve insulin resistance in newly diagnosed diabetic subjects, which was demonstrated by a significant reduction in HOMA-IR score[47,48], the mechanism by which glimepiride reduce insulin resistance was unknown till recent time[49]. The extra-pancreatic effects of glimepiride made its combination with metformin more effective in improving glycemic control (synergistic effect) by reducing glucose level and HbA$_{1c}$% more than monotherapy[50,51]. While the combination of metformin and glimepiride, as monotherapy of each one, showed significant decrease in HOMA-IR score compared with pre-treatment, similar to the effect of glimepiride but it significantly less than metformin effect.

Obesity, now a day considered as a major risk factor for T2DM and cardiovascular disease[52]. In our study, we examine overweight to obese patients to evaluate the role of obesity on adipokines and inflammatory markers[53,54]. We detected no correlation between resistin level and BMI in newly diagnosed T2DM patients. Weight loss or the lack of weight gain has been a consistent finding in T2DM treated with metformin[55]. In our study like others, metformin therapy was accompanied by a small but statistically significant reduction in BMI. It reduced slightly the rates of weight gain and body fat accumulation in diabetic and non-diabetic adults[56]. Preliminary short-term studies suggest that the effects of metformin on BMI may be mediated in part by reductions in food intake[60], this is related in fact to the effect of metformin to

suppress appetite in a dose-dependent manner[57]. Actually, the studies approved that significant weight loss in type 2 diabetic and non-diabetic adults, who is taking metformin, is associated with increases in insulin sensitivity and reductions in FSI level[58].

Conflicting results about the effect of glimepiride on body weight, our study consistent with others showed slightly increase in BMI after treatment with glimepiride[43,45,59], while combination of metformin and glimepiride showed no effect on BMI due to glimepiride effect consistent with other study[46]; glimepiride cause weight gain and the use of metformin with it decreases weight gain by decreasing energy intake, therefore it is recommended to use metformin in combination with insulin secreting agents in patients with T2DM[60].

This study has some limitations; small sample size may limit some of the conclusions to be drawn. In addition, the follow-up period of 3 months does not consider the possible return to pre-study conditions among participants. Another possible limit- ation is that physical activity was not considered as having significant effect on resistin levels, as suggested by another recent study[61]. Further long-term studies are suggested to respond to this possibility.

In conclusion, circulating resistin is unlikely to play a major role in obesity, insulin resistance, or energy homeostasis in human since resistin levels are not associated with markers of insulin resistance and/or obesity. Metformin and glimepiride as mono- therapy and combination showed good improvements for hyperglycemia and insulin sensitivity.

Acknowledgment:

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