# Comparative Study between Oral Hypoglycemic Drugs Repaglinide, Glibenclamide and Rosiglitazone on Some Biochemical Parameters in Type 2 Diabetic Patients

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## Abstract

Type 2 diabetes mellitus is often characterized by hyperglycemia as a result of increased insulin resistance in hepatic/peripheral tissues and pancreactic B-cell dysfunction. Approximately 92% of patients with type 2 diabetes mellitus demonstrate insulin resistance, however hyperglycemia is always a consequence of insulin deficiency. This study was done on 120 patients newly diagnosed diabetes type 2 characterized by dyslipidemia that is increased triglycerides and decreased HDL. Hypoglycemia and weight gain are common problem with oral sulfonyl urea drugs. In this work three different oral hypoglycemic drugs repaglinide and glibenclamide (insulin secretagogues) and rosiglitazone (insulin sensitizer) were used for treatment of patients with type 2 diabetes mellitus. The effect of these drugs on fasting and postprandial blood glucose levels, lipid profiles, alanine aminotransferase and serum creatinine were studied.Three groups of newly diagnosed type 2 diabetic patients ,group 1 (40 patients) were subjected to treatment with repaglinide (2 mg three time daily) ,group 2(45 patients) were subjected to treatment with glibenclamide (5 mg once daily) ,group 3,(35 patients) were subjected to treatment with rosiglitazone (4 mg twice daily) . Fasting and postprandial blood glucose levels, lipid profiles (TC, TG, HDL and atherogenic index), alanine aminotransferase and serum creatinine were analyzed for these patients before and 4 and 8 weeks after oral hypoglycemic drug treatment. The same parameters were recorded for 40 normal individuals as control.The results demonstrated that repaglinide has a greater postprandial glucose regulator effect than glibenclamide and rosiglitazone. In addition the hypoglycemic episode and weight gain were less in patients treated with repaglinide than those treated with glibenclamide. Repaglinide produces greater percent reduction with respect to fasting blood glucose levels, postprandial blood glucose levels and atherogenic index compared to glibenclamide and rosiglitazone.

**Key words: oral hypoglycemic, repaglinide, glibenclamide, rosiglitazone.**

**الخلاصة**

دراسة مقارنة لتأثيرات ريباكلينايد , كليبنكلامايد و روزيكليتازون على بعض التحليلات الكيميائية الحياتية لمرضى السكري من نوع ٢. مرض السكري نوع ٢ ينتمي إلى مجموعة الأمراض المزمنة والذي يتصف بارتفاع في مستوى السكر في الدم الناتج عن وجود قصور في إفراز أو نشاط الأنسولين أو خلل في كليهما، تقريباً ٩٢% من مرضى السكري يبدون مقاومة للأنسولين . تم وصف عدة أدوية ريباكلينايد , كليبنكلامايد و روزيكليتازون والتي تم أخذها عن طريق الفم لمعالجة النوع الثاني من مرض السكر . أجري هنا البحث على ١٢٠مريضاً مصاباً بمرض السكري من نوع ٢والذين تم تشخيصهم حديثاً وتم توزيعهم عشوائياً إلى ثلاث مجاميع وكما يلي , المجموعة الأولى (٤٠ مريضاً) تم معالجتهم بعقار ريباكلينايد ٢ملغم ثلاث مرات يومياً , المجموعة الثانية (٤٥مريضاً) تم معالجتهم بعقار كليبنكلامايد ٥ملغم مرة واحدة يومياً , أما المجموعة الثالثة ( ٣٥مريضاً) تم معالجتهم بعقار روزيكليتازون ٤ملغم مرتين يومياً كما تم اختيار ( ٤٠شخصاً) من الأصحاء كمجموعة سيطرة . تم قياس مستوى الكلوكوز في الدم بعد الصوم , مستوى الكلوكوز في الدم بعد ساعتين من وجبة الغداء كذلك تم قياس الشحوم في الدم ( كولسترول الكلي , ترايكليسيرايد , كولسترول البروتين الشحمي واطئ الكثافة , كولسترول البروتين الشحمي عالي الكثافة وإنزيمات الكبد ALT ومستوى الكرياتينين في الدم قبل وبعد ٤و ٨أسابيع من بدء العلاج , أظهرت النتائج لدى مرضى السكري والذين تمت معالجتهم بعقار ريباكلينايد انخفاضاً معنوياً واضحاً في مستوى الكلوكوز في الدم بعد ساعتين من الوجبة الغذائية أكثر من كليبنكلامايد و روزيكليتازون كما وجد أن العلاقة كانت عالية بين مستوى الكلوكوز في الدم بعد الصوم ومستوى الكلوكوز في الدم بعد ساعتين من وجبة الطعام لدى المرضى المعالجين بعقار ريباكلينايد و روزيكليتازون بعد ٤ و ٨أسابيع من العلاج كما كان الانخفاض في مستوى السكر في الدم والزيادة في الوزن اقل حدوثاً لدى المرضى الذين تمت معالجتهم بعقار ريباكلينايد مقارنة مع كليبنكلامايد بعد ٤و ٨أسابيع من العلاج .

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## Introduction

Diabetes mellitus is a metabolic disorder characteriszed by hyperglycemia, abnormal lipid and protein metabolism along with specific long term complication affecting the retina, kidney and nervous system [(1)]. Hyperglycemia is an important factor in the development and progression of the complications of diabetes mellitus [(2)]. Diabetes mellitus may be categorized into several types, but the two major types are type I and type 2 [(3)].Type 2 diabetes is the commonest form of diabates and is characterized by disorder of insulin secretion and/ or insulin resistance [(4)]. In the non pharmacological treatment, weight management and exercise are the initial focus because insulin resistance can be dramatically improved with minimal weight loss (10: of body weight) and drug therapy is rement [(5)]. In sulfonylureas, oral hypoglycemic agent, glibenclamide is a second generation which is more potent than first generation sulfonylureas [(6)]. It is valuable in the treatment of non obese patient with type 2 diabetes, who fails to respond to dietary measures alone. It stimulates the secretion and enhances the utilization of insulin by appropriate tissues [(7)].Repaglinide (non sulfonylureas) is abenzoic acid derevative of the meglitinide family which is reported to be more potent insulinotropic agent than glibenclmide and other sulfonylureas [(8)]. Rosiglitazone (thiozolidinediones) is introduced in 1999 and widely used as monotherapy or in fixed dose combination with either metformin or glimepiride [(9)]. It is a potent hypoglycemic agent [(10, 11)].The present work was conducted to investigate the effects of repaglinide, glibenclamide and rosiglitazone on fasting, 2hr postprandial blood glucose, lipid profile, ALT enzyme and serum creatinine in type 2 diabetic patients. Evaluation of the correlation between fasting and postprandial blood glucose in patients treated with repaglinide, glibenclamide and rosiglitazone separately were also conducted.

## Materials and Methods

- ***Patients***

The study included 120 patients (50 male and 70 female) of newly diagnosed type 20 diabetes mellitus and 40 healthy subjects (20 male and 20 female) as control. Patients were interviewed according to the patient information sheets. All newly diagnosed type 2 diabetic patients enrolled in the study were treated and followed by specialized physician.patients were randomized into three groups. Group I included 40 patients (16 male and 24 female), their ages range between 40-69 years (49.3 ± 5.8) treated with repaglinide 2mg three times daily before meal. Group 2 included 45 patients ( 20 male and 25 female) theirs ages range between 45 – 65 years (51.2 ± 7.6) treated with glibenclamide 5mg once daily before meal. Group 3 included 35 patients (14 male and 21 female), their ages range between 38 – 64 years (53.8 ± 6.5) treated with rosiglitazone 4 mg twice daily after meal. All patients were followed after 4 and 8 weeks of treatment.

- ***Control***

Forty healthy subjects (20 male and 20 female) with ages range between 40 – 60 years (42.6 ± 6.8) were enrolled in the study and served as a control group.

Drugs used were as followed

- ***Drugs***

| Drug | Dose | Supplier |
|---|---|---|
| Repaglinide | 2mg tablet | Novo Nordisk/Danmark |
| Rosiglitazone | 4mg tablet | Pharmasyer/ Syria |
| Glibenclamide | 5mg tablet | Hikma/ Jordan |

- ***Blood Samples***

Before drug treatment, eight ml of venous blood was drawn from each patient of newly diagnosed type 2 diabetes mellitus who was fasted at least for 8 hours. Using sterile disposable syringe 23G, the blood was transferred into disposable plain tube and let stand for 30 minutes to clot. Serum was separated by centrifugation at 3000 rpm for 5 minutes, which was collected in plain tube and kept frozen unless analyzed immediately. The serum was utilized for determination of total cholesterol (TC), triglyeride (TG), high density lipoprotein cholesterol (HDL-C) low density lipoprotein chelestrol (LDL-C), glucose, alanine aminotransferase (ALT), and serum creatinine (SCr). The same procedurs were carried out in blood samples from patients after 4 and 8 weeks of treatment.

- ***Commercial Kits***

For biochemical analysis, the following kits were used:

| Kits | Supplier |
|---|---|
| Kit for determination of serum glucose | Biolabo SA/ France |
| Kit for determination of serum cholesterol | Biolabo SA/ France |
| Kit for determination of serum HDL cholesterol | Biolabo SA/ France |
| Kit for determination of serum triglycerides | Biolabo SA/ France |
| Kit for determination of serum creatinine | Biomeriex/ France |
| Kit for determination of serum ALT | Biomeriex/ France |

- ***Statistical analysis***

All values were represented as mean ± SD. Analysis of variance (ANOVA) were used to find the differences among groups.Duncan test was used to find the factor effect. P values less than 0.05 was considered significant. Correlation coefficient (r) was used to determine the relationship between fasting and two hours postprandial blood glucose for each diabetic group who was treated by specific drug.

## Results

Table 1 showed the effect of repaglinide on fasting and 2hr postprandial blood glucose levels in diabetic patients treated with repaglinide (group 1) at 4 and 8 weeks of treatment. Significant reduction in fasting and postprandial blood glucose levels were observed in treated patients after 4 and 8 weeks of treatment when compared to zero level values (before treatment). However, the fasting and postprandial blood glucose levels after 8 weeks of treatment were higher than the control (healthy) but statistically insignificant. The same table also showed that repaglinide significantly increases HDL-C, and decreased TG after 4 weeks of treatment when compared to zero level values. Reduction of atherogenic index was also observed in treated patients when compared to zero levels values, while these values after 4 and 8 weeks of treatment were similar to the values of control individuals. ALT values were significantly reduced in treated diabetic patients compared to zero level values.

**Table 1: Effects of Repaglinide on serum fasting blood glucose, 2hrs postrandial glucose, total cholesterod, Low density lipoprotein cholesteros, high density lipoprotein cholesterol, triglycerides, alanine aminotransferase and serum creatinine after 4 and 8 weeks of treatment.**

| Parameters | Control (n=40) | Before treatment (n=40) | 4 weeks after treatment (n=40) | 8 weeks after treatment (n=40) |
|---|---|---|---|---|
| FBG mmol/L | 5.64±2.22[a] | 9.86±1.98[b] | 7.30±1.77[c] | 6.17±1.76[a] |
| 2hr PPG mmol/L | 7.94±3.10 [a] | 15.22±2.21[b] | 9.90±2.38[c] | 8.10±2.21[a] |
| TC mmol/L | 4.88±1.89 [a] | 5.06±1[a] | 4.99±1.60[a] | 4.95±1.13[a] |
| LDL-c mmol | 2.45±0.94 [a] | 2.76±0.77[b] | 2.59±0.58[a] | 2.55±0.40[a] |
| HDL-c mmol | 1.52±0.43 [a] | 0.99±0.34[b] | 1.40±0.42[a] | 1.41±0.53[a] |
| TG mmol | 1.94±0.90 [a] | 2.90±0.90[b] | 2.19±0.93[a] | 2.14±0.78[a] |
| Atherogenic index TC:HDL | 3.21[a] | 5.11[b] | 3.56[a] | 3.51[a] |
| Atherogenic index LDL:HDL | 1.61[a] | 2.78[b] | 1.85[a] | 1.80[a] |
| ALT (IU) | 16.82±5.31[a] | 27.32±4.37[b] | 18.05±3.63[a] | 18.18±5.09[a] |
| S cr mmol/L | 62.73±7.73 [a] | 63.84±6.07[a] | 63.86±6.10[a] | 63.89±6[a] |

Data represented by mean ± SD.
N= number of subjects
Values with non-identical superscript (a, b, c) for the same parameter indicate significant difference at level P< 0.05

Table 2 showed the effects of glibenclamide on fasting and 2hr postprandial blood glucose levels in diabetic patients treated with glibenclamide (group 2) at 4 and 8 weeks of treatment. Significant reduction in fasting and postprandial blood glucose levels were observed in treated patients when compared to zero level values. However, the reduction in postprandial blood glucose levels with repaglinide were significantly higher than that with glibenclamide after 8 weeks of treatment. Other parameters were similar to that observed with repaglinide.Table 3 showed the effects of rosiglitazone on fasting and 2hr postprandial blood glucose levels in diabetic patients treated with rosighitazone (group 3) at 4 and 8 weeks of treatment.Significant reduction in fasting and postprandial blood glucose levels were observed when compared to the zero level values. The reductions were similar to that observed with glibenclamide, however the HDL-C, LDL –C and TC were significantly increased at 4 and 8 weeks of treatment when compared to zero level values.Table 4 showed the percentage decrease of fasting and postprandial blood glucose in diabetic patients treated with repaglinide, glibenclamide and rosiglitazone after 4 and 8 weeks of treatment.

**Table 2: Effects of Glibenclamideon the serum fasting blod glucose , 2hrs-postprandial glucose , lipid profile ,alanine aminotransferase , and serum creatinine after 4 and 8 of weeks of treatement .**

| Parameters | Control (n=40) | Before treatment (n=45) | 4 weeks after treatment (n=45) | 8 weeks after treatment (n=45) |
|---|---|---|---|---|
| FBG mmol/L | 5.64±2.22[a] | 9.77±1.70[b] | 7.32±1.92[c] | 6.23±1.78[a] |
| 2hr PPG mmol/L | 7.94±3.10 [a] | 14.56±2.3[b] | 10.42±2.53[c] | 9.27±2.11[a] |
| TC mmol/L | 4.88±1.89 [a] | 5.01±1.25[a] | 4.93±1.60[a] | 4.90±1.32[a] |
| LDL-c mmol | 2.45±0.94 [a] | 2.68±0.81[a] | 2.57±0.68[a] | 2.54±0.63[a] |
| HDL-c mmol | 1.52±0.43 [a] | 0.99±0.29[b] | 1.38±0.37[a] | 1.39±0.49[a] |
| TG mmol | 1.94±0.90 [a] | 2.93±0.81[b] | 2.16±0.81[a] | 2.12±0.62[a] |
| Atherogenic index TC:HDL | 3.21[a] | 5.06[b] | 3.57[a] | 3.52[a] |
| Atherogenic index LDL:HDL | 1.61[a] | 2.70[b] | 1.86[a] | 1.84[a] |
| ALT (IU) | 16.82±5.31[a] | 26.55±6. 7[b] | 18.02±4.47[a] | 18.30±5.26[a] |
| S cr mmol/L | 62.73±7.73 [a] | 63.11±6. 76[a] | 63.07±6.91[a] | 63.32±6.95[a] |

Data represented by mean ± SD.
N= number of subjects
Values with non-identical superscript (a, b, c) for the same parameter indicate significant difference at level P< 0.05

**Table 3: Effects of Rosiglitazone on the serum fasting blod glucose , 2hrs-postprandial glucose , lipid profile ,triglycerides , alanine aminotransferase , and serum creatinine after 4 and 8 of weeks of treatment**

| Parameters | Control (n=40) | Before treatment (n=35) | 4 weeks after treatment (n=35) | 8 weeks after treatment (n=35) |
|---|---|---|---|---|
| FBG mmol/L | 5.64±2.22[a] | 9.56±1.76[b] | 7.40±0.76[c] | 6.54±1.93[a] |
| 2hr PPG mmol/L | 7.94±3.10 [a] | 14.30±2.23[b] | 10.60±2.53[c] | 9.50±2.20[a] |
| TC mmol/L | 4.88±1.89 [a] | 5.03±1.65[a] | 5.52±1.57[b] | 6.14±1.48[c] |
| LDL-c mmol | 2.45±0.94 [a] | 2.63±0.90[a] | 3.13±0.80[b] | 3.54±0.83[c] |
| HDL-c mmol | 1.52±0.43 [a] | 1.07±0.40[b] | 1.46±0.35[a] | 1.64±0.63[c] |
| TG mmol | 1.94±0.90 [a] | 2.91±0.73[b] | 2.07±0.71[a] | 2.10±0.54[a] |
| Atherogenic index TC:HDL | 3.21[a] | 4.70[b] | 3.78[a] | 3.78[a] |
| Atherogenic index LDL:HDL | 1.61[a] | 2.45[b] | 2.14[a] | 2.15[a] |
| ALT (IU) | 16.82±5.31[a] | 28.52±6. 55[b] | 18.22±3.96[a] | 18.72±4.59[a] |
| S cr mmol/L | 62.73±7.73 [a] | 65.80±6. 7[a] | 65.69±5.37[a] | 65.83±5.37[a] |

Data represented by mean ± SD.
N= number of subjects
Values with non-identical superscript (a, b, c) for the same parameter indicate significant difference at level P< 0.05

**Table 4 : Percentages decrease of fasting and 2 – hours postprandial blood glucose in group1 , 2 and 3 of diabetic patients after 4 and 8 weeks of treatment**

| Drugs | Decrease of fasting blood glucose | | % Decrease of two hour post prandial blood glucose | |
|---|---|---|---|---|
| | After 4 weeks | After8 weeks | After 4 weeks | After 8 weeks |
| Repaglinide | 26.16% | 37.61% | 34.95% | 46.78% |
| Glibenclamide | 25.07% | 36.23% | 28.43% | 36.33% |
| Rosiglitazone | 22.59% | 31.58% | 25.87% | 33.56% |

It is obvious from the table that repaglinide produces higher percentage decrease in fasting and postprandial blood glucose level after 4 and 8 weeks of treatment when compared to glibenclamide and rosiglitazone.In table 5 the percentage of changes in atherogenic index (TC:HDL) is higher in diabetic patients treated with repaglinide and glibenclamide, while diabetic patients treated with rosiglitazone showed no changes after 4 and 8 weeks of treatment. Percent atherogenic index LDL: HDL showed higher reduction than the atherogenic index TC:HDL in diabetic patients treated with repaglinide, glibenclamide and roiglitazone after 4 and 8 weeks of treatment.Table 6 showed high percent of adverse effects (hypoglycemia 15% and headache 11%) in glibenclamide treated patients compared to repaglinide and rosiglitazone treated patients.

**Table 5 : Percentage changes of atherogenic index TC : HDL and LDL :HDL in groups 1,2 and 3 of diabetic patients after 4 and 8 week of treatment**

| Drugs | % change of atherogrnic index TC:HDL | | % change of atherogenic index LDL:HDL | |
|---|---|---|---|---|
| | After 4 weeks | After 8 weeks | After 4 weeks | After 8 weeks |
| Repaglinide | 30.33% (↑) | 31.31%(↑) | 33.45% (↑) | 35.25(↑) |
| Glibenclamide | 29.44%(↑) | 30.43%(↑) | 31.11%(↑) | 31.85(↑) |
| Rosiglitazone | 19.57%(↑) | 19.57% (↔) | 12.6%(↑) | 12.2%(↓) |

- ↑ = Increase lowering atherogenic .
- ↓ = Decrease Lowering atherogenic
- ↔= unchanged atherogenic

**Table 6 Adverse – ettects in the three groups of diabetic patients treated with Repaginide ,Glibenclamide and Rosiglitazone after 8 weeks of treatment**

| Adverse effects | Group1 Repaglinide | Group 2 Glibenclamide | Group 3 Rosiglitazone |
|---|---|---|---|
| Hypoglycemia (mild ) | 10% | 15% | 0% |
| Hypersensitivity | - | 1 | - |
| Tolerability | Good | Good | Good |
| Headache | 5% | 10% | 2.5% |

## Discussion

The present study demonstrates that fasting blood glucose and post prandial blood glucose levels were significantly reduced in type 2 diabetic patients treated with repaglinide after 4 and 8 weeks of treatment. This result is quite similar to that reported by Goldberg etal 1998 [12], who found that repagtinide is highly effective in controlling both fasting and postprandial blood glucose levels. The effect of repaglinide on the postprandial blood glucose level is significant because of the rapid onset of action and the short half life of bypoglycemic effect, which makes repaglinide an ideal drug for controlling postprandial hyperglycemia [13]. Glibenclamide showed significant reduction in fasting and postprandial blood glucose after 4 and 8 weeks of treatment. This result is in agreement with the observation of kolterman etal 1984 [14], and Rosak etal 2002 [15] who found that glibenclamide significantly reduced blood glucose levels . Both glibenclamide and repaglinide have the same mechanism of action in lowering blood glucose. Repaglinide, like sulfonylureas, acts by linide stimulating the release of insulin from the Bcell of the pancreas by inhibiting ATP-sensitive K channels, thereby activating the Ca++ channel with increase in intracellular calcium to release insulin [16]. However, repaglinide acts on a different binding site than that of sulfonylureas [17].The present work showed that fasting blood glucose and postprandial blood glucose in diabetic patients treated with rosiglitazone were significantly decreased after 4 and 8 weeks of treatment. This result is compatible with that reported by Miyazaki etal 2001[18], and Tan etal, 2005 [19] who found that rostiglitazone significantly reduced both fasting and postprandial blood glucose in type 2 diabetes mellitus.Postprandial glucose level is an important factor in the development of diabetic complications and increase risk factor for cardiovascular diseases Marfella etal [20]

found that hyperglycemia has been implicated as a cause of endothelial dysfunction in normal as well as diabetic subjects. Hyperglycemia, particularly postprandial hyperglycemia has great effect on the development of diabetic complications[21]. Postprandial hyperglycemia is an important risk factor associated with the development of macrovascular and microvascular complications, especially coronary heart diseases [13]. Moreover it appears that the management of postprandial plasma glucose level, rather than fasting plasma glucose level, is important to prevent complications associated with type 2 diabetes [22]. Therefore repaglinide is a noval and superior to glibenclamide and rosiglitazone in controlling postprandial glucose profile in type 2 diabetic complications.Regarding lipid profile in type 2 diabetic patients treated with repaglinide and glibenclamide, there were no significant changes after 4 and 8 weeks of treatment. These results were supported by Ykijarvinan 2004 [23] study, where lipid profile changes as a result of improved glycaemic control are not uniform findings associated with anti- diabetic therapy (insulin secretagogues). However diabetic patients treated with rosiglitazone showed significant increase in HDL- C, LDL-C and total cholesterol after 4 and 8 weeks of treatment compared with the base line. This result is similar to that reported by Raskin etal 2000 [24] who showed that total cholesterol and LDL-C were significantly increased in patients treated with rosiglitazone.Concerning other parameters like a therogenic index, ALT, and serum creatinine, no significant changes were reported in diabetic patients treated with repaglinide compared to rosiglitazone and glibenclamide.The results showed that the the correlation (R2 values) between fasting and postprandial blood glucose in diabetic patients treated with repaglinide was 0.743 in comparing with R2 values in diabetic patients treated with glibenclamide 0.624 and rosiglitazone 0.499. These results indicated that correlation is more significant in repaglinide treated group.The results indicated that the incidence of hypoglycemia was about 15% with glibenclamide, while it was 10% with repaglinide and 0% with rosiglitazone. This finding is consistent with the finding of Damsbo etal 1999 [25] who indicates that repaglinide therapy was associated with less frequent hypoglycemic events compared with glibenclamide.The results also indicated that diabetic patients developed weight gain which was least in diabetic patients treated with repaglinide and higher in diabetic patients treated with glibenclamide and rosiglitazone. There results are similar with that reported by Marbury etal 1999 [26] who showed that patients given repaglinide may gain less weight than those treated with glyburide. This weight gain may be explained by increased adipocyte differentiation, increased appetite or water retention [27]. Generally, adverse effects of rosiglitazone include weight gain.In conclusion repaglinide regulates postprandial blood glucose in diabetic patients greater than glibenclamide and rosiglitazone, while the weight gain was less in patients treated with repaglinide than glibenclamide and rosiglitazone. The correlation between fasting and postprandial blood glucose in diabetic patients treated with repaglinide was greatert than that with glibenclamide and rosiglitazone.

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