Repaglinide dose Titration in Patients with Type 2 Diabetes Mellitus: A Comparative Study between Diet Treated and Metformin Treated Patients

Taha O Mahwi **Roshna Shawkat Aziz**

ABSTRACT

Background and Objectives: Repaglinide is a nonsulfonylurea insulin secretagogue which has a fast onset and short duration of action that is used for prandial glucose regulation in type 2 diabetic patients, alone or in combination with other antidiabetic agents. The present study aimed to compare the effects of various doses of repaglinide in controlling blood glucose levels, especially postprandial blood glucose, as a monotherapy and in combination with metformin.

Methods: Patients with type 2 diabetes mellitus, which were poorly controlled with diet modification or metformin alone, were enrolled in this prospective study. The total number of the patients was 97, females (55) and males (42), at a mean age of 53 ± 8.1 years (range 31 − 69), 43 on Repaglinide monotherapy and 54 on repaglinide and metformin combination. Preprandial, postprandial blood glucose and glycated hemoglobin were recorded to determine repaglinide effect.

Results: the results showed that patients receiving repaglinide alone achieved glycemic control by 0.5 mg or 1 mg repaglinide before each main meal, while those receiving repaglinide in combination with metformin received higher doses (1mg, 2mg, and 4mg) of repaglinide before each main meal. Still, glycemic control was not achieved in some patients. **Conclusions:** small doses of repaglinide (0.5−1.0 mg before main meals) was enough in type 2 diabetic patients with suboptimal control on diet alone to reach optimal glycemic control; but further dose titration up to (4 mg before main meals) is required in individuals who were previously on metformin with longer diabetes duration and advanced diabetic stages.

Key words: Repaglinide, metformin, dose titration, type 2 diabetes mellitus

INTRODUCTION:

The long-term goals of treatment of diabetic patients are to reduce symptoms, prevent diabetes-related complications, and prolong life. These goals are accomplished through education, medication use, meal planning, weight control, exercise, foot care, and careful self -testing of blood glucose levels. [1,2] By definition, patients with type1 diabetes mellitus (T1DM) require lifelong treatment with insulin, while type2 diabetes mellitus (T2DM) is initially treated by adjustment in diet and exercise, and by weight loss, especially in obese patients. If these measures fail, then oral antidiabetic agents agents can be classified into functional categories as follows:

- Insulin Secretagogues (sulfonylureas, meglitinides) which stimulate insulin release;
- Insulin sensitizers (biguanides, thiazolidinediones), which reduce insulin resistance;
- Medications that slow the digestive/ absorptive process (alpha-glucosidase inhibitors). [5]

Repaglinide is a relatively new insulin secretagogue from a chemical class known as meglitinides. Repaglinide (Prandin, NovoNorm, GlucoNorm) is a carbomethyl benzoic acid (CMBA) derivative. It was

*** F.I.C.M.S, Assistant professor in Medicine College of Medicine, Sulaimania University .**
****M.B.ch.B, M.Sc in pharmacology College of Medicine, Sulaimania University.**

introduced to clinical use late in 1998 [6, 7].It promotes insulin release by binding to potassium channels in pancreatic β cell membrane. It has been introduced mainly for controlling postprandial hyperglycemia (PPH).[8, 9] Repaglinide is taken prior to meals. In contrast to those receiving longer -acting insulin secretagogues such as sulfonylureas (SUs), patients treated with repaglinide are free with their eating pattern. [10]. It is a prandial glucose regulator used for the treatment of T2DM at different stages of the disease, from uncomplicated to severe renal impairment. It has an equivalent HbA1c lowering effect to conventional SUs but predominantly reduces PPG levels. The drug does not cause insulin release in the absence of glucose, or during voltage-clamping. Repaglinide can be used as monotherapy both in obese and non-obese T2DM patients; it appears particularly useful in early stage T2DM or in combination with metformin.[11-13] Many studies indicate a decreased risk of hypoglycaemias, particularly nocturnal or in the case of a shift or omission of a meal. One potential benefit of repaglinide, particularly in patients who are being encouraged to lose weight, also for those who eat irregularly, is the concept of flexible dosing. The rapid action and short duration means that by the time of the next meal there is no significant concentration of the drug unless a further dose is taken. Thus the meal can be voluntarily omitted, not supplied, or forgotten without a major risk of hypoglycemia occurring if the drug is not taken, in contrast to those receiving longer-acting insulin secretagogues such as SUs. Thus the concept of its use includes "one meal, one dose-no meal, no dose." The flexible regimen of repaglinide is of particular relevance to those patients with irregular eating habits, or those whose religion recommends a period of fasting or abstinence from certain foods. [6, 10, 11] The improvement in glycemic control is also independent of degree of obesity and age, repaglinide has been shown to augment insulin secretion within the first 30 min of commencing a meal, with no residual secretagogue activity detectable 4 hours later.[14] Several sets of experimental data suggest that the drug could preserve β cell function over time better than hypoglycemic SUs, and that the improvement of PPG levels could exert a long term protective cardiovascular effect. It decreases HbA1c by ~ 1.5 percentage points[11].The recommended starting dose is 0.5 mg to be taken no more than 30 minutes before a main meal. A dose of 1mg may be needed in patients who were previously on another oral antidiabetic agent. The dose of should be adjusted at intervals of 1-2 weeks according to response. The recommended maximum single dose is 4 mg and the total daily dose 16 mg [15.] Combined metformin and repaglinide therapy resulted in superior glycemic control compared with repaglinide or metformin monotherapy in patients with T2DM whose glycemia had not been well controlled on metformin alone. This combination rapidly reduced FPG values to a steady state in 4 weeks and had a stable effect on HbA1c values by 12 weeks [16, 17]. Repaglinide and rosiglitazone were well tolerated and had a better effect than the use of either drug alone. [18] Repaglinide has primarily a role in the treatment of T2DM when metformin cannot be used due to adverse effects, when metformin fails to adequately control blood glucose levels, when there is a need for flexible dosing (i.e. the elderly or during Ramadan fasting), or when there is a specific wish to lower PPG. Repaglinide may also have an advantage when an oral agent is needed in diabetic patients with renal impairment. [19,20].The Insulin sensitizers two classes of oral hypoglycemic drugs (the biguanides and thiazolidnediones) improve insulin action, these agents lower blood sugar by improving target –cell response to insulin without increasing pancreatic insulin secretion. [21]

PATIENTS METHODS:

The study was performed in Sulaimani diabetic clinic. Among the patients attending the diabetes clinic 109 patients aged between 30 to 70 years were selected to constitute the subject material. Starting from 15 May 2007 and under the supervision of the physician attending the clinic, selection of suitable patients was done. Selected patients fell into three categories:1- T2DM patients, who were on diet restriction and exercise for three months who had inadequate glycemic control.2- T2DM patients, who received metformin, and had inadequate glycemic control.3- T2DM patients, who were already receiving repaglinide at time of presentation. All subjects needed to be able to perform home blood glucose monitoring. (Patients or a relative must own a blood sugar measuring device), the exclusion criteria was for-Type 1 diabetes, Patients with T2DM using insulin therapy, Pregnant or lactating patients, Patients with hepatic impairment (aspartate or alanine aminotransferase more than three times the upper limit of normal), Patients with renal impairment (creatinine >120 µmol/l), Individuals with any illness rendering them unable to fully understand and participate in the study; were also excluded. The use of other oral hypoglycemic agents (including sulfonylureas or thiazolidinediones) was not permitted**.** The study was designed as a prospective study in which 109 diabetic patients were interviewed during their visit to the diabetic clinic. A study form was arranged and changes in their medications were made and followed up for at least six months. After gaining informed consent, subjects started on 0.5 mg repaglinide 15-30 minutes before each main meal (i.e., three times daily), which was doubled every four weeks until a maximum dose of 4 mg three times daily was reached in order to achieve optimal glycemic control (actually patients were told to take it before each main meal, some patients took it twice daily as they had only two main measure their fasting blood glucose and postprandial blood glucose levels (2 hours after eating) at least once daily and record them in a diagram. The results were evaluated every week. Repaglinide dose titration was done according to these results. Appearance of any adverse effect or hypoglycemic attacks was recorded. HbA1c levels, liver function and renal function were recorded before starting repaglinide therapy and then after three months. These values were determined using standard laboratory tests at the Sulaimani central laboratory, and a consulting evening clinic.The current ADA recommendations for glycemic control (2006) were used in this study:

HbA1c of < 7.0 %

Preprandial blood glucose: 90 to 130 mg/dl

2-hour postprandial blood glucose: <180 mg/dl

From the total (109) selected subjects most of them (97) were followed up for an average of six months. Only 12 patients were lost. The data of the present study was analyzed by the STATA version 9.2 software programs. Age was stratified to four categories with ten year intervals for each stratum. Standard methods were used to obtain descriptive analysis as means, percentages, and standard deviations; P-value was calculated for the categorical variables. Also, a paired t-test was applied for determining the difference between means. All differences were

RESULT:

From the total of 97 patients who completed the study period: (56.7%) were female and 42 (43.3%) were male. (Table 1)

Age ranged from 31 to 69 years with a mean age of 53±8.1and a highest frequency of 50−59 years. (Table 1)

Thirty eight patients were on diet restriction for more than 3 months. (Table 2)

Only five patients were already receiving repaglinide, so the total number of patients with repaglinide monotherapy was 43

Patients on repaglinide(R) monotherapy had duration of diabetes ranging between 3 and 25 months with a mean of 7.6 months; while those on combination therapy had duration of diabetes ranging between 3 − 78 months (six and a half year) with a mean of 32.4 months. (Table 3)

For the 43 subjects (44.3%) who received repaglinide monotherapy:

- The HbA1c mean was 9.1, FPG 191 mg/ dl, PPG 255 mg/dl at presentation;
- Among them, 32.5 %(14 patients) got benefit of only 0.5 mg repaglinide before each main meal and their HbA1c level reduced from 8.8% to 6.4%, their FPG reduced from 178 mg/dl to 122 mg/dl and their PPG reduced from 230 mg/dl to 156 mg/dl. (Table 4)

The remaining 67.5% (29 patients) needed 1 mg of repaglinide before each main meal to lower their HbA1c from 9.4% to 6.6% , FPG from 195 mg/dl to 129mg/dl and PPG from 264mg/dl to 162 mg/dl.(Table 4)

For the 54 patients (55.7%) who received metformin:

- They continued on their prestudy dose of metformin, with the addition of repaglinide starting from 0.5 mg before each main meal titrated up to 4 mg before each main meal according to their glycemic profile.
- Only 7.4 % (4 patients) got benefit from 0.5 mg with an HbA1c level fall from 8.2 % to 6.4 %,FPG from 185 mg/dl to133mg/dl and PPG from 250 mg/ dl to 160 mg /dl. (Table 5)
- Most of them 48.2% (26 patients) needed 1mg to lower their HbA1c from 9.1 % to 6.6 %, FPG from 212 mg/dl to 133 mg/dl and PPG from 278 mg/dl to 159 mg/ dl
- Other 33.3 % (18 patients) received 2 mg of repaglinide before main meals and their HbA1c just decreased from 9.4 % to 7.9 %, FPG from 232 mg/dl to 182 mg/dl and PPG from 295 mg/dl to 207 mg /dl.

The remaining 11.1 %(6 patients) received 4 mg of repaglinide before each main meal (not more than 16 mg per day) with an HbA1c level fall from 10.7 % to 8.5%, FPG 239 mg/dl to 145 mg/dl and PPG from 340 mg/dl to 230 mg/dl.(Table 5)

There was a significant difference between baseline HbA1c levels and after three months of repaglinide therapy in both groups. (Table 6)

Fig 1 shows that patients on combination therapy had higher HbA1c levels than those on repaglinide monotherapy.

1: HbA1c <6.5%
2: HbA1c of 6.5–7.5%
3:HbA1c>9%

Table 1: Demographic Character of Patients

Variable	N	%
Age		
30-39	7	7.2
40-49	33	34.1
50-59	37	38.1
60-69	20	20.6
Gender		
Male	42	56.7
Female	55	43.3
Total	97	100

Table 2: Classification of patients according to their treatment at presentation

Treatment category	N	%
Repaglinide monotherapy	43	44.3
Metformin +Repaglinide	54	55.7
Total	97	100

Table 3: Diabetes Duration

	R monotherapy patients (43) patients	R+ metformin combination (54) patients
Mean of diabetes duration (months)	7.6(±7.2)	32.4(±18.4)
Min/max (months) ± SD	3/25	3/78

Table 4: Effects of Repaglinide Monotherapy

Dose of R (mg)	No. of patients	%	At presentation (before starting R)	After 6 months R therapy
0.5	14	32.5		
Mean± SD: **FPG**			178 (± 23.3)	122 (± 12.2)
PPG			230 (± 29.9)	156 (± 16.8)
HbA1c			8.8 (± 1.3)	6.4 (± 0.6)
1	29	67.5		
Mean± SD: **FPG**			195 (±29.6)	129 (± 15.5)
PPG			264 (±56.4)	162 (±16.9)
HbA1			9.4 (±1.7)	6.6 (± 0.9)

Table 5: Effects of Repaglinide and Metformin Combination

Dose of R (mg)	Number of patients	%	At presentation (before starting R)	After 6 months R therapy
	4	7.4		
Mean± SD: **FPG**			185 (±29.9)	133 (±16.9)
PPG			250 (±85.6)	160 (±10.6)
HbA1c			8.2 (±0.6)	6.4 (±0.8)
1	26	48.2		
Mean± SD: **FPG**			212 (±39.8)	133 (±20.1)
PPG			278 (±59.6)	159
HbA1c			9.1 (±1.4)	(±25.6) 6.6 (±0.9)
2	18	33.3		
Mean± SD: **FPG**			232(±28.0)	182(±46.8)
PPG			295(±33.4)	207(±41.1)
HbA1c			9.4 (±1.3)	7.9 (±2.0)
4	6	11.1		
Mean± SD: **FPG**			239(±23.8)	145(±11)
PPG			340(±17.4)	230(±49.7)
HbA1c			10.7(±0.7)	8.5(±0.8)

Table 6: Changing in HbA1c

	R monotherapy	R+metformin
Baseline		
Mean	9.1	9.3
SD	2.0	1.5
Minimum	6.1	5.8
Maximum	14.5	13
Change from baseline to end of study		
Mean	6.5	7.1
SD	1	1.6
Confidence Interval	-1.8—3.2	-1.6—2.8

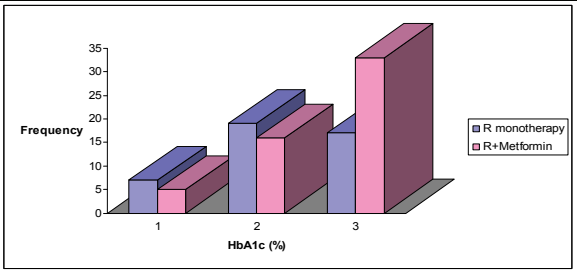

Figure 1: HbA1c levels

DISCUSSION:

T2DM can be treated effectively with oral antidiabetic drugs, with or without insulin. The natural history of T2DM is that of progressive beta-cell deterioration, secondary failure of oral agents, and the subsequent need for insulin therapy. The patient most likely to respond well to oral antidiabetic agents is one who develops diabetes after age forty and has had diabetes for less than five years [22, 23]. Repaglinide is an oral antidiabetic agent taken with main meals with a fast onset and short duration of action. It can be used in both mono- and combination therapy for the treatment of both fasting and postprandial hyperglycemia in patients with T2DM. Combination therapy is usually initiated as either first-line therapy in drug-naïve patients or added to stable doses of current therapy if glycemic goals have not been achieved. [24] It can be used in patients at different stages of the disease, from uncomplicated to severely complicated cases. In spite of the fact that the drug has been tested in a large number of clinical trials and an observational study, its world-wide use is far less than, for example, SUs. [25] .Repaglinide monotherapy and its combination with metformin are efficacious in glycaemic control in patients with inadequate glycemic control by diet restriction or metformin monotherapy. Adding a second agent is usually better than increasing the dosage of an agent that is already being given in a nearly maximum dosage, because combining agents is usually more effective than stopping one agent and substituting another [7].The American Diabetes

less as the target for glycemic control, with a level persistently over 8 % serving as a signal to reassess and revise treatment[7]. Newly diagnosed patients who have never been treated with antidiabetic agents and those HbA1c < 8% respond more profoundly to repaglinide than poorly controlled individuals already on treatment. [26] .This study was designed to compare effects of various doses of repaglinide on the FPG and PPG profiles as a monotherapy and in combination with metformin. It also showed a good correlation between HbA1c and mean blood glucose levels.

Although fasting hyperglycemia is used commonly to diagnose T2DM, there is increasing interest in the role of PPG for both the diagnosis and management of T2DM. Postprandial hyperglycemia develops early in the course of T2DM and is often evident even before FPG elevations are seen. In addition, PPG is a marker of glycemic burden and is as predictive or more predictive of the risk for complications of diabetes when compared with FPG [27-29]. M. Hollingdal et al reported that short-term treatment with the prandial glucose regulator repaglinide augments first-phase insulin secretion and insulin secretary burst mass during glucose giving in T2DM patients 12 hours after the last dose of repaglinide. [30] In a comparative study of incremental doses of repaglinide in T2DM patients done by Lawrence S. Cozma at el in the U.K, patients were categorized according to their HbA1c levels to early diabetics (HbA1c of 6.5–7.5%), late diabetics (HbA1c of 7.5–9%) and advanced diabetics (HbA1c >9%) . Significant dose-related increases in early insulin secretion were found only in less advanced diabetic subjects. In advanced diabetic patients, only the maximum dose (4 mg) was significant compared with placebo. [31] The present study showed that patients who reached a dose of 4 mg (Table 5) had an HbA1c mean of 10.7 % (advanced diabetics).This may be because of that early postprandial hyperglycemia is excess or "rebound" insulin secretion in the postprandial period. In the early diabetic stages, the pancreas can sustain supranormal levels of insulin production in response to hyperglycemia. By contrast, in advanced diabetic stages, ß-cell mass loss eventually results in inappropriately low insulin secretion; this decline in pancreatic insulin secretion is the result of gradual ß-cell loss compounded by the "toxic" effects of hyperglycemia on the surviving islets. Consequently, the benefits of insulin secretagogue medication are expected to be maximal in the early stages of diabetes. [9, 31] R Moses et al in Australia published “Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with T2DM, in a 4-month double-blind randomized controlled trial”, where they compared repaglinide alone (0.5 mg three times daily, increased stepwise to 1 mg, 2 mg and 4 mg), metformin alone and repaglinide plus metformin in 83 patients with T2DM who had been on metformin alone for more than 6 months without achieving adequate control. In the combined-therapy group, HbA1c concentration fell from baseline by 1.4% (p=0.0016). No significant changes were seen in HbA1c or FPG in patients switched to repaglinide or in those remaining on metformin alone. [16] In this study the combined-therapy group HbA1c concentration fell from baseline by 2.2% (p=0.001). In addition significant changes were seen in HbA1c and FPG in patients on repaglinide alone. However in another study done in January 2008 in Denmark by Lund SS et al, “Impact of metformin versus the prandial insulin secretagogue, repaglinide, on fasting and postprandial glucose and lipid responses in non-obese patients with T2DM” metformin was found to be similar to repaglinide in reducing PPG of T2DM patients.[32] In Denmark Ole Schmitz et al performed the study of “Optimizing Insulin Secretagogue therapy in Patients with T2DM”. They concluded that significant steeper initial rises in postprandial insulin levels versus baseline

repaglinide, despite the reduction in glucose levels that had occurred because repaglinide treatment augments early-phase ß-cell secretion rather than reducing insulin clearance [10]. Tian H et al in China published "Improvement of insulin sensitivity and beta-cell function by nateglinide and repaglinide in T2DM patients - a randomized controlled double-blind and double-dummy multicentre clinical trial" which showed that repaglinide could improve insulin sensitivity and beta-cell function [33].The present study indicated that the (0.5–1.0 mg) doses used in T2DM patients for whom control is suboptimal using diet alone, was enough to reach optimal glycemic control; but further dose titration was expected in individuals who were previously on metformin with longer diabetes duration and advanced stages. This may reflect inadequate ß-cell reserve at this stage of the disease when insulin secretagogues might be expected to be less efficacious. This study also revealed that repaglinide effectively decreases HbA1c as a monotherapy and when added to metformin, but larger doses were required in the later state. HbA1c concentration fell from baseline by 2.6 % in the monotherapy state and by 2.2 % in the combination state.

CONCLUSION

This study indicated that small doses of repaglinide (0.5-1.0 mg before main meals) was effective in T2DM patients with suboptimal control on diet alone and was enough to reach optimal glycemic control with optimal glycated hemoglobin levels. However, further dose titration up to (4 mg before main meals) is expected to be required in individuals who were previously on metformin with longer diabetes duration and advanced diabetic stages, reflecting inadequate ß-cell reserve at this stage of the disease when insulin secretagogues might be expected to be less efficacious.

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