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ORIGINAL ARTICLE

A time to revisit the two oldest prandial anti-diabetes agents: acarbose and repaglinide

Parisa Pishdad[1] · Reza Pishdad[2] · Gholam Reza Pishdad[3] · Yunes Panahi[4]

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Abstract

Purpose Compared with newer prandial anti-diabetes agents, repaglinide and acarbose are unique in being globally available in generic versions, being oral, and being the cheapest of all. The aim of this study was to compare their efficacy when used alone or in combination.

Methods In a randomized, double-blind, prospective study, 358 recently diagnosed type 2 diabetes (T2D) patients, who on a combined therapy with metformin and insulin glargine had a fasting plasma glucose (FGP) of <7.2 mmol/L but a 2-h postprandial plasma glucose (2hPPG) >10 mmol/L, were assigned to three groups of additional treatment with either repaglinide, acarbose, or repaglinide-plus-acarbose for 4 months.

Results With intention-to-treat analysis, 63% of repaglinide group, 45.4 percent of acarbose group, and 75.7% of repaglinide-plus-acarbose group reached the primary endpoint of 2hPPG < 10 mmol/L while maintaining FPG < 7.2 mmol/L. Treatment adherence rate was 75.6% with repaglinide, 61.4% with acarbose, and 81.3% with repaglinide-plus-acarbose ($p = 0.001$). Among the groups, weight was significantly lower in acarbose group ($p < 0.05$). Twenty-one percent of repaglinide patients, 4.9% of acarbose subjects, and 10.3% of repaglinide-plus-acarbose cases reported at least one episode of hypoglycemia ($p < 0.005$). HbA1C and basal insulin requirement were significantly lower in repaglinide group ($p = 0.004$, $p = 0.0002$). Triglycerides were lowest in acarbose group ($p = 0.005$).

Conclusions Both acarbose and repaglinide were vastly effective in lowering postprandial hyperglycemia of recently diagnosed T2D. When combined, they were even more efficacious and the disease had a better outcome. Compared with newer peers, these two are particularly useful where and when cost consideration in diabetes treatment is a prime concern.

Keywords Type 2 diabetes (T2D) · Postprandial hyperglycemia · Acarbose · Repaglinide · Treatment adherence

Introduction

Epidemiological studies have shown that postprandial hyperglycemia considerably contributes to elevated HbA1C levels and is linked to the pathogenesis of chronic diabetes complications particularly cardiovascular issues [1–7]. Of all antidiabetic agents that specifically target postprandial hyperglycemia, the two oldest introduced to market are repaglinide and acarbose. These two have some outstanding qualities that the newer ones do not: both are oral, cheap, and globally available [8–18]. They are effective and are especially in wide use in Asian and Middle Eastern countries [19–25]. Acarbose represents alpha-glucosidase inhibitors, which also include voglibose and miglitol, and decreases intestinal glucose absorption [19–24]. Repaglinide is the prototype of non-sulfonylurea insulin secretagogues, which also include mitiglinide and nateglinide [19–23, 25]. Although both have been in use in the treatment of postprandial hyperglycemia of type 2 diabetes (T2D) for more than two decades, so far, there are little comparative data regarding their efficacy when used alone or in combination [11, 26–28]. This work was designed for a head-to-head assessment of the effectiveness of these two

✉ Gholam Reza Pishdad
pishdadg@sums.ac.ir

[1] Shiraz Medical School, Shiraz University of Medical Sciences, Shiraz, Iran

[2] Department of Internal Medicine, Rutgers New Jersey Medical School, Newark, NJ, USA

[3] Endocrine and Metabolism Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[4] Chemical Injuries Research Center, Tehran's Baqiyatallah University of Medical Sciences, Tehran, Iran

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medicines, when used either alone or in combination, in achieving the pre-specified primary endpoint of 2-h postprandial plasma glucose (2hPPG) levels of <10 mmol/L (180 mg/dL). The study was conducted in a group of recently diagnosed type 2 diabetic patients whose fasting plasma glucose (FPG) levels were <7.2 mmol/L (130 mg/dL) while on a combined treatment with basal insulin and metformin.

Methods

Study design and patients

Estimation of sample size for this trial was based on data from two comparable previous studies [11, 26]. Similar to a preceding study [11], the patients were selected from among type 2 diabetic patients who were being seen and followed in our diabetes and endocrinology clinics between January 1, 2012 and December 31, 2014. The inclusion criteria included patient's age of 20–65 years, diabetes duration of less 24 months since diagnosis, and BMI < 40 kg/m^2. Exclusion criteria were established coronary artery or cerebrovascular disease, intestinal disease or elevated liver enzymes, and elevated serum creatinine > 123.76 mmol/L (1.4 mg/dL). Diabetic women who were pregnant or intended to become pregnant during the course of the study were not included. Patients who were on metformin alone—in doses of not <2 g per day for at least 2 months—were screened. Those with FPG > 7.2 mmol/L (130 mg/dL) and 2hPPG >10 mmol/L (180 mg/dL) were individually interviewed. From patients who met the study criteria, those who consented to participate in the study were enrolled. The study protocol, as well as the consent form, was approved by local ethics committees. Each patient and their family were reeducated in hypoglycemia symptoms and signs and its treatment. Each was provided with a glucometer and was thoroughly re-instructed in self-monitoring of blood glucose. While continuing diabetes diet and metformin (Fig. 1), the selected patients were treated with once daily insulin glargine, starting at 0.1 unit per kg, with titration rate of 1 unit per day, decreasing for fasting glucose levels < 4.4 mmol/L (80 mg/dL) or increasing for levels >7.2 mmol/L (130 mg/dL). After 2 months, those who had achieved and maintained FPG of <7.2 mmol/L (130 mg/dL) but still had 2hPPG > 10 mmol/L (180 mg/dL) were randomly assigned to one of three types of treatment as add-on therapy: placebo-plus-acarbose (acarbose group), repaglinide-plus-placebo (repaglinide group), or repaglinide-plus-acarbose treatment (repaglinide-plus-acarbose) group (Fig. 1). Random allocation of participants to individual treatment groups was through using pre-sealed envelopes containing drug codes of X00X, 0YY0, and 00ZZ, unknown both to investigators and participants. The pharmacist, while not disclosing the name of medicines, dispensed repaglinide-plus-placebo, placebo-plus-acarbose, or repaglinide-plus-acarbose according to the patient's randomly assigned treatment code.

Medications and/or placebos were given three times daily: in repaglinide group the starting dose for repaglinide was 0.5 mg just before meal and acarbose's placebo 12.5 mg with the first mouthful of meal. In acarbose group, repaglinide's placebo was started with 0.5 mg dose before meal and acarbose 12.5 mg with the first mouthful of food. In the repaglinide-plus-acarbose group, the initial doses of medications were repaglinide 0.5 mg just before meal and acarbose 12.5 mg with the first mouthful of food. For every patient, while maintaining FPG levels < 7.2 mmol/L (130 mg/dL) with basal insulin continuation and adjustment, we aimed to achieve the primary endpoint of 2hPPG of <10 mmol/L (180 mg/dL) with our prandial agents. The main secondary endpoints were determinations of drug adherence rate and changes in weight, lipid levels, HbA1c, basal insulin requirement, and hypoglycemia occurrence. We tried to reach the primary endpoint by dose escalation of repaglinide, acarbose, and their placebos (Fig. 1). The increment per dose for medicines and placebos was at 14-day intervals—repaglinide 0.5 mg, acarbose's placebo 12.5 mg, repaglinide's placebo 0.5 mg and acarbose 12.5 mg, and repaglinide 0.5 and acarbose 12.5 mg for the groups of repaglinide, acarbose and acarbose + repaglinide, respectively (Fig. 1). Therapeutic enhancements were made by the patients themselves under the close supervision of the authors. Patients were counseled to measure and record glucose levels just before and 2 h after each meal and at bed time on days the agents' doses were enhanced, and also at any time they suspected hypoglycemia. Minor hypoglycemia (plasma glucose level <3.9 mmol/L (70 mg/dL)) was

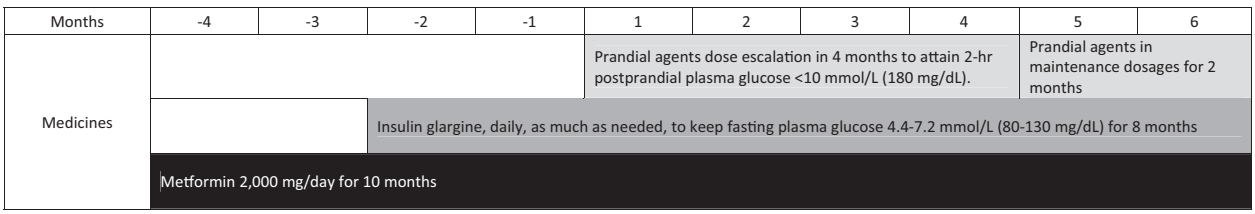

Fig. 1 Time of commencement and duration of treatment with metformin, insulin glargine, and prandial agents acarbose, repaglinide, and repaglinide-plus-acarbose

defined as episodes that could be self-treated. Major hypoglycemic episodes were those that required a third party's assistance. In case of hypoglycemia, patients were instructed to take 15-g oral glucose (3–4 glucose tablets) and recheck plasma glucose 15 min after and repeat the retreatment if needed. Otherwise doses of the prandial agents and placebos were increased until the primary endpoint of the 2-h post meal glucose of <10 mmol/L (180 mg/dL) was achieved or else the maximum recommended dosage of medication—4 mg tid for repaglinide and 100 mg tid for acarbose—or adverse effects intervened. Then the same therapeutic regimen was maintained for 2 months after final dose escalation of prandial agents and their corresponding placebos (Fig. 1). For each patient data regarding weight, systolic and diastolic blood pressures, FPG, 2hPPG, HbA1C, units of basal insulin requirement, and a lipid profile were obtained before the commencement of prandial agent (on day 0), 30 days later, and 60 days after the final dose escalation of the prandial agents (Fig. 1).Statistical analysis: SPSS software (version 22; SPSS Inc, Chicago, IL) was used for statistical analysis of the data. Results are expressed as mean ± standard deviation (SD). Student's *t* test and one-way ANOVA test were employed to compare the means of groups' data and chi-square test was used to compare proportions. Results with $p < 0.05$ were considered as statistically significant.

Results

As depicted in Fig. 2, there were 2501 patients with endocrinologist-ascertained diagnosis of T2D who were being treated with metformin alone, in a daily dose of 2000 mg/day for at least 2 months. Of these, 1003, with FPG > 7.2 mmol/L (130 mg/dL) and 2hPPG not <180 mg (10 mmol/L), met the study criteria. A total of 471 agreed to start insulin as an

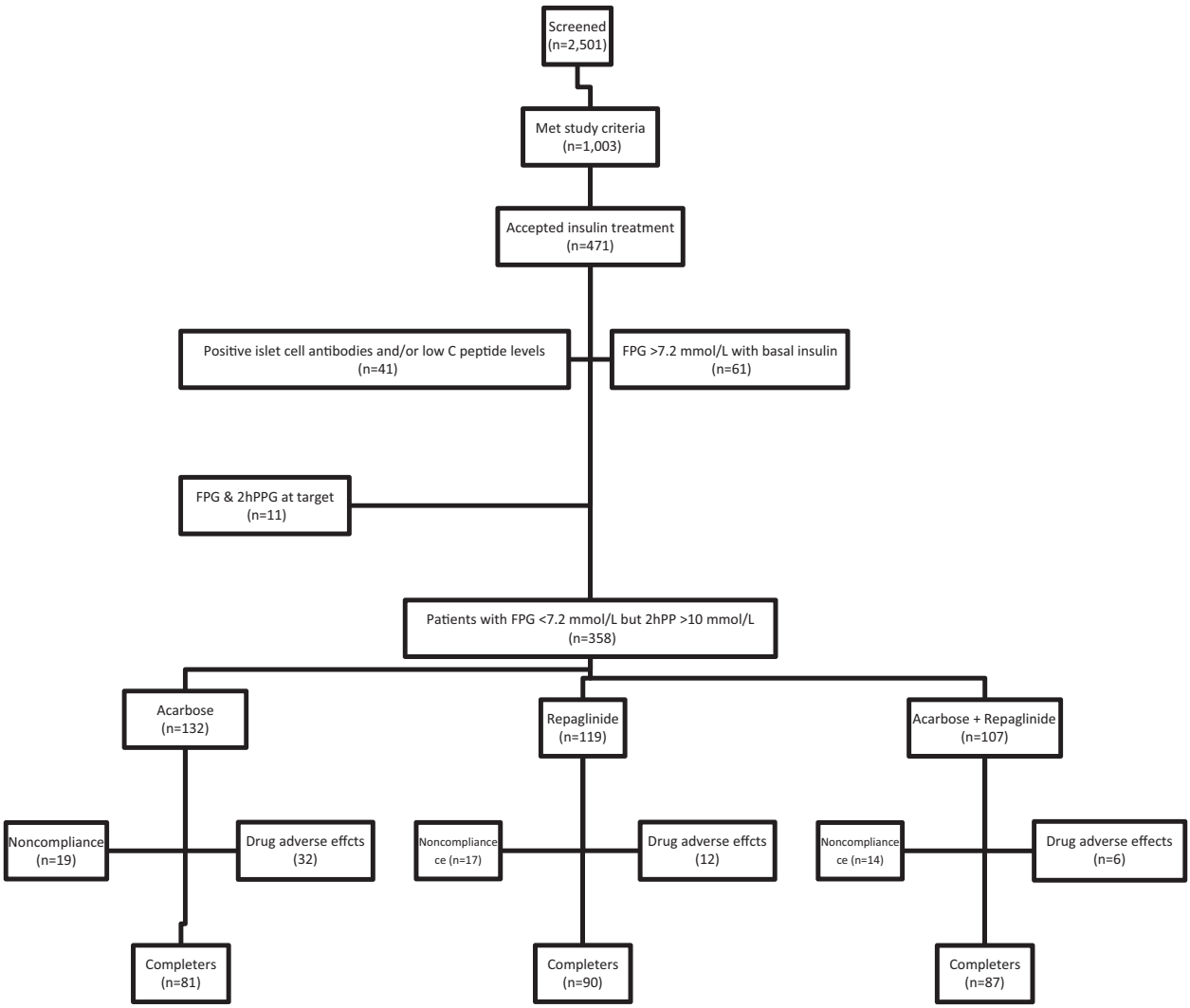

Fig. 2 Flow of patients through the study

add-on therapy; the rest were not agreeable to injections (Fig. 2). Of these, 41 were excluded because they tested positive for islet cell antibodies and 61 more were not included because they failed to attain and/or maintain fasting glucose levels of <7.2 mmol/L (130 mg/dL) after 2 months of insulin therapy. Eleven more were excluded since they had already reached target values not only for FPG but also for 2hPPG (Fig. 2). The remaining 358 patients had postprandial hyperglycemia (2hPPG > 10 mmol/L (180 mg/dL)) with at target FPG (<7.2 mmol/L (130 mg/dL)) (Fig. 2). Repaglinide group had received 119 patients, acarbose group 132, and repaglinide + acarbose group 107 patients (Fig. 2). As shown in Table 1, statistical analysis of data obtained just before the commencement of the prandial agents revealed that the patients of the three groups were matched in gender, age, duration of diabetes, body weight, HbA1C, triglycerides (TG), LDL cholesterol, and basal insulin requirement.

Because of noncompliance and unavailability of data, 17 of repaglinide group, 19 of acarbose patients, and 14 of repaglinide-plus-acarbose subjects were excluded from the study (Fig. 2). Twelve of repaglinide group, 32 of acarbose patients, and 6 of repaglinide-plus-acarbose group withdrew because of drug adverse effects (Fig. 2). In repaglinide group, these were unwanted weight gain in 5 (41.5%), hypoglycemia in 5 (41.5%), irritability and nervousness in 1 (8%), and insomnia in 1 (8%). In acarbose group, the adverse effects were flatulence in 18 (56%), abdominal cramps in 6 (19%), nausea in 4 (12.5%), diarrhea in 3 (9%), and acid regurgitation in 1 (3%). With repaglinide-plus-acarbose, these were flatulence in 3 (50%), nausea in 1 (16.5%), and hypoglycemia in 2 (33.3%). In total, 90 of 119 repaglinide subjects, 81 of 132 acarbose cases, and 87 of 107 repaglinide-plus-acarbose patients were true completers of the study, yielding adherence rates of 61.4%, 75.6%, and 81.3%, respectively ($p < 0.002$).

With intention-to-treat analysis, just 30 days after the inception of prandial agents, the primary endpoint of reaching 2hPPG of <10 mmol/L (180 mg/dL) while maintaining FPG levels of <7.2 mmol/L (130 mg/dL) had been achieved in 42% of patients in repaglinide group, 26.5% of those in acarbose group, and 61.6% of subjects in repaglinide-plus-acarbose group ($p < 0.003$). At the end of study, the corresponding figures were 63%, 45%, and 76%, respectively ($p < 0.04$) (Table 2). Also, at the end, among

Table 1 Demographic characteristics and data on HbA1c, lipids, and basal insulin dose in the study participants just before the initiation of repaglinide, acarbose, or repaglinide-plus-acarbose

Prandial agents	Repaglinide	Acarbose	Acarbose + repaglinide	*p*
Number of patients	119	132	107	
Male/female ratio	50/69	53/79	42/65	0.7
[a]Age in years	50.1 ± 10.2	51.2 ± 9.4	52 ± 10.4	0.35
[a]Weight in kg	80.4 ± 12.2	79.2 ± 11.6	78.54 ± 10.5	0.46
[b]T2D duration months: [a]M ± SD (median)	[a]14.0 ± 4.5 (14)	[a]13.2 ± 4.8 (13.5)	[a]13.8 ± 4.6 (14)	0.36
[a]HbA1c%	7.7 ± 0.74	7.6 ± 0.73	7.6 ± 0.72	0.47
[a]TG in mmol/L	2.70 ± 0.7	2.60 ± 0.7	2.78 ± 0.8	0.16
[a]LDL cholesterol in mmol/L	3.60 ± 0.6	3.60 ± 0.5	3.70 ± 0.5	0.27
[a]Insulin glargine units	14 ± 4.6	15 ± 4.8	14.66 ± 5.4	0.27

T2D type 2 diabetes, *HbA1C* glycated hemoglobin, *TG* triglycerides, *LDL* low density lipoprotein

[a]Data are shown as mean ± standard deviation (M ± SD)

[b]Duration of diabetes since diagnosis

Table 2 Data on achievement of the glycemic target, treatment adherence, weight, hypoglycemic episodes, HbA1C, TG, LDL cholesterol, and dose of basal insulin 2 months after the final dose escalation of prandial treatment with repaglinide, acarbose, and repaglinide-plus-acarbose

Prandial agent(s)	Repaglinide	Acarbose	Repaglinide + acarbose	*p*
Percent of patients at glycemic target	63%	44.7%	75.7%	<0.05
Treatment adherence rate	75.6%	61.4%	81.3%	0.001
[a]Weight	81.8 ± 11.6	77.6 ± 11.2	78.6 ± 10.8	<0.05
[b]Number (%) with hypoglycemia	19 (21%)	4 (4.9%)	9 (10.3)	<0.005
[a]HbA1c%	6.5 ± 0.5	6.8 ± 0.7	6.7 ± 0.6	0.004
[a]TG	2.60 ± 0.6	2.4 ± 0.6	2.7 ± 0.6	0.005
[a]LDL cholesterol	3.70 ± 0.6	3.50 ± 0.6	3.64 ± 0.5	0.06
[a]Insulin glargine (units)	10.2 ± 3.8	13 ± 4.8	11.0 ± 4.6	0.0002

HbA1C glycated hemoglobin, *TG* triglycerides, *LDL* low density lipoprotein

[a]Data are shown as mean ± SD (standard deviation)

[b]Number (%) that reported at least one episode of hypoglycemia

the groups, HbA1C and basal insulin requirement were lowest in repaglinide group ($p = 0.004$ and $p = 0.0002$, respectively), and TG were lowest in the acarbose group ($p = 0.005$). There remained no significant difference for LDL cholesterol level between the groups (Table 2). Among the groups, weight was significantly lower in the acarbose group ($p < 0.05$) (Table 2). Twenty-one percent of repaglinide patients, 4.9% of acarbose subjects, and 10.3% of repaglinide-plus-acarbose cases reported at least one episode of minor hypoglycemia ($p < 0.005$). There were no reports of any major hypoglycemia in any of the groups. The average of total daily doses of medicines during the last 2 months of the study were 5.7 ± 3.4 (mean ± SD) mg repaglinide in repaglinide group, 155.6 ± 87.8 mg acarbose in acarbose patients, and 3.3 ± 2.0 mg repaglinide and 83.3 ± 51.4 mg acarbose in repaglinide-plus-acarbose subjects. As seen, the mean doses of prandial agents in the repaglinide-plus-acarbose group were significantly lower than those in the other 2 groups (p values of <0.03 and <0.002 for repaglinide and acarbose, respectively).

Discussion

Many patients with diabetes who have acceptable FPG levels may still have elevated HbA1C values owing to elevated postprandial glucose (PPG) levels [1]. Epidemiological studies have revealed that postprandial hyperglycemia is particularly linked to the cardiovascular morbidity in diabetes [2–7]. As nearly 65 percent of patients with T2D die from atherosclerotic cardiovascular complications [2–7], due importance should also be given to the treatment of postprandial hyperglycemia [1]. While the newer prandial agents are costly and may not yet be globally available, acarbose and repaglinide are the two oldest antidiabetic prandial agents that are cheap and available in generic versions worldwide [11–18]. Nowadays that long-acting, peakless insulin analogues can conveniently control fasting and pre-prandial glucose levels, acarbose and repaglinide, for the reasons cited, might be particularly useful in the management of postprandial hyperglycemia of T2D [15–22]. But, so far, there are little data regarding the comparative efficacy of these two medications when used alone or in combination [11, 19–25]. This study was carried out in a group of recently diagnosed type 2 diabetic patients with isolated postprandial hyperglycemia. Here we aimed to compare the two agents head-to-head when used alone and in combination by the pre-specified primary endpoint of achieving 2PPG level of <10 mmol/L (180 mg/dL). We observed the following between-groups differences: (1) the rate of drug adherence was lowest with acarbose and highest with acarbose-plus-repaglinide; (2) acarbose-alone had the best impact on TG levels; (3) acarbose-alone caused weight loss while repaglinide-alone did the opposite; (4) lowering of basal insulin requirement was most significant with repaglinide alone; (5) owing to added efficacies, the target glycemia of 2hPPG of <10 mmol/L (180 mg/dL) could be reached sooner and with much smaller doses of prandial agents when used in combination; and (6) because of smaller amount of either medication, drug adverse effects became least frequent with combined prandial therapy (and this probably was the reason for the best drug adherence rate seen in this group). Drug adverse effect was mainly gastrointestinal with acarbose and hypoglycemia and weight gain with repaglinide.

So far, in the literature, there are few investigations that compare these two agents [11, 26–28]. In one, the investigators studied 38 cases of obesity and T2D that were randomly treated with either insulin glargine and repaglinide or insulin glargine and acarbose for 13 weeks, and they found that repaglinide and acarbose were equally effective in diabetes therapy of their patients [26]. In another relatively small sample study, when repaglinide or acarbose was added to a double oral antidiabetic treatment with sulfonylurea and metformin, both were found to have a similar effect on postprandial plasma glucose [27]. Other investigators found that on the whole acarbose was a weaker agent than repaglinide at reducing blood glucose levels in T2D [11, 28]. In one study it was demonstrated that addition of acarbose to repaglinide helps control PPG further [29].

Our study is unique in the following ways: (1) it is carried out in recently diagnosed type 2 diabetic patients when pancreatic β-cells are not yet exhausted and are quite responsive to insulin secretagogue (here, repaglinide); and (2) the prandial agents (here, acarbose, and/or repaglinide) are used when fasting glucose level has already been dealt with and is at goal. Thus, an isolated postprandial hyperglycemia is used for the assessment of the true effectiveness of our prandial agents. Although probably more effective management of postprandial hyperglycemia is possible with ultra-short-acting insulin analogues, short-acting glucagon-like peptide-1 receptor agonists, and pramlintide [16–20], the fact of the matter is—as was seen in this and also another study—the majority of type 2 diabetic patients do not like injections and prefer to be treated with oral agents, even when not considering the cost of treatment [11]. Dipeptidyl peptidase-4 inhibitors, sodium-glucose co-transfer-2 inhibitors, and inhaled insulin, although not among injectable prandial agents, are costly and not yet widely available in developing or low-income communities of the world [11, 13–18]. Acarbose and repaglinide are cheap and globally available [11–18]. (In our region, as elsewhere, the cheapest prandial agents are repaglinide and acarbose. And for comparison, the cost of 1-month treatment with a dipeptidyl peptidase-4 inhibitor, like sitagliptin, is approximately twice that of 1 month of full daily dosage of either repaglinide or acarbose [11]. For an ultra-short-acting insulin, like aspart, that proportion is more than 25 [11]. And for a glucagon-like

peptide-1 receptor agonist the percentage is over 220 [11].) Based on this study and a previous one [11] it can be concluded that acarbose can help decrease TG and weight in the obese, dyslipidemic diabetic patient while repaglinide can be particularly useful in the recently diagnosed nonobese patient with enough of functioning pancreatic β-cells. When acarbose is used with repaglinide in such patients, treatment compliance is significantly improved and target glycemia is reached much sooner with smaller doses of medicines, and with less frequent adverse effects.

In conclusion, so far, there has been a paucity of data regarding the comparative efficacy of acarbose vs. repaglinide vs. their combined use in diabetes treatment [11, 26–29]. Our study revealed that in recently diagnosed T2D in the context of at-goal FPG level, repaglinide was a significantly stronger agent and with remarkably better drug adherence than acarbose. Acarbose lowered weight and TG levels and was much less frequently associated with hypoglycemia. When repaglinide was used in combination with acarbose, treatment adherence was best, and the glycemic target was achieved in a much shorter time and with much smaller doses of prandial agents. We suggest it is time pharmaceutical industry introduced fixed-dose combinations of these two cheap and effective oral agents to further boost treatment adherence and reduce healthcare utilization and cost [30]. Based on data from this study as well as those from a previous investigation [11], we suggest fixed-dosage combinations in strengths of 0.5 mg repaglinide/12.5 mg acarbose, 1 mg repaglinide/25 mg acarbose, and 2 mg repaglinide/50 mg acarbose tablets be made available.

But in the literature, other than the risk of severe hypoglycemia with repaglinide in combination with insulin, there are some more data in favor of acarbose and against repaglinide: in one study in type 2 diabetic patients, it was found that repaglinide was associated with a higher risk of hospitalized heart failure than acarbose [31]. Also, other studies have demonstrated that in subjects with impaired glucose tolerance, acarbose can delay development of T2D and may also be associated with a reduction in hypertension and cardiovascular disease [32, 33].

And, on the whole, our study showed that both acarbose and repaglinide had a very good impact on postprandial hyperglycemia of recently diagnosed type 2 diabetic patients. Their combined use was superior to the use of either agent alone. Compared with other prandial antidiabetic agents, these two are particularly useful where and when cost consideration in diabetes treatment is a prime concern.

Limitations of the study

The sample size is not sufficient for assessing the risk of severe hypoglycemia. Also, the hypoglycemia data are based only on patient's self-measurement and not continuous glucose monitoring; thus, the possibilities of detecting asymptomatic/oligosymptomatic hypoglycemic episodes are almost nil. And the duration of the trial is not long enough to establish efficacy and safety for the medications studied.

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Author contributions G.R.P., P.P., R.P., and Y.P. designed and carried out the study. R.P. and P.P. reviewed the literature and gathered references. G.R.P. analyzed the data. G.R.P., R.P., P.P., and Y.P. wrote the paper. G.R.P. had the final decision to submit the paper for publication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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