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Full Length Research Paper

Repaglinide as a safe alternative against hypoglycemia in fasting elderly diabetic patients: A single blinded, placebo-controlled, six period, cross-over study

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Elderly are more prone to develop hypoglycemia or miss meals. Repaglinide and nateglinide are suggested to have glucose-dependent insulinotropic effect. The aim of the present work was to test the effect of both drugs on serum glucose and insulin levels in fasting elderly diabetic patients. Eight elderly diabetics underwent a fixed dose single blinded, placebo controlled, six period, cross-over study at the Department of Geriatrics and Gerontology - University hospital. Patients received either repaglinide 2 mg, nateglinide 120 mg or a placebo, both under fasting and non-fasting states. Serum glucose and insulin were measured at 30 min intervals for four hours, following drug or placebo administration. None of the eight patients developed hypoglycemia under the fasting state in response to repaglinide and only one patient developed mild hypoglycemia (3.7 mmol/L) under the fasting state in response to nateglinide. Area under the serum insulin concentration-time curve was significantly lower (p = 0.039) in the fasting state, compared to the non-fasting state, in response to repaglinide, but not to nateglinide. The present study suggests that in case of elderly diabetic patients, who may miss meals, repaglinide is a safe alternative to other antidiabetics. As for nateglinide, further studies are required.

Key words: Repaglinide, nateglinide, hypoglycemia, fasting, elderly.

INTRODUCTION

Type 2 diabetes is a major public health problem especially in elderly. Its prevalence in elderly, in the USA, is more than double its prevalence in the adult age group (National Diabetes Information Clearinghouse). Treatment decisions for this age group are particularly influenced by age and life expectancy, comorbid conditions and severity of the vascular complications. Furthermore, adherence to life style modification may be compromised in the elderly due to comorbid conditions and psycho-social limitations (Rosenstock, 2001). Elderly subjects may skip meals (Posner et al., 1993), and those with poor memory are more than twice as likely to do so (Perkins et al., 1999). This increases the risk of hypoglycemic coma that is proved to be increased in elderly frail patients

(Ben-Ami et al., 1999). Changes in pharmacokinetics that occur in the elderly also lead to potential adverse effects and drug interactions and therefore, should be considered when selecting pharmacological therapy (Rosenstock, 2001).

Repaglinide and nateglinide are short acting non-sulfonylurea insulin secretagogues of the meglitinides group, that are considered of lower hypoglycemic risk (Miwa et al., 2004; Meneilly, 2011). Hu et al. (2001) reported that nateglinide showed a glucose-dependent insulinotropic effect *in-vitro*, while repaglinide failed to demonstrate such effect. On the other hand, repaglinide resulted in a blunted β cell insulin secretory response in healthy subjects during euglycemic and modest clamp

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Table 1. Demographic characteristics of the patients.

Characteristic	Value
Gender (female/male)	6/2
*Age (years)	63.1 (60 - 75)
* Body mass index (Kg/m^2)	35 (29 - 40)
*Known duration of diabetes (years)	1.9 (0 - 5)
*HbA1c(%)	6.1 (5.0 - 7.48)
*ALT (IU/L)	27.1 (9 - 60)
*AST (IU/L)	31.2 (17 - 77)
*Serum creatinine (micromol/l)	76.25 (35.4 -256.4)
*#Estimated creatinine clearance (ml/min)	135.8 (36.4 - 247.9)
Co-morbidities (N)	
Hypertension	2 (controlled on enalapril)
Ischemic heart disease	1 (on nitroglycerin and aspirin)
Renal impairment	1 (S.Cr. 256.4 µmol/L; Estimated creatinine clearance 36.4 ml/min)
Chronic liver disease (AST, ALT)	1 Hepatitis C virus (AST 60 IU/L, ALT 77 IU/L); 1 Portal hypertension (AST 21 U/L, ALT 29 U/L)

* Data are presented as means (range). #Estimated Creatinine clearance was calculated using Cockroft Gault formula.

studies (Aldhahi et al., 2004). These results suggest a low risk of hypoglycemia for both drugs, even if they were administered without meals.

However, differences might exist between the controlled hypoglycemia conditions produced in clamp studies and real world hypoglycemia in patients using insulin secretagogues (Aldhahi et al., 2004). This is a special concern in elderly, where a progressive loss in reserve capacity affects the endocrine system, with loss of homeostatic regulation (Gruenewald and Matsumoto, 2009). Besides, in another study, C-peptide levels were estimated during a hyperglycaemic and an euglycaemic clamp in Type 2 diabetic patients after repaglinide or placebo. Though C-peptide concentrations were lower after repaglinide administration in the normoglycaemic state than in the hyperglycaemic one they remained higher than after placebo (Rudovich et al., 2004). In addition, plasma insulin levels rose following nateglinide administration before glucose injection in recently diagnosed type 2 diabetes patients (Whitelaw et al., 2000).

The effects of repaglinide and nateglinide on blood glucose and serum insulin levels have never been measured in the fasting state. Although the effect of omitting lunch on blood glucose level was studied in patients on repaglinide treatment, no repaglinide dose was administered (Damsbo et al., 1999). The aim of the present work was to study the safety of repaglinide and nateglinide, if the patient missed or delayed his meal by estimating their effect on blood glucose and serum insulin levels in the fasting state.

METHODOLOGY

Study protocol

The study was approved by the Research Ethics Committee of the faculty of medicine, Ain Shams University, Cairo, Egypt. The investigation was carried out in accordance with the Declaration of Helsinki. Written informed consents were obtained from all participants.

Subjects

Nine Egyptian Type 2 diabetic elderly subjects (≥ 60 years) were recruited for the study. Eight completed the study and one subject dropped out after one day for personal reasons (did not tolerate the multiple needle pricks). Demographic characteristics of the patients are shown in Table (1). Three of the eight subjects that completed the study were previously treated with metformin and five were newly diagnosed. Exclusion criteria were: current use of insulin secretagogues, fasting blood glucose above 15 mmol/L, late complications of diabetes or severe concurrent disease. Since comorbidities are common in elderly patients, patients with stable comorbidities that did not represent a contraindication to either drug were not excluded from the study.

Study design

This study was a fixed dose, single blinded, placebo controlled, six period, cross-over study. All patients underwent comprehensive geriatric assessment and laboratory evaluation before the beginning of the study. Metformin morning dose was skipped on the days of the study. Each patient was studied for six non-consecutive days (three days on the fasting protocol and three on the non-fasting protocol). On the mornings of the tests, patients were admitted to the Geriatrics and Gerontology Department at Ain Shams University Hospital. For the non-fasting protocol, two baseline venous samples were collected at 30 min interval, starting at 8:30 am. Immediately afterwards, repaglinide 2 mg (Novonorm, Novo Nordisk, Manufactured by Boehringer Ingelheim Pharma GMbH & Co. KG, Ingelheim am Rhein, Germany), nateglinide 120 mg (Starlidine, International Drug Agency for Pharmaceutical Industries, Port Said, Egypt) or a placebo (Alexandria Company for Pharmaceuticals and Chemical Industries, Egypt) were administered to the patient, followed by an ordinary Egyptian

breakfast composed of bran mixed bread and brown beans (500 kcal, 55% carbohydrate, 30% fat, and 15% protein). Eight venous samples were collected at 30 min intervals afterwards (starting 30 min after meal). Patients were closely observed during the time of study to detect any symptoms suggestive of hypoglycemia. The same procedure was performed for the fasting protocol with the exception of meal serving. During the fasting protocol, capillary blood glucose was checked at 30 min intervals or as needed to early detect any possible hypoglycemia. A glucose level of 3.33 mmol/L was set as a threshold to terminate the sampling and correct hypoglycemia. In case the patient presented with symptoms of hypoglycemia and requested termination of the study, this request was honored, even if blood glucose level was above 3.33 mmol/L. At the end of each day, samples were centrifuged and the serum decanted and stored at -20°C, till they were analyzed. Serum glucose and insulin concentrations were estimated in each sample.

Laboratory determination

Samples were assayed for glucose and insulin at the Clinical Pathology Department at Ain Shams University Hospital, Cairo. Serum glucose was measured using a glucose oxidase method. Serum insulin was measured using enzyme-linked immunosorbent assay (Accu Bind ELISA Microwells, Monobind Inc, Lake Forest, CA). The assay has < 1% cross-reactivity with proinsulin, with no detectable reaction with C-peptide and inter- and intra-assay CV of 5%. The detection range was 35 to 2080 pmol/L. Hemolyzed samples were not included in analysis.

Statistical analysis

The sample size of eight patients was estimated based on the data provided by Rudovich et al. (2004) to detect a 50% difference between insulin levels in the fasting and non fasting state with a power of 80% at the 5% level of significance. Data are expressed as mean ± S.E.M. Significant differences between groups of data were assessed using the paired Student's t-test, and statistical significance was assumed if P < 0.05. Area under the curve (AUC) was calculated using graphpad prism (version 3.02). The mean of the two baseline samples was used for comparison with the other time points. There were 12 missing values (2.5%), 10 samples due to hemolysis and two samples because study was terminated for one patient in one day after 3 h. Missing values were substituted by imputed data (calculated by the expectation-maximization method (EM), SPSS version 17.0, SSPS Inc, Chicago, IL, USA).

RESULTS

Effect on serum glucose level

Mean baseline serum glucose levels were not significantly different among the six testing days. The standard meal resulted in an elevation of serum glucose level after placebo administration. This elevation was significant two hours after breakfast (p = 0.047) compared to baseline level and to fasting state at the same time point (paired Student's t test). On the other hand, placebo did not induce any significant effect on blood glucose level, when administered in the fasting state (Figure 1A). Both repaglinide (2 mg) and nateglinide (120 mg) administered before breakfast prevented this elevation in serum glucose level. Mean glucose level at

each time point -following the administration of either drug- was not significantly different from baseline serum glucose level (Figure 1B and C).

In the fasting protocol, repaglinide did not cause hypoglycemia in any of the eight patients. Serum glucose level was not significantly different between any of the eight time points following drug administration and the baseline level (paired Student's t test). Comparing each time point to the corresponding time point of the non-fasting state did not result in any significant difference (paired Student's t test). The area under the concentration-time curve (AUC_{BL-4h}) was not significantly different either (paired Student's t test). The lowest serum glucose level detected after repaglinide, in the fasting protocol was 4.3 mmol/L.

On the other hand, nateglinide induced one mild hypoglycemic event in the fasting state. The patient experienced tachycardia, sweating and drowsiness, three hours after nateglinide administration. His serum glucose level was 3.7 mmol/L. The study was terminated for this patient on that day, upon his request. Mean serum glucose level (for the eight patients) was slightly, but significantly lower than baseline level at the same time point (1.35 ± 0.96 mmol/L; p = 0.005; paired Student's t test; Figure 1C). However, there was no significant difference in the AUC_{BL-4h} between the fasting and non-fasting states.

Effect on serum insulin level

Baseline serum insulin levels were not significantly different on different days. Repaglinide induced a significant increase in serum insulin level when administered before breakfast. This increase was significantly different from baseline level at 1.5, 2.5, 3, 3.5 and 4 h (p < 0.05; paired Student's t test; Figure 2A). In the fasting state, however, there was no significant difference between baseline serum insulin level and any of the eight time points following repaglinide administration. Furthermore, there was significant difference between serum insulin level in the fasting and the non-fasting states at 2.5, 3 and 3.5 h following repaglinide administration (p < 0.05; paired Student's t test; Figure 2A). The area under the time concentration curve (AUC_{BL-4h}) was significantly different between the fasting and non-fasting state (p = 0.039; paired Student's t test; Figure 2B).

Similarly, nateglinide induced an increase in serum insulin level when administered before breakfast. This increase was significantly different from baseline level at 1.5, 2.5, 3.5 and 4 h (p < 0.05; paired Student's t test; Figure 2C). In the fasting state, however, there was no significant difference between baseline serum insulin level and any of the eight time points following nateglinide administration. Comparing each time point to its corresponding one in the non-fasting state showed significant difference only at 4 h following nateglinide administration

A

B

C
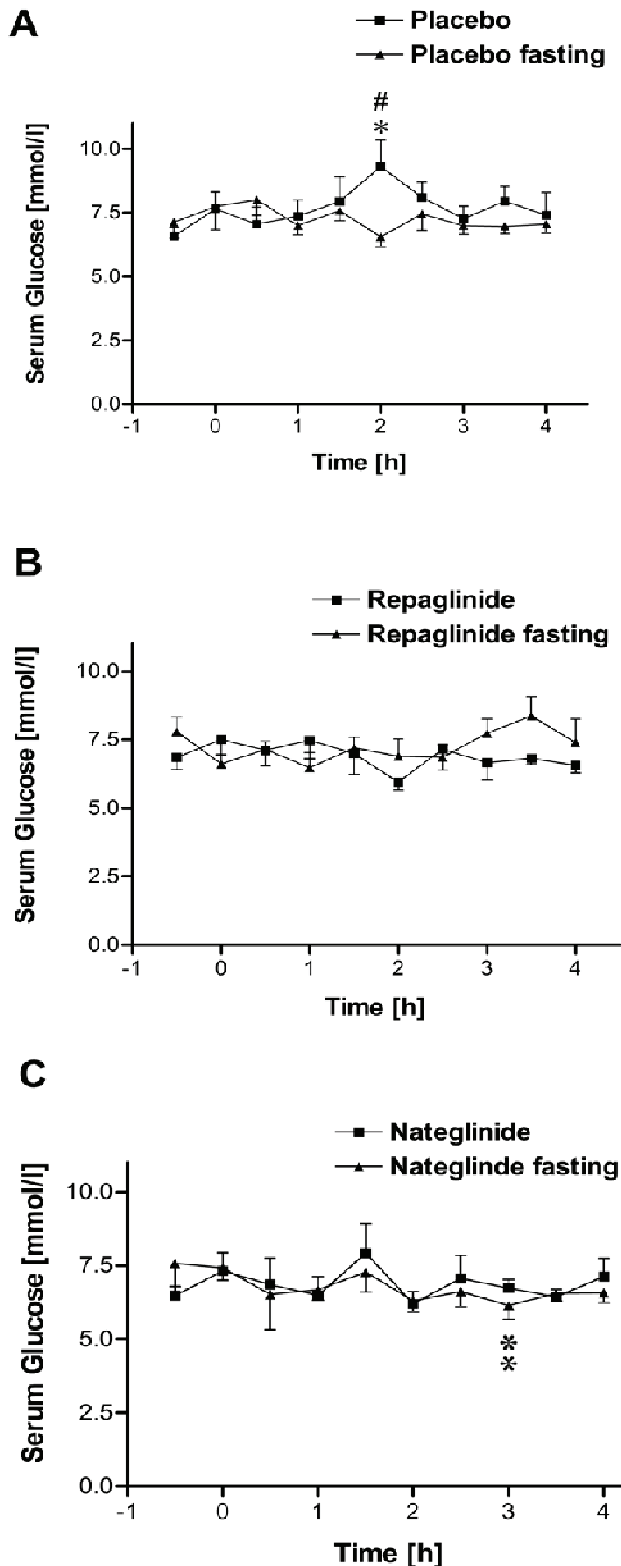
Figure 1. Mean serum glucose concentrations (± SEM) after treatments with a placebo (A), 2 mg repaglinide (B), and 120 mg nateglinide (C) in the fasting and non-fasting state. *indicates p < 0.05; **indicates p < 0.01 compared to baseline values; #indicates p < 0.05 compared to the corresponding time point of the fasting protocol; paired Student's t test.

(p < 0.05; paired Student's t test; Figure 2C). AUC_{BL-4h} was not significantly different between the fasting and non-fasting states (Figure 2D).

On the other hand, placebo, did not induce a significant increase in serum insulin level compared to baseline levels. However, there was a significant difference between serum insulin levels in the fasting and non-fasting state at 0.5 and 2 h following placebo administration (p < 0.05; paired Student's t test; Figure 2E). This resulted in a significant difference in AUC_{BL-4h} (p =0.033; paired Student's t test; Figure 2F).

DISCUSSION

Drug-induced hypoglycaemia is an important consideration when treating diabetes especially in the elderly. This magnifies the importance of nutritional assessment as a part of comprehensive geriatric assessment, as well as considering comorbidities that may influence the pharmacokinetics of the medications used. Medications with lower hypoglycemic risk, particularly when adherence to dietary plans is questionable, may represent a safe option.

Earlier studies suggested a glucose-dependent insulinotropic effect for both repaglinide and nateginide, as mentioned earlier. However, the first adverse effect reported in prescribing information of both drugs is hypoglycemia (Prandin®; Starlix® prescribing information). Further, a systematic review showed that repaglinide and second-generation sulfonylureas conferred similar risks for hypoglycemia (Bolen et al., 2007). Similarly, the overall rate of hypoglycemic events was similar with nateglinide and gliclazide combinations with metformin in a one year-double-blind, double-dummy, multicentre study (Ristic et al., 2007).

The present study was conducted on patients who did not use either drug before, and are therefore at increased risk of hypoglycemia according to data from prescription-event monitoring cohort study that showed a higher incidence of hypoglycemia at the beginning of treatment with nateglinide or repaglinide (Vlckova et al., 2009). However, this adverse effect was not reported during the present study in the non fasting state. In the fasting state though serum glucose level was significantly lower than baseline levels, three hours following nateglinide administration, it did not decrease beyond the hypoglycemic threshold set for this study (3.33 mmol/L). This decrease in serum glucose level was not seen with repaglinide in fasting patients.

The difference in frequency of hypoglycemic events between repaglinide and nateglinide is not consistent in literature. In a multicenter-16 week trial conducted in the US, repaglinide monotherapy induced minor hypoglycemic episodes (blood glucose < 2.78 mmol/L) in 7% of subjects enrolled compared to none of nateglinide treated patients (Rosenstock et al., 2004). In this study, both drugs were initiated at the starting dose and stepwise

Serum Insulin Concentrations

Area under the serum insulin time concentration curve
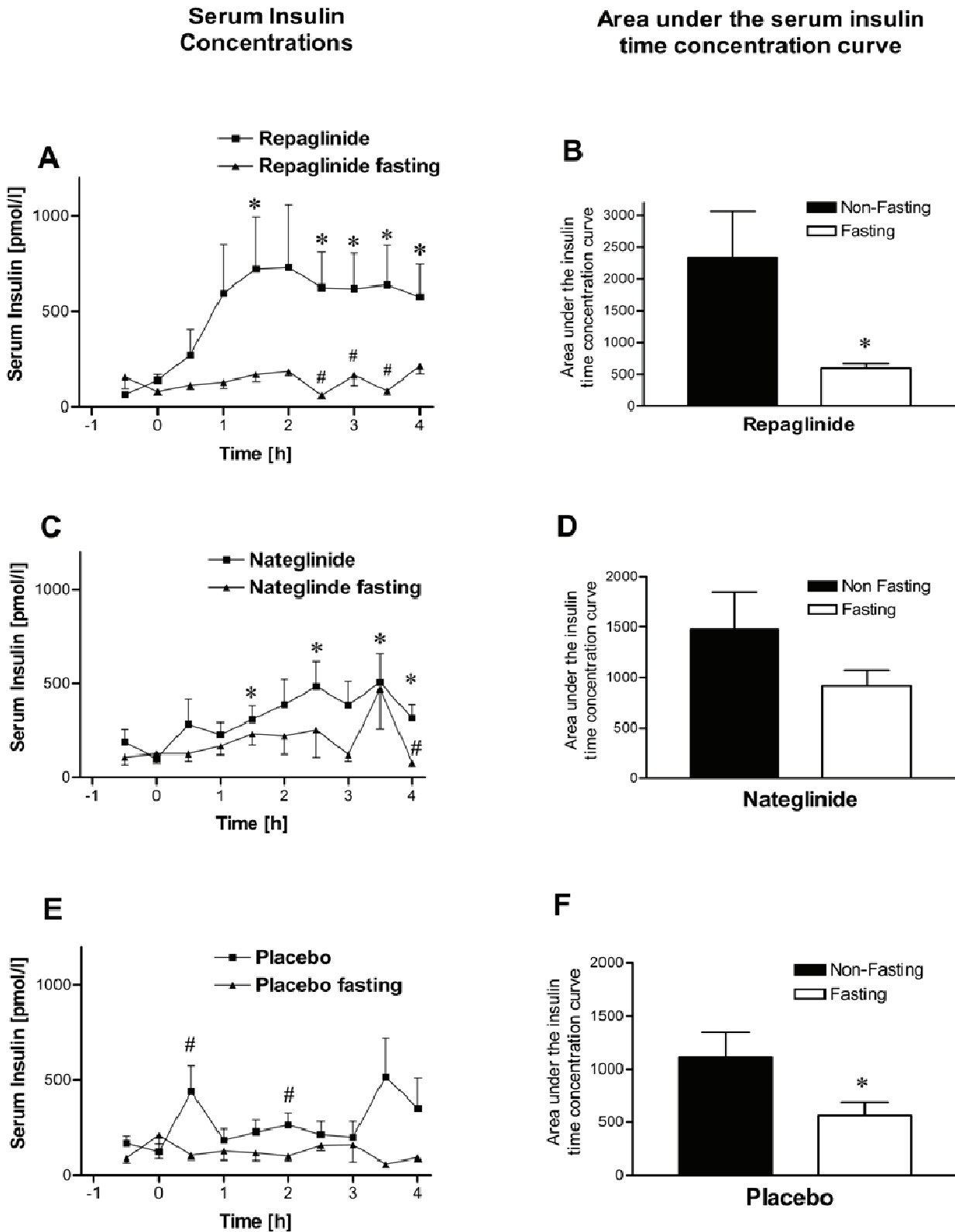
Figure 2. Mean serum insulin concentrations (± SEM) and the area under the time insulin concentration curve (AUCBL-4h) after treatments with 2 mg repaglinide (A&B), 120 mg nateglinide (C&D) and placebo (E&F) in the fasting and non-fasting state.

For serum insulin concentrations, *indicates p < 0.05; compared to baseline values; # indicates p < 0.05 compared to the corresponding time point of the fasting protocol. For area under the time insulin concentration curve, * indicates p < 0.05 compared to the non fasting state; paired Student's t test.

increased, if needed, to the maximum dose. On the other hand, in a pooled-analysis of four studies on Chinese patients, the rate of adverse reaction in nateglinide treated group for signs of hypoglycaemia was 2.11%, while that in repaglinide treated group was 1.05%. This was attributed to the use of a low dose of repaglinide (1 mg) and the maximum dose of nateglinide (120 mg) in one of the four studies (Li et al., 2009). The doses used in the present study were the maximum mealtime dose of nateglinide, and four times the starting dose of repaglinide. The maximum mealtime dose of repaglinide (4 mg) was not used because HbA1c of all patients was below 7.5%. Therefore using the 4 mg dose -8 times the starting dose- is not indicated. Further, repaglinide at the dose used, blunted the rise in serum glucose level, after breakfast, indicating that the dose used was adequate for the patients enrolled and no further increase in dose would have been required for these patients. Nateglinide, as well, blunted the rise in serum glucose level in the present study.

The modest rise in serum glucose level two hours postprandial in case of placebo administration may be due to the type of meal served, as both bran mixed bread and brown beans are low glycemic index foods. It has been shown that low glycemic index food induced a lower increment in the one hour posprandial plasma glucose levels (Wolever et al., 2008). Moreover, most of the enrolled patients were either newly diagnosed or controlled on metformin with HbA1c around 7%.

In the present study, both drugs showed a lower level of serum insulin level in the fasting state, though it was more pronounced and persistent in case of repaglinide. It is known that incretins, including glucagon like peptide (GLP-1) and glucose-dependent insulinotropic peptide (GIP), increase meal related insulin secretion. Nateglinide was shown to increase GLP-1 plasma level by inhibiting dipeptidyl peptidase IV (Duffy et al., 2007). Further, a recent study showed that nateglinide directly stimulates GLP-1 release by intestinal L cells *in vitro* as well as *in vivo* in the rat portal blood (Kitahara et al., 2011). Increasing insulin secretion through GLP-1 explains at least in part the mechanism, through which nateglinide does not release insulin as much in the fasting state. Repaglinide, on the other hand, did not affect plasma GLP-1 or GIP after oral glucose tolerance test in man (Stephens et al., 2011). Possible explanations for the glucose-dependent insulinotropic action of repaglinide are suggested to include altered counter regulatory hormone levels that are sufficient to inhibit insulin release in response to repaglinide in the fasting state (Aldhahi et al., 2004).

In light of the present results, the relatively low insulin levels after drug administration as compared to placebo, may be explained based on the composition of the meal served that resulted in a modest rise in plasma glucose level. In the present study, some of the enrolled patients had stable co-morbidities. None of these co-morbidities is

a contraindication for the use of repaglinide or nateglinide. Meglitinides can be used in liver dysfunction, with the exception of severe cases (Inzucchi et al., 2012). Renal excretion of both drugs is minimal and they are considered an appropriate choice in individuals with more severe degrees of renal impairment (Del Prato et al., 2003; Hasslacher, 2003). As for ischemic heart disease, repaglinide appear to be associated with a lower cardio-vascular risk than other insulin secretagogues (Schramm et al., 2011). Nateglinide was not among the insulin se-cretagogues studied. However several findings suggest a low cardiovascular risk with the use of nateglinide (Tentolouris et al., 2007).

Limitations

We used a generic formulation of nateglinide, since the reference listed drug (Starlix®) is not marketed in Egypt or Saudi Arabia at present. Therefore the authors decided to study the formulation available for clinical use for their patients. However, confirming the results concer-ning nateglinide in the fasting state using the reference formulation is warranted. Missing values is another limitation, however as mentioned above, they were substituted by EM method and were only 2.5% of the samples. The study was only performed in 8, almost treatment-naïve type II diabetic patients. However, as described earlier in the methods section, this rather small sample size was calculated based on the data provided by Rudovich et al. (2004). Enrolling more patients to our study would have not been approved by the ethical committee.

Conclusion

The present study suggests that in case of elderly who are at risk of missing meals, repaglinide may be a safe alternative to other anti-diabetics. Further studies are required, especially for nateglinide.

ACKNOWLEDGMENTS

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