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Oral repaglinide versus insulin injection in type II diabetes mellitus; a randomized clinical trial

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ABSTRACT

Introduction: Glycemic control at the level of normal condition is considered as a key point for preventing of complications like metabolic disturbances as well as renal pathologies in type II diabetes mellitus (DM).

Objectives: Presented study was designed to find suitable method for reducing hyperglycemic pathologies like normalizing of albuminuria, postprandial blood sugar (BS), HbA1c, fasting blood sugar (FBS) and C-peptide levels by administration of insulin injection versus oral repaglinide.

Patients and Methods: A total of 56 cases of type II DM were enrolled in this study and randomly divided into two groups of 28 subjects receiving regular insulin (control group) and repaglinide tablets (cases group) in accordance with inclusion and exclusion criteria. Glycemic profile and levels of albuminuria were measured and analyzed during 12 weeks.

Results: Changes in levels of FBS, 2 hours postprandial (2hpp) BS and HbA1c were not showed in both groups ($P=0.096$) but C-peptide levels were decreased in the repaglinide group ($P=0.001$). Hypoglycemia was observed in 21.4% of control group. Statistically significant reduction in HbA1c levels was not observed despite a greater impact of regular soluble insulin on postprandial glucose ($P=0.096$). Weight gain in insulin group was more ($P=0.042$) and hypoglycemic events were lower in repaglinide group. Additionally, reduction in microalbuminuria was not statistically significant ($P=0.73$) in both groups.

Conclusion: Based on our findings, repaglinide is suitable candidate for preventing undesirable side effects through regular soluble insulin using for type II DM treatment.

Implication for health policy/practice/research/medical education:
In a study on 56 patients with type II DM who divided into case and control groups, and received repaglinide tablets for 28 patients (case group) and injection of regular insulin for other 28 patients (control group), we found repaglinide decreased proportion of microalbuminuria and severity and frequency of hypoglycemia but in the manner of non-statistical significance differences.

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Introduction

Diabetes is the most common chronic metabolic disease and it is characterized by insulin resistance, impaired insulin secretion and increase in hepatic glucose production. The main therapy is handled by oral hypoglycemic drugs. Insulin is usually used for people who are unable to tolerate oral medication and/or blood sugar (BS) and target HbA_{1c} levels are not desirable despite therapy (1,2). Studies have shown that postprandial hyperglycemia is a risk factor for macro-vascular damages. Poor control of postprandial hyperglycemia exacerbates insulin resistance and provides disability to insulin secretion later. Repaglinide is a meglitinide derivative and acts through ATP-dependent K^+ channel inhibition in pancreatic ß cell membrane. It is easily absorbed if it is pre meal consumed and following insulin secretion will be happened after 1

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hour. Repaglinide pharmacokinetic profile is partly similar in the young and elderly. Furthermore, regular insulin is often administered for BS adjustment after routine NPH insulin therapy and its following hypoglycemic state is one of the usual boring conditions for diabetic patients (3,4).

Objectives

In accordance with mentioned facts, this study was planned to evaluate repaglinide use in contrast of regular insulin for BS adjustment through routine NPH insulin therapy. On the other hand, presented study was designed to assess oral repaglinide effects/side effects (versus regular/soluble insulin injection) on urinary albumin excretion, HbA_{1c}, fasting blood sugar (FBS) and C-peptide levels as a marker of pancreatic beta cell function.

Patients and Methods

Study population

A total of 56 patients were included to the trial and randomly putted into repaglinide (28 cases) and regular insulin injection (28 cases) groups using blocked randomization method. Allocation concealment was performed using sequentially numbered containers method and blinding was done as open-label trial for masking. This study was launched on patients with type 2 diabetes who were treating using the maximum therapeutic dose of oral hypoglycemic drugs (The minimum dose of glibenclamide was 10 mg daily and in the case of metformin, it was 1.5 g/d). Enrolled patients had inappropriate control of BS (HbA_{1c} levels higher than 7.5% and postprandial BS greater than 180 mg/dL) as well as body mass indices (BMIs) higher than 25 kg/m^2 and therefore were considered to start insulin therapy. Cases with the history of coma, repeated episodes of hypoglycemia, severe hypoglycemia, liver, kidney and heart problems as well as patients receiving the drugs with effects on hepatic cytochrome P450 enzymes such as rifampin, carbamazepine, erythromycin, nifedipine, warfarin and glucocorticoids were excluded. All included patients were hospitalized for starting insulin therapy. Anthropometric indices as well as questionnaires about the basic data of patients in terms of age, gender, weight, height, waist circumference, BMI, amount of energy intake, duration of diabetes and blood levels of glucose, HbA_{1c}, albumin excretion rate and c-peptide at the starting and termination time of study were obtained. Also, physical activity and calorie intake questionnaires were provided for cases and all patients were instructed for adjusted diets by dietitian. Age, gender and BMI matching were also performed on participants into cases and control groups. Standardized glucometer based sampling for FBS**,** BS 2hpp and BS 4PM (post meridiem) as well as albumin excretion rate determination were performed before the oral medication changing to insulin injection as well. Albumin excretion rate determination was repeated every day and the value of 30 mg/d was considered normoalbuminuria level. On the other hand, all participants who had albumin excretion rate higher than 30 mg/d were entitled microalbuminuria condition. The cases higher than 300 mg/d albumin excretion (macro-albuminuria) considering as exclusion criteria were not observed in our study. Increasing of the drugs doses in the both groups were performed to therapy optimization. All patients were discharged from the hospital after repaglinide and insulin doses adjusting. Patients have been advised to keep their self-monitoring of blood glucose (SMBG) and report any hypoglycemia. NPH dose adjustment was performed due to SMBG, FBS and BS 4PM levels during the 12-week treatment period. Mentioned tests were repeated again and the results were compared with the initial results of the tests as well as SMBG changes after 12 weeks of treatment.

Ethical issues

1) The research followed the tenets of the Declaration of Helsinki and its later amendments. 2) Informed consent was obtained; and 3) permission of the ethical review committee of Zanjan University of Medical Sciences was obtained prior to execution of the study (#A-11312-11). The main part of this study was registered in the Iranian Registry of Clinical Trials website (identifier: IRCT201109177568N1, http://www.irct.ir/).

Statistical analysis

Paired *t* test was used for data matching between pre-treatment and post-treatment conditions. Independent *t* test was also performed for determining of mean variations into each group. Chi- square test was applied for qualitative values and regression analysis was also used for determination of linear correlation among HbA_{1c} variation and other variables.

Results

A part of 82.1% of control group and 85.7% of case group were female without any statistical significant differences between both groups in the case of gender parameter ($P = 0.50$). Other criteria among groups did not show statistical significant differences as well (Table 1).

As it is shown in Table 2, changes in mean and standard deviation of the interested variables between the two groups were shown statistical significant differences between groups except of HbA_{1c} levels ($P=0.702$).

The changes in the cases of weight and waist circumference were not statistically significant into the groups at the end of study, while changes in the amount of energy intake, FBS, BS 2hpp, HbA_{1c} and C-peptide levels showed a statistically significant difference within groups. In the case of variations between groups, no statistically significant differences were observed among patients in terms of BMI, waist circumference, energy intake, HbA_{1c} and FBS at the end of study. Whereas statistically significant differences of weight ($P=0.04$), C-peptide ($P=0.001$) and 2 hpp BS ($P=0.004$) among patients receiving insulin (control group) in comparison with the repaglinide users (case group) was observed at the end of trial (Table 3).

Table 1. Baseline demographic and metabolic values of the patients

	Cases group (Mean ± SE)	Control group (Mean ± SE)	*P**
Ages (y)	55.18±6.45	53.46±5.21	0.55
Weight (kg)	69.71±8.17	68.64±8.91	0.52
Height (cm)	162.61±1.93	162.86±2.01	0.88
BMI (kg/m^2)	26.67±3.21	26.22±2.99	0.41
Waist circumference (cm)	81.43±4.97	81.39±4.01	0.96
Energy Intake (kcal/d)	3235.71±180.12	3144.64±167.34	0.58
FBS (mg/dL)	191.25±7.18	185.39±6.45	0.66
BS2hpp (mg/dL)	305±25.55	295.3±30.11	0.54
HbA_{1c} (%)	9.7±1.01	9.73±1.21	0.92
C-peptide (ng/mL)	2.92±0.64	2.93±0.44	0.96
Albumin excretion rate (mg/d) #	69[34, 72]	72[37, 81]	0.73

**P* lower than 0.05 was considered as statistically significant.
Variables expressed as median IQR (interquartile range).

Table 2. The mean and standard deviation of the metabolic values between the trial groups.

Variables	Groups	Mean	SD	*P
FBS (mg/dL)	Cases group	141.43	34.39	0.043
	Control group	123.68	55.66	
BS2hpp (mg/dL)	Cases group	246.64	47.47	0.003
	Control group	225.32	44.91	
HbA1c (%)	Cases group	8.4	1.37	0.702
	Control group	8.12	1.2	
C-peptide (ng/mL)	Cases group	3.68	2.1	0.008
	Control group	2.76	1.97	

Table 3. Comparison of changes in variables between the trial groups at the end of study

Variables (Changes through study duration)	CI 95%		*P
	Upper	Lower	
Weight (kg)	2.800	2.056	0.042
BMI (kg/m^2)	1.414	-0.854	0.121
Waist circumference (cm)	4.840	-1.595	0.308
Energy Intake (kcal/d)	248.592	-345.020	0.746
FBS (mg/dL)	6.024	-29.810	0.189
BS2hpp (mg/dL)	51.454	10.402	0.004
HbA1c (%)	0.057	-0.678	0.096
C-peptide (ng/mL)	-0.496	-1.346	0.0001

**P* lower than 0.05 was considered as statistically significant.

A part of patients (21.4%) in control group experienced hypoglycemia during the study, while none of the patients in the case group experienced hypoglycemia. This difference was statistically significant ($P=0.04$).

Discussion

The impact of administration of repaglinide on FBS levels (not in the case of HbA_{1c} value) was also shown in other studies as same as our findings and the number of episodes of hypoglycemia were also diminished in accordance with our study (5,6). Other studies showed statistically significant decrease in 2hpp BS at the both groups; however, in patients with regular insulin therapy reduction was greater in comparison with repaglinide treated group. It was shown that repaglinide adjuvant therapy provided the same effect in comparison with glibenclamide (7,8). The impact of repaglinide on reduction of 2 hpp BS as well as HbA_{1c} levels was shown in other clinical trials handling by metformin, which the results were similar to the study of Civera et al (9). However, a few studies (with lower number of cases in comparison with our study) showed contrast effects of repaglinide on BS 2hpp as well as weight gaining (each group in Furlong et al study was adjusted for statistical analysis based on cases energy intakes) (10). However, despite the relatively small impact of repaglinide on 2hpp BS in comparison with regular insulin this fact was significant in general. In contrast to our findings, Duran et al showed statistically significant decrease in HbA_{1c} levels due to administration of repaglinide against acarbose concomitant consumption with glargine insulin (11). In contrast of our study, episodes of hypoglycemia were not reduced in Davies et al trial which was handled by insulin use through repaglinide and metformin administration (12). Totally, albumin excretion rates were slightly diminished and changes were dependent on the administration route of drugs. On the other hand, the amount of albumin excretion reduced during repaglinide administration in comparison to insulin administration, however the effect was not statistically significant ($P=0.50$). This finding is not consistent with the study of Berwort et al (13).

Conclusion

The results of this study showed no significant decrease in the amount of urinary albumin excretion and FBS after administration of repaglinide in comparison to regular insulin. The regular insulin showed better effect on 2hpp BS levels (beside of its more hypoglycemic outcomes) despite significant decrease in 2hpp BS levels through repaglinide using. The values of HbA1c and microalbuminuria were slightly diminished and showed no statistically significant changes. Therefore, repaglinide is a good alternative of regular insulin for 2 pp BS control in diabetic patients. Regular insulin contains multiple side effects like the weight gaining and hypoglycemic episodes

as well.

Study limitations

It is recommended to conduct further studies with larger sample size to compare the efficacy and side effects of other drugs affecting blood sugar.

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Authors' contribution

HC and MHM participated in all experiments, coordinated the data-analysis and contributed to the writing of the manuscript. AP and ZA coordinated the acquisition of data. MAK and HC designed the research plan and organized the study. SM performed analysis and interpretation of data. MAK prepared the final manuscript.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflict of interests

The authors declare no conflict of interests.

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