

Comparative effectiveness of antidiabetic drugs glibenclamide versus glibenclamide plus metformin on serum glucose concentration and serum c-peptide concentration in Iraqi diabetic type 2 patients

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مقارنة تأثيرات الأدوية الخافضة للسكر، الكليبنكلاميد ضد الكليبنكلاميد مع الميتفورمين
على مستوى السكر ومستوى السي - ببتايد في مصل الدم لدى العراقيين من مرضى
السكري النوع الثاني

الخلاصة

يتميز مرض السكري النوع الثاني بزيادة مستوى السكر في مصل الدم وهذا ناتج من خلل في وظيفة خلايا بيتا البنكرياسية في إفراز كمية كافية من الأنسولين والذي بدوره يحافظ على مستوى السكر في مصل الدم، أما السي ببتايد وهو من ٣١ حامض أميني فإنه يلعب دور في تصنيع الأنسولين وألان يستخدم كمقياس موثوق لإفراز الأنسولين لدى مرضى السكري النوع الثاني. لقد درسنا تأثيرات الأدوية الخافضة للسكر الكليبنكلاميد ضد الكليبنكلاميد مع الميتفورمين على مستوى السكر ومستوى السي ببتايد في مصل الدم بالمقارنة مع مجموعة الكنترول. ٨٤ مريض شارك في هذه الدراسة وقسموا إلى ٣ مجموعات، المجموعة الأولى تضم مرضى عولجوا بعقار الكليبنكلاميد، المجموعة الثانية تضم مرضى عولجوا بعقاري الكليبنكلاميد مع الميتفورمين، وبينما المجموعة الثالثة تضم أشخاص طبيعيين جعلوا كمجموعة كنترول. بعد ذلك قمنا بقياس مستوى السكر ومستوى السي ببتايد في مصل الدم لكل مريض ولكل المجاميع. ثم حللنا النتائج إحصائياً وتبين لنا إن هنالك فرق معنوي في زيادة مستوى السكر في مصل الدم في مجموعة الكليبنكلاميد ومجموعة الكليبنكلاميد مع الميتفورمين عند المقارنة مع مجموعة الكنترول، أيضاً هنالك فرق معنوي في نقصان مستوى السي ببتايد في مصل الدم في مجموعة الكليبنكلاميد ومجموعة الكليبنكلاميد مع الميتفورمين عند المقارنة مع مجموعة الكنترول. هذه النتائج تبين وبقوة إن هنالك فشل في تأثير الأدوية الخافضة للسكر المستخدمة من قبل المرضى العراقيين وأيضاً هنالك خلل واضح في خلايا بيتا البنكرياسية في جعل مستوى السكر في مصل الدم عند المستوى الطبيعي.

Abstract

Diabetes type2 is characterized by hyperglycemia, this hyperglycemia result from dysfunction of beta – cells to secret adequate insulin that maintain serum glucose concentration. C- peptide is an peptide with 31 amino acid this peptide play an important function in the synthesis of insulin, and now used as reliable indicator for insulin secretion in diabetes mellitus type 2. We studied the effects of antidiabetic drug glibenclamide versus glibenclamide plus metformin on serum glucose concentration and serum c- peptide concentration in comparison with control group. 84 patients enrolled in this study and divided into 3 groups, in the first group patients treated with glibenclamide. In the second group patients treated with glibenclamide plus metformin. While the third group normal patients represent as control group. Then we estimated the postprandial serum glucose concentration and serum c- peptide concentration for each patient in all groups. Data collected and statistically analyzed. We find that there is significant increase in serum glucose concentration in glibenclamide group and glibenclamide plus metformin when compared with control group; also there is

significant decrease in serum c- peptide concentration in glibenclamide group and glibenclamide plus metformin group when compared with control group. These results strongly indicate that, there is a failure in effects of antidiabetic drugs used by Iraqi patients and there is dysfunction of beta –cells of pancreas to normalized serum glucose concentration.

Introduction

According to the world health organization ,at least 171 millions people suffer from diabetes ,or 2.8%of the population , its incidence is increasing rapidly and it is estimated that by 2030 this number will almost double(1). Also the prevalence of diabetes increased sharply with age until 75 in both sexes, and the prevalence of type 2 mellitus is generally higher in developed countries it is increasing most rapidly in developing countries (2). Type 2 diabetes is characterized by hyperglycemia resulting from insulin resistance in the setting of inadequate beta- cell compensation (3). And the causes of type 2diabetes involve both genetic susceptibility and environmental factors, although the genetic component may be greater than in type 1(4). In type 2 diabetes delayed insulin secretion result in higher peak glucose concentration particularly when suppression of glucagon is impaired whereas insulin resistance prolong the duration of hyperglycemia (5).The diagnostic criteria for diabetes mellitus recommended by the world health organization in 2000 are either ;

Fast plasma glucose =or >126 mg /100ml or Postprandial plasma glucose =or >200 mg /ml (6).

Also many investigators have used c- peptide level as biomarker of beta –cell function (7). C- peptide is an active peptide with molecular weight 3600 containing 31 amino acid ,c- peptide has an essential function in the synthesis of insulin and c- peptide is the more reliable indicator of insulin secretion than insulin itself (8).And it became a most useful independent indicator of insulin biosynthesis (9). The antidiabetic drugs used are glibenclamide and metformin, the glibenclamide used in the treatment of type 2 diabetes, the drug works by inhibit ATP-sensitive K⁺ channel in pancreatic beta –cells this causes membrane depolarization which causes voltage dependent Ca⁺⁺ channel s to open which cause an increase in intra cellular Ca⁺⁺in the beta –cell which stimulate insulin release (10). While metformin exert its effect primarily by decreasing hepatic glucose out put and has a comparatively minor effect in increase insulin sensitivity (11).

1. Patients and methods

Patients:

84 patients were participated in this study of both sex and from different ages groups ,are selected randomly from diabetic center in Marjan hospital in Hilla city .these patients are classified in three groups ;

Group 1; included 28 patients with diabetes type 2, treated with glibenclamide antidiabetic drug only.

Group 2; included 31 patients with diabetes type 2, treated with glibenclamide plus metformin antidiabetic drugs.

Group 3; included 24 normal and healthy patients, consider as control group

Data about sex, age, type of drugs treated, and duration of disease are collected.

2. Biochemical analysis

Serum glucose concentration:

We estimated the postprandial serum glucose concentration according to the Trinder reaction (enzymatic colorimetric method), the glucose is oxidized to d-gluconate by the glucose oxidase with formation of hydrogen peroxide, in the presence of peroxidase a mixture of phenol and 4- aminoantipyrin is oxidized by hydrogen peroxide to form a red quinoneimine dye proportional to the concentration of glucose in the sample (12, 13).

Serum c- peptide concentration:

Also we estimated the serum c- peptide according to enzyme –linked immunosorbent assay (ELISA),based on the principle of competitive binding , endogenous c –peptide of a patient sample competes with a c- peptide –horseradish peroxidase conjugate for binding to the coated antibody ,after incubation the unbound conjugate is washed off ,the amount of bound peroxidase conjugate is inversely proportional to the concentration of c- peptide in the sample ,after addition of the substrate solution, the intensity of color developed is inversely proportional to the concentration of c- peptide in patient sample (14).

3. Statistical analysis:

The data was analyzed by method analysis of variance (ANOVA) by utilizing SPSS program, to determine the significance level of difference in serum glucose concentration and serum c- peptide concentration in all three groups.

Results

In comparison glibenclamide group and glibenclamide plus metformine group, the serum glucose concentration increase significantly than control group $p < 0.001$, table 1. While there is no significantly difference between glibenclamide group and glibenclamide plus metformin group according to serum glucose concentration $p > 0.05$, table 1.

While in comparison the glibenclamide group and glibenclamide plus metformin group the serum c-peptide concentration is significantly decrease than control group $p < 0.05$ (glibenclamide versus control) , and $p < 0.01$ (glibenclamide plus metformin versus control), table 2. While there is no significant differences between glibenclamide group and glibenclamide plus metformin group related to serum c-peptide $p > 0.05$, table 2.

Also in this study the distribution of patients according to age, showing that the most patients age between 40 years to 69 years old figure 1.

In figure 2 showing the distribution of patients according to sex, in this study the males more than females, also the figure 3 showing the duration of diabetes disease.

Table 1; serum glucose concentration (mg/100ml) in different groups, data expressed as mean $\pm$ SD

	Glibenclamide plus metformin group	Glibenclamide group	Control group
	244.16$\pm$91.06	217.22$\pm$88.46	96.68 $\pm$27.48
Control group	***	***	
Glibenclamide group	n.s		

Glibenclamide plus metformin group			
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*** p<0.001 significant

n.s = non significant

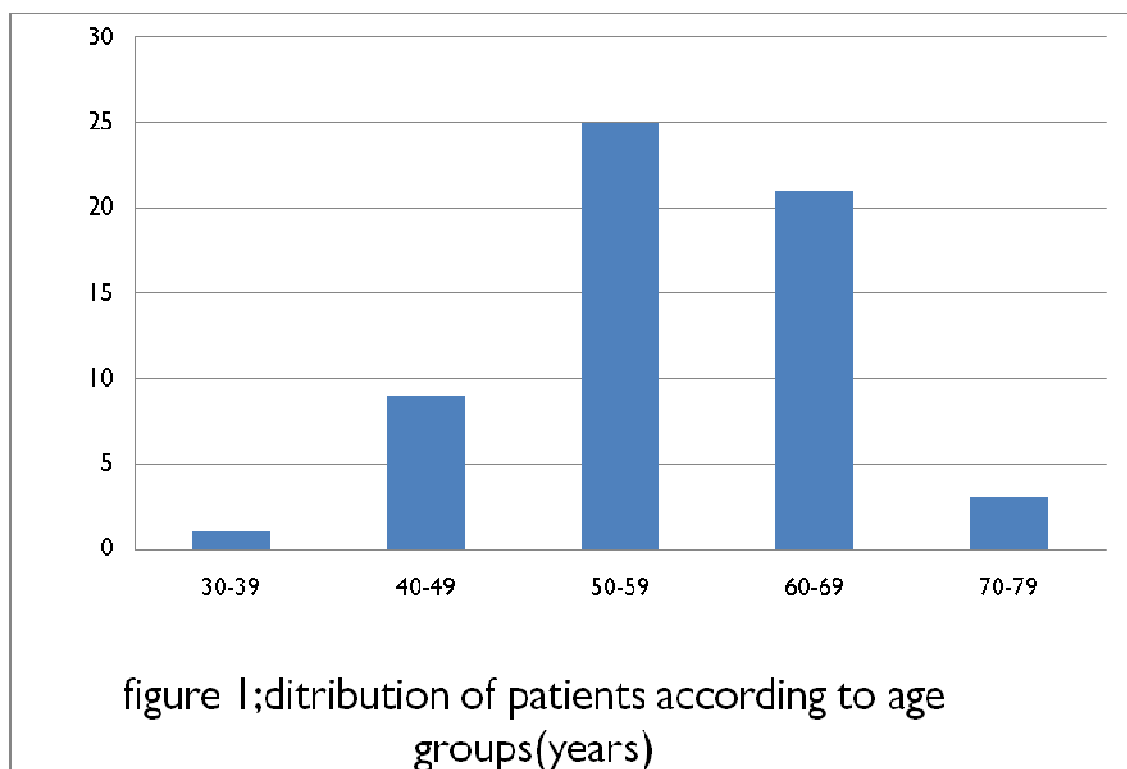
Table 2; serum c- peptide concentration (ng/ml) in different groups, data expressed as mean $\pm$ SD

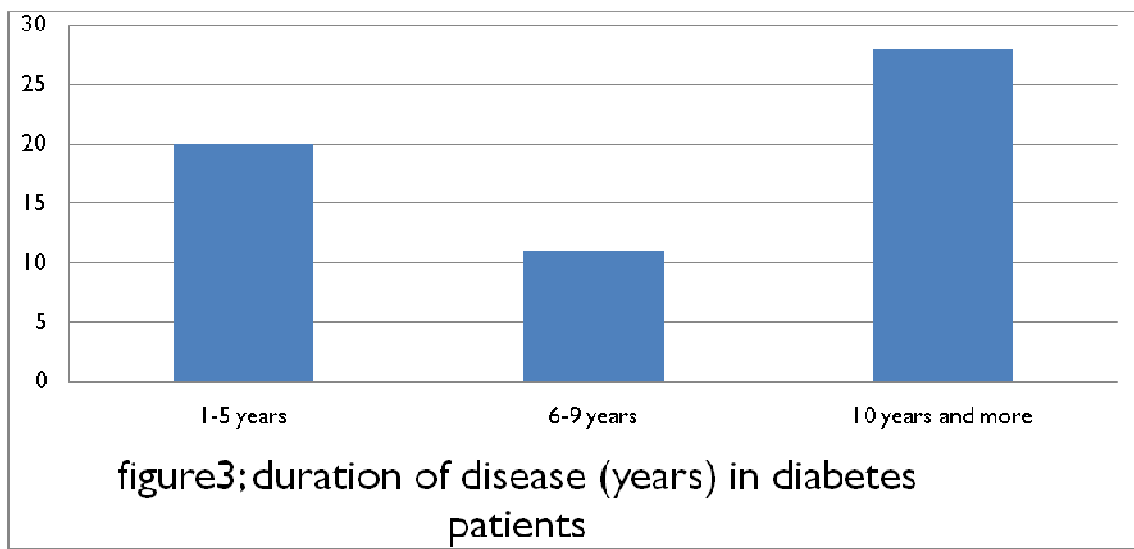
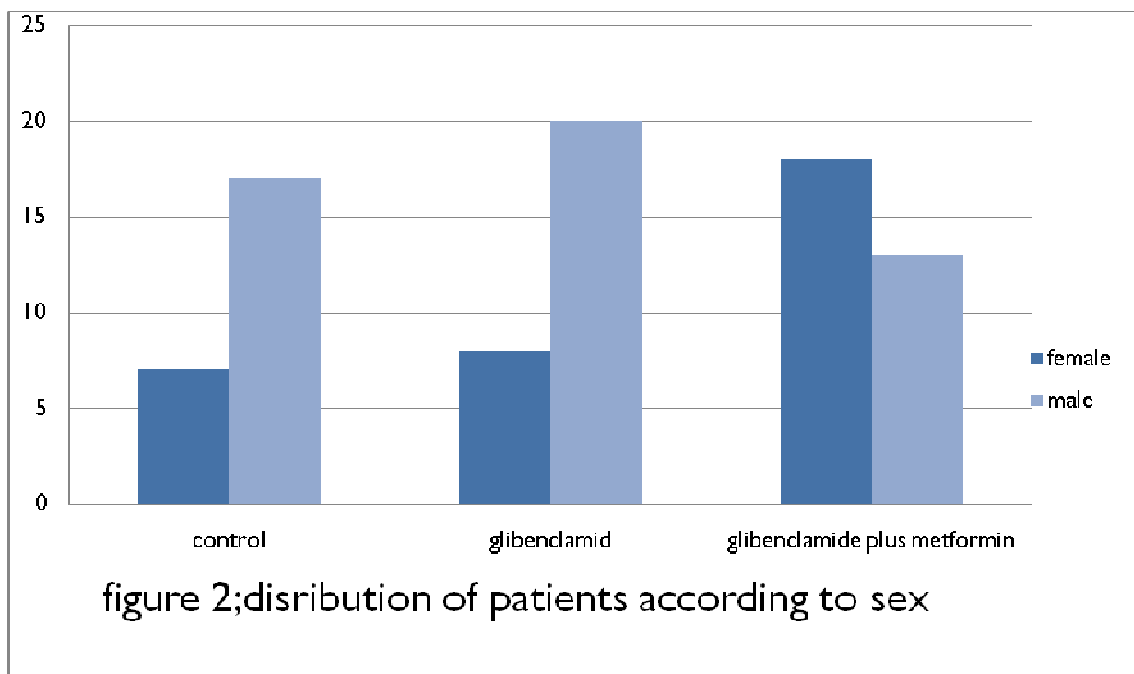
	Glibenclamide plus metformin group	Glibenclamide group	Control group
	2.96$\pm$1.94	3.24$\pm$1.91	4.61$\pm$2.55
Control group	**	*	
Glibenclamide group	n.s		
Glibenclamide plus metformin group			

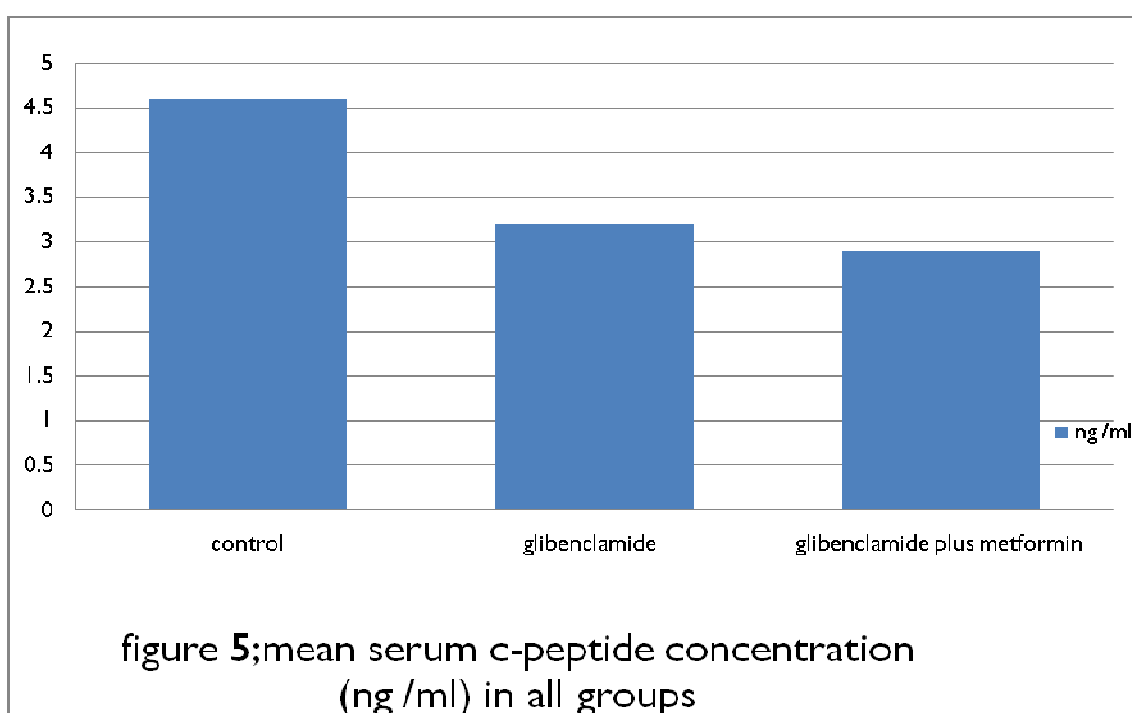
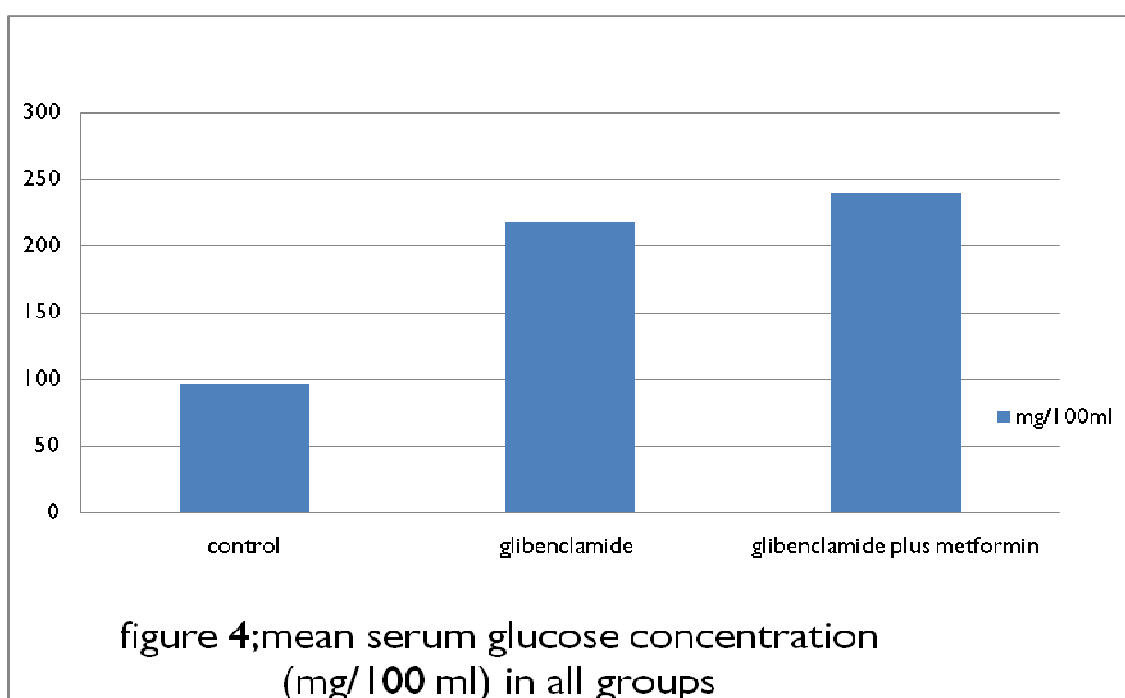
*p<0.05 significant

**p<0.01 significant

n.s = non significant







Discussion

the most patients duration of diabetes disease is 10 years and more and as a result the insulin secretion decrease with duration of diabetes as seen by decrease in the level of c- peptide and this indicate that beta –cells dysfunction increase with the duration of diabetes figure 5 , this finding is the same finding by Bilal Bin Abdullah et al(15).So it is not surprising that the postprandial serum glucose concentration level can increase to 200 mg /100ml and over in patients with type 2 diabetes figure 4 ,this result is same study reported by Craigw Spellman (16). This finding explain the failure of antidiabetic drugs to maintain serum glucose level and fail to increase serum c-peptide level ,in part due to beta – cells defect and increase beta –cells apoptosis in human with type 2 diabetes (17). Chag-ChenK J et al wrote that hyperglycemia and elevated free fatty acids negatively impact beta-cell function, This happens by numerous mechanisms, including the generation of reactive oxygen species, alterations in metabolic pathways, increases in intracellular calcium and the activation of endoplasmic reticulum stress, these processes adversely affect beta-cells by impairing insulin secretion, decreasing insulin gene expression and ultimately causing apoptosis (18). So the chronic hyperglycemia by itself has an adverse effect on beta –cells , Kathrin Maedler et al wrote that high serum glucose levels resulted in increase production and release of interleukin -1b and followed by release necrosis factor –kb ,this finally lead to glucotoxicity in human pancreatic islets (19). Also Marc Y.Donath et al strongly believe that beta cells destruction is an important etiological factor in the development and progression of type 2 diabetes (20).And finally the united kingdom prospective study showed that insulin deficiency was a progressive condition that did not seem to be affected by whether a patient received sulfonylurea or metformin (21). So that the physician should change antidiabetic treatment much sooner or use treatment are less likely to fail (22).

Conclusion

- 1-C-peptide is an indicator for insulin secretion in diabetic patients type 2
- 2-Failure the old antidiabetic drugs to maintain serum glucose concentration.
- 3-Shifting toward the new generation of antidiabetic drugs.

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