Int J Pharm Bio Sci 2015 Oct; 6(4): (P) 370 - 377

Research Article **Pharmacology**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

COMPARATIVE STUDY OF EFFICACY OF GLIBENCLAMIDE VERSUS METFORMIN IN NEWLY DIAGNOSED PATIENTS WITH TYPE 2 DIABETES MELLITUS

DR.RAMYA RACHAMANTI* AND DR.ZAHEDA BANO

Department of Pharmacology, Guntur Medical College/Government General Hospital, Guntur, Andhra Pradesh, India.

ABSTRACT

Diabetes mellitus is a spectrum of common metabolic disorders arising from various mechanisms all resulting in hyperglycemia. Oral anti diabetic drugs are most common type of treatment given in newly diagnosed cases. This cross sectional, single blinded study compared the efficacy of oral Glibenclamide 5 mg with oral Metformin 500mg in the treatment of 100 newly diagnosed cases in General Medicine department outpatient division of Government General Hospital, Guntur for 6 months. Patients were newly diagnosed as diabetes basing on their fasting blood glucose levels. Results of the study were analyzed statistically at the end of 6 months using paired student's 't' test. Fasting blood glucose levels were equally decreased by both the drugs where as Glycated hemoglobin levels were reduced more by Glibenclamide when compared to Metformin. It was concluded that Glibenclamide is more efficacious and cost effective drug when compared to Metformin.

KEYWORDS: Diabetes mellitus, Efficacy, Glibenclamide, Metformin, Fasting Blood Glucose.

DR.RAMYA RACHAMANTI
Department of Pharmacology, Guntur Medical College/Government General Hospital, Guntur, Andhra Pradesh, India

INTRODUCTION

Diabetes mellitus is a common metabolic disorder which causes hyperglycemia. There are three main types of diabetes of which Type 2 diabetes mellitus or non insulin-dependent diabetes mellitus is caused by insulin resistance and beta cell dysfunction. This constitutes about 90% of total diabetic cases. Causative factors include increasing age, hypertension ,elevated cholesterol, sedentary life style, high calorie diet, stress, lack of sleep and genetic factors. The mechanism involved is decreased insulin secretion from beta cells which lead to increased insulin resistance, inappropriate release of glucose from liver into blood[1], increased breakdown of lipids within cells, resistance to incretin, increased retention of salt and water by the kidneys. The main symptoms of diabetes are polyuria, polydipsia, polyphagia. Other symptoms include weight loss, blurred vision, itchiness, peripheral neuropathy, recurrent vaginal infections and fatigue. It was stated that 347[2] million people suffered from diabetes in 2013 worldwide and this number is expected to rise to 366 million[3] by 2030. World Health Organization stated diabetes as 7th most common cause of death in 2013.Nearly 1 million Indians die due to diabetes every year. In India, it affects more than 62 million people, which is 7.1% of India's adult population indicating that it is a very common condition in India and oral anti diabetic drugs are most common type of treatment given in newly diagnosed cases. Though many new treatment options are emerging now days, the cost effective and 1st line of treatment includes the usage of Glibenclamide and Metformin. The present study was done to compare the efficacy of oral 5mg Glibenclamide and oral 500mg Metformin in 100 newly diagnosed type 2 diabetes mellitus patients and also to identify the cost effective drug with less adverse effects. Study was done in General Medicine department, outpatient division of a tertiary care hospital (Government General Hospital), Guntur. Necessary facilities were available there for checking fasting blood glucose, body weight and blood pressure. The similar study which compared the efficacy of two oral anti diabetic drugs was done by Bianca Hemmingsen[4,] Jeppe B. Schroll et al., ''Sulfonylurea versus Metformin monotherapy in patients with type 2 diabetes: a Cochrane systematic review and meta-analysis of randomized clinical trials and trial sequential analysis'' This study and the present study proved that Sulphonylurea drug Glibenclamide is better in efficacy than Biguanide drug Metformin.

MATERIALS AND METHODS

This was a prospective, randomized, single blinded, interventional study conducted in Out Patient division, General Medicine department of Government General Hospital, Guntur done for 6 months. The sample size was 100 patients meeting the criteria of the study. Inclusion Criteria: patients aged 41-60 Years, Both Male and Females with Fasting Blood glucose levels up to 250 mg/dl, Patients with Blood Pressure up to 140/90., Exclusion criteria: Pregnant and lactating women, patients with Type 1 diabetes mellitus, Diabetic Keto-acidosis, Patients with history of acquired immunodeficiency syndrome, cardiac, respiratory, renal impairment. Institutional ethical committee approval was taken before starting the study. Each Patient was explained the whole procedure, advantages, probable adverse effects of drugs included in the study. After he/she accepted, an informed consent form was given in a local understandable language (Telugu) and the person was asked to sign it or put a thumb impression. The patient was educated about the possible adverse effects and asked to discontinue the drug immediately if there was any allergic reaction to the drug. 100 patients who were newly diagnosed based on fasting blood glucose levels with type 2 diabetes were taken into study. These 100 patients were divided into two groups 'A' and 'B' by randomization, each group containing 50 patients. The study was a single blinded study. The patient did not know the drug prescribed to him/her. The identity of drugs was concealed by pasting a non transparent white paper on the back of tablet strips to conceal the name of drug. Researcher knew the drug given. Group

'A' patients were given Glibenclamide 5 mg and Group 'B' Patients were given Metformin 500 mg. All the patients were informed to take the given drugs daily once just before breakfast. Patients were instructed to avoid alcohol, to avoid skipping of meals and to avoid severe or prolonged exercise as it may increase the risk of hypoglycemia. Each patient was asked to come to hospital every 2 weeks till 6 months for check up, to report adverse effects if any and to get the free supply of drugs. All patients were followed up for 1 month after the study to monitor the adverse effects.

Parameters taken in the study were:

1) Fasting blood glucose levels
2) HbA_{1c} levels (Glycated Hemoglobin)
3) Body weight
4) Systolic and Diastolic Blood Pressure and 5) B.M.I (Basal Metabolic Index)

RESULTS

Results of the study were analyzed statistically at the end of 6 months using paired student 't' test and the significance of results was tested by taking probability value at 0.05.

Table 1
Age distribution analysis in each group

Age (years)	Glibenclamide Group No. of patients	Metformin Group No. of patients
41-45	9	13
46-50	14	11
51-55	12	14
56-60	15	12
TOTAL	50	50

The numbers of patients were more in 56-60 years of age group indicating that incidence of diabetes increases with age.

Table 2
Sex distribution analysis in each group

Sex	Glibenclamide Group	Metformin Group	Total
Males	28(56%)	26(52%)	54(54%)
Females	22(44%)	24(48%)	46(46%)

Males were more in Glibenclamide group and females were more in Metformin group

Table 3
Patients with Pre Hypertension in Each Group

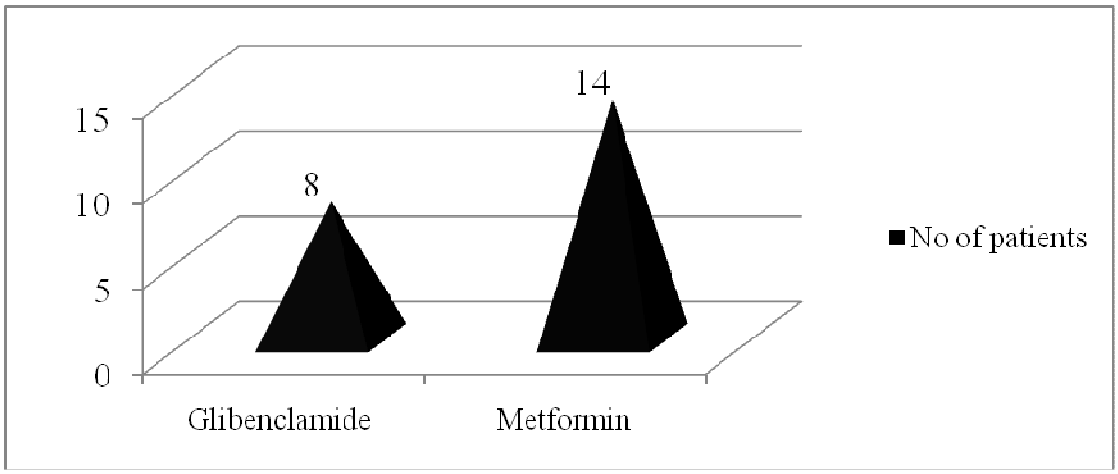
Glibenclamide Group	18/50(36%)
Metformin Group	24/50(48%)
Total	42/100(42%)

Table 4
Patients with Family History of Diabetes in Each Group

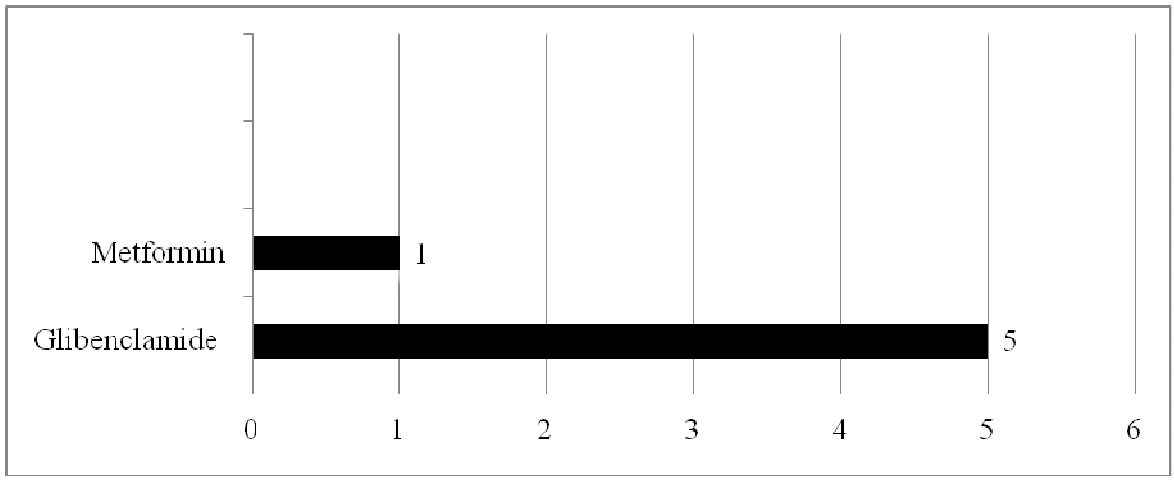
Glibenclamide Group	18/50(36%)
Metformin Group	16/50(32%)
Total	34/100(34%)

This indicates that diabetes is commonly associated with pre hypertension and family history

Graph 1
No. of Patients with BMI ≥ 30 in each group



Graph 2
No. of Hypoglycemia cases in each group



Graph 3
No of patients suffered with gastrointestinal symptoms in both groups

Graph 4
Total No. of patients showing adverse effects in both groups

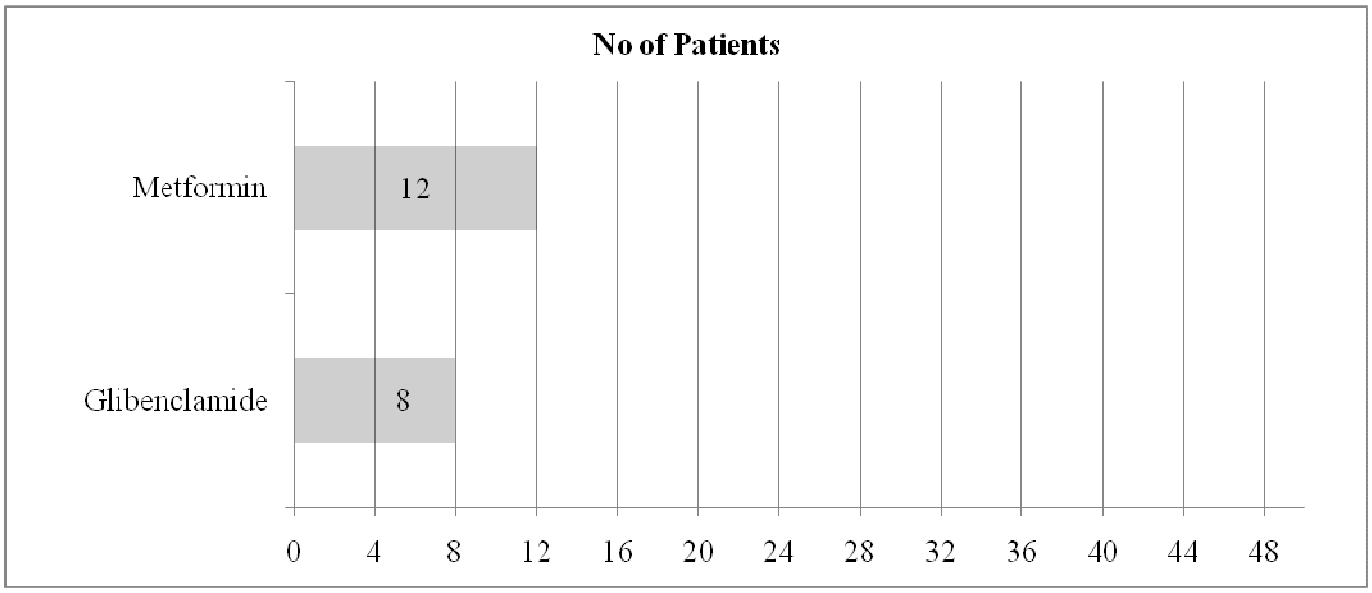


Table 5
All parameters comparison in each group at the end of six months

Parameters	Group- A/ Glibenclamide Group			Group- B/ Metformin Group		
	Initial value	After 6 months	% Change	Initial value	After 6 months	% Change
Mean Fasting Blood Glucose(mg/dl)	180.36 mg/dl ± 24.51	138.8 ± 19.58 mg /dl	23.3%	179.04 ± 22.52	139.96 ± 20.70	21.7 %
Mean HbA_{1C} (%)	7.90 % ± 0.89	6.5 % ± 0.75	16.5%	7.8 % ± 0.75	6.9 ± 0.71	11.5%
Mean Body weight (kg)	69.24 ± 7.11	70.94 ± 7.5	2.45%	69.92 ± 8.04	67.36 ± 7.44	3.66%
Mean BMI(kg/m^2)	27.84 ± 2.95	28.29 kg/m^2 ± 3.0	1.61%	28.66 Kg/m^2 ± 3.31	27.6 kg/m^2 ± 3.14	3.4%
Mean Systolic B.P Mm of Hg	120.2 ± 8.4	123.4 ± 10.4	2.5%	124 Mm ± 7.8	121.8 ± 9.1	1.7%
Mean Diastolic B.P Mm of Hg	78.4 ± 10.4	79.6 ± 8.0	1.8%	77.6 ± 10.21	75.8 ± 8.5	2%

DISCUSSION

In this study Metformin and Glibenclamide were chosen because Glibenclamide and Metformin are cost effective drugs and they are most commonly prescribed in a tertiary care hospital like Government General Hospital, Guntur. Also they are easily available in Generic shop of this hospital at all the times. The diagnosis was done based on the definition of World Health Organization[5] raised values on two occasions of either

1. Fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or

2. With a glucose tolerance test, two hours after the oral dose a plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

In this study diagnosis was made based on fasting blood glucose levels because it was more convenient to the patients when compared to oral glucose tolerance test. In diabetes mellitus, higher amounts of glycated hemoglobin (HbA_{1C}) indicates poor control of blood glucose levels which may lead to cardiovascular disease, nephropathy and retinopathy. So, monitoring of HbA_{1c} in type 2 diabetic patients improves the patient's outcomes by preventing the complications. American Diabetes Association recommends HbA_{1c} to be below

53 mmol/mol (7.0%) for diabetic patients The results in the present study proved that both Glibenclamide and Metformin reduced Fasting blood glucose levels very significantly during 6 months period in 100 subjects ($p<0.001$). Both were found to be equally effective. These results were consistent with the study of Hermann LS, Bitzen PO, Kjellstrom T [6] ''Comparative efficacy of Metformin and Glibenclamide in patients with non-insulin dependent diabetes mellitus.'' In the present study Glibenclamide decreased glycated hemoglobin levels significantly in 6 months period. The decrease in HbA1c levels was 1.3% in 6 months. These results were consistent with the study of Kenneth L. Cohen, M.d, And Susanne Harris[7], ''Efficacy of Glyburide in Diabetics poorly Controlled on First-Generation Oral Hypoglycaemic'' Their results concluded that 2nd generation Sulphonylurea drug Glibenclamide effectively reduced Glycated haemoglobin levels significantly ($p<0.05$) by 1.4 % in 3 months. In the present study Glibenclamide reduced Glycated hemoglobin levels 0.4% more than Metformin in 6 months. These results were consistent with the study of Leif S.Harmann Bengt Schersten, Arne Melander [8.] ''Therapeutic Comparison of Metformin and Sulfonylurea alone and in Various Combinations.'' Their results showed that Metformin alone reduced Glycated hemoglobin levels by 0.9% from baseline and Glibenclamide reduced the levels by 1.3% from baseline the difference being 0.4%. In the present study, Glibenclamide showed increase in body weight after treatment while Metformin showed decrease in body weight. Weight gain with Glibenclamide was explained by Haffner SM, Hanefeld M [9] ''Glibenclamide, but not acarbose, increases leptin concentrations parallel to changes in insulin in subjects with NIDDM'' This study concluded that Glibenclamide increases circadian leptin which explains weight gain in subjects with Type 2 diabetes mellitus patients. In the present study, in Metformin group, the mean decrease in body weight after treatment was 2.6 kg in 6 months among 50 patients. These results were similar to the study conducted by Michael Stumvoll, Nurjhan[10]et al. ''Metabolic Effects of Metformin in Non-Insulin-Dependent Diabetes Mellitus''. Their study concluded that patients lost around 2.7 kg weight with Metformin therapy in type 2 diabetes. Systolic BP was increased by 3 Mm of Hg in Glibenclamide group although no significant increase in Diastolic BP was seen in the present study. In Metformin Group, both systolic and diastolic blood pressures were not changed significantly after treatment which was consistent with the study conducted by Sundaresan P, Lykos D, Daher A[11] In the present study, hypoglycemia was seen in 5 patients of Glibenclamide group and in 1 patient of Metformin group indicating that the incidence of hypoglycemia was more with Glibenclamide when compared to Metformin. The reason was explained by Azim S. Gangji, MD, Catherine M. Clase[12] that Glibenclamide has a relatively long terminal half-life in chronic dosing compared with other Sulphonylureas, owing to its high affinity for the beta-cell sulfonylurea receptor and the accumulation of active metabolites that are excreted through the kidney. In the present study 9 (18%) patients reported diarrhea with Metformin. These results were consistent with the study of Paresh DandonaAnne[13] et al .''Diarrhea and Metformin in Diabetic Clinic'' In their study it was concluded that the prevalence of diarrhea in patients treated with Metformin was around 20%. The present study compared the efficacy between Glibenclamide and Metformin, identified Glibenclamide as the drug with less adverse effects and more patient compliance and cost effective drug and the results proved that: Glibenclamide has got more efficacy when compared to Metformin. It provided long term Glycemic control better than Metformin

Limitations of the study

1. In this study the sample size was 100 indicating that the study sample was small. Interpretation of results for small studies was less reliable when compared to larger studies.
2. Fasting blood glucose levels were used to diagnose and for monitoring of blood glucose levels in this study. Patient has to come on fasting to the hospital to check the blood glucose levels.

3. Varying doses and dose titrated effects comparison was not done in this study. Dose was not titrated in this study as patients responded to the actual proposed doses in the study.

CONCLUSION

Type 2 Diabetes Mellitus is a very common disorder which can lead to coronary artery disease, cerebro- vascular disease, Nephropathy, Diabetic retinopathy, Neuropathy, Alzheimer's disease. So, early treatment is necessary to prevent these complications. In this regard, many drugs are used to treat diabetes. The most commonly prescribed drugs- Sulphonylureas and Biguanides were included in our study and Glibenclamide showed promising results when compared to Metformin. Glibenclamide and Metformin reduced the fasting blood glucose levels equally in 6 months with weight loss in Metformin group and slight weight gain and increase in Blood pressure in Glibenclamide group. Glibenclamide reduced the Glycated hemoglobin levels more than Metformin indicating that long term Glycemic control was more with glibenclamide when compared to Metformin. There were no serious adverse effects in both the groups. Glibenclamide caused more hypoglycemia and Metformin caused more Gastro intestinal adverse effects. Over all adverse effects were more with Metformin and patient's compliance was more with Glibenclamide. In conclusion, long term Glycemic control was better achieved with Glibenclamide. Since diabetes is a chronic disease with long duration Glibenclamide might be preferred to Metformin.

Recommendations for further studies/Future scope

1. To gather more information about the problem and treatment options, cross over studies and dose titrated effect studies should be done with varying doses.
2. Comparison between monotherapy with combination drug therapy should be done to promote rational usage of drugs.
3. Studies on fixed dose combination in advance and resistant cases should be done.
4. Drug utilization and prescription pattern studies could help to have better understanding about safe usage of medicines
5. Multi centre trails and studies in specialized clinics are recommended.

ACKNOWLEDGEMENT

I express my sincere and deep felt gratitude to Dr.A.Meena Kumari, Dr.K.Solomon Raju Dr.V.L.M.Raman, Dr.S.Vijaya kumari, Dr.Ch.Jhansi vani, Dr.M.Usha Rani, Dr.Muneer Kanha, Dr.P.Raghunatha Rao, Mr.G.Vijay Bhaskar, and Mr Lokesh for their co-operation in completing this dissertation. I am thankful to all the patients who co-operated with me in this study.

REFERENCES

1. Riserus U, Willett WC, Hu FB., Dietary fats and prevention of type 2 diabetes. Progress in Lipid Research, 48 (1): 44–51,(2009)
2. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ et al., National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet, 378(9785):31–40,(2011)
3. Wild S, Roglic G, Green A, Sicree R, King H., Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care, 27 (5):1047-53(2004)
4. Bianca Hemmingsen, MD, Jeppe B. Schroll, MD et al., Sulfonylurea versus Metformin monotherapy in patients with type 2 diabetes: a Cochrane systematic review and meta-analysis of randomized

clinical trials and trial sequential analysis.CMAJ,2 (3): E162-E175(2014)

5. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. Geneva: World Health Organization. 2006. P. 21. ISBN 978-92-4-159493-6.
6. Hermann LS, Bitzen PO, Kjellstrom T, Lindgarde F ,Schersten B.,Comparative efficacy of Metformin and Glibenclamide in patients with non-insulin dependent diabetes mellitus.Diabete & Metabolisme,171:201-208(1991)
7. Kenneth L. Cohen, Md, And Susanne Harris., Efficacy of Glyburide in Diabetics poorly controlled on First-Generation Oral Hypoglycemics. Diabetes Care, 10:555-57(1987).
8. Leif S.Harmann Bengt Schersten, Per-Olof Bitzen,Thomas Kjellstrom,Folke Llndgard, Arne Melander., Therapeutic Comparison of Metformin and Sulfonylurea Alone and in Various Combinations.J.Diabetes care, 17(10):1104(1994).
9. Haffner SM, Hanefeld M, Fischer S,., Glibenclamide, but not acarbose, increases leptin concentrations parallel to changes in insulin in subjects with NIDDM,J Diabetes care.; 20(9):1430-4.3,1997.
10. Michael Stumvoll, Nurjahan , Gabriele Perriello et al., Metabolic Effects of Metformin in Non-Insulin-Dependent Diabetes Mellitus.N England J Med, 333: 550-554(1995)
11. Sundaresan P, Lykos D, Daher A, Diamond T,., Comparative effects of Glibenclamide and Metformin on ambulatory blood pressure and cardiovascular reactivity in NIDDM. Diabetes Care, 20(5):692-697(1997)
12. Azim S. Gangji, MD,Tali Cukierman, MD, Hertzel C. Gerstein, MD, Charles H. Goldsmith, PHD2 and Catherine M. Clase., A Systematic Review and Meta-Analysis of Hypoglycemia and Cardiovascular Events:A comparison of Glyburide with other secretagogues and with insulin. Diabetes Care, 30 (2): 389-394(2007).
13. Paresh Dandona, vivien fonseca, Anne et al., Diarrhea and Metformin in Diabetic Clinic. J. Diabetes Care, 6(5) 462-465(1983)