Use of Glimepiride and Insulin Sensitizers in the Treatment of Type 2 Diabetes — A Study in Indians

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Abstract

Aim : Short-term efficacy of glimepiride, metformin and pioglitazone in newly diagnosed type 2 diabetes was compared with a group treated with diet and exercise. Effects on insulin secretion and sensitivity were also assessed.

Methods : New type 2 diabetic subjects, aged 30-60 years with BMI< 30 kg/m^2 were selected. Subjects having glycosylated haemoglobin (HbA_1c) of < 8.5% were advised diet and exercise (control group). Others having $HbA_1c \geq 8.5$ to 11.0% were randomized to receive glimepiride (group 2), metformin (group 3) and pioglitazone (group 4). At the final review between 12-14 weeks, changes in plasma glucose, HbA_1c, lipid profile, HOMA insulin resistance (HOMA-IR), β cell function (HOMA-BF) and insulinogenic index (Δ I/G) were measured. Comparisons were made using appropriate statistical analyses.

Results : Seventy-seven of the 97 subjects randomized equally into four groups, were available for review. Glycaemic parameters improved in all groups. Mean cholesterol decreased significantly in groups treated with metformin and pioglitazone. HDL-cholesterol increased with pioglitazone. Insulin resistance decreased significantly with metformin and pioglitazone, β cell function also showed improvement.

Conclusions : Glycaemic control was seen in all study groups, the improvement was better in drug treated groups than in the control group. Glimepiride improved insulin secretion including the early phase secretion and reduced plasma triglycerides. Metformin and pioglitazone had beneficial effects on lipid levels, improved insulin sensitivity and improved insulin secretion also. ©

Introduction

Type 2 diabetes is a complex metabolic disorder with two major biochemical defects namely impaired insulin secretion and impaired insulin action at the periphery. Chronic hyperglycemia results from these defects. Management of diabetes therefore involves targeting both the defects which are interrelated. Diet modification and enhanced physical activity facilitates weight reduction and helps to reduce hyperglycemia.[1,2] However only a small percentage of newly diagnosed diabetic patients are able to maintain glycaemic control with the above intervention.

Anti-diabetic agents such as sulphonylureas and metformin, have been used as monotherapy and also in combination, to reduce hyperglycemia and maintain glycaemic control.[3] Recently newer drugs such as glimepiride[4,5] and thiozolidinediones[6-8] have also found a place in the treatment of type 2 diabetes.

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The insulin sensitizers, both metformin[9,10] and glitazones are mainly used in subjects with type 2 diabetes who are obese.[6] There is paucity of data regarding the usefulness of insulin sensitizers in non-obese subjects with type 2 diabetes. Most of the subjects having type 2 diabetes in India and South East Asia are non-obese.[11] In this study we have compared the efficacy of metformin, glimepiride and pioglitazone in newly diagnosed type 2 diabetic subjects with moderate hyperglycaemia. Effects of the drugs on insulin secretion and insulin action have been assessed in comparison with the control group, i.e. the group treated with diet and exercise. Glimepiride is the most recently approved second generation sulphonylurea for the treatment of type 2 diabetes.[5] Glimepiride does not show adverse effect on cardiac functions.[12] Pioglitazone has been shown to be effective in improving glucose control and has beneficial effect on the lipid profile also.[7,8]

Material And Methods

This was an open labelled study in newly diagnosed subjects with type 2 diabetes who had not received any anti-

diabetic treatment earlier. Subjects with type 2 diabetes diagnosed by standard oral glucose tolerance test according to the WHO criteria,[13] in the age group of 30-60years with a body mass index (BMI) of less than 30kg/m^2 were recruited. Subjects having a glycosylated haemoglobin (HbA_1c) of < 8.5 % were advised diet and exercise only and were considered as the control group (group 1). Diabetic subjects with HbA_1c >11.0% and / or fasting plasma glucose (FPG) ≥ 200 mg/dl were excluded in order to have a homogenous group. The remaining subjects (i.e. HbA_1c 8.5 - 11%) were individually randomized in the following three groups. The three groups were : group 2 : Glimepiride, 1-2 mg/day, group 3: metformin, 250 - 850 mg/day and group 4 : pioglitazone, 15 - 30 mg/day. All of them were advised an appropriate diet with restricted calories, high carbohydrate (60%) and low fat (<20%) content1. A total of 97 subjects of both genders were recruited. Height and weight were measured and body mass index (BMI) (kg/m^2) was calculated. A detailed clinical history including the symptoms of diabetes was recorded. Patients were asked to report for review between 6 - 14 weeks to assess glycaemic control and also to titrate the dose of drugs, if necessary. Anthropometric measurements and biochemical parameters were repeated during a review between 12 - 14 weeks.

Laboratory Tests

Plasma glucose was estimated by glucose oxidase peroxidase method, HbA_1c was estimated using immuno-turbidimetric procedure. Lipid parameters including total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (TG) were estimated in the fasting serum sample using standard enzymatic procedures. The estimations were done using reagents of Roche Diagnostics, Mannheim, Germany on Hitachi 912 auto analyzer. Plasma insulin was estimated in the fasting, 30min and 120min samples using radioimmunoassay (Diasorin, France). C-peptide was estimated in fasting and 120 min plasma samples by radio-immunoassay using reagents of Diagnostic Products Corporation, USA.

Measurement of insulin resistance (HOMA-IR) and β cell function(HOMA-BF)

Insulin resistance (IR) and β cell function index (BF) were derived using the Homeostasis Model Assessment (HOMA) calculation. HOMA has been proposed to assess IR and secretion using the fasting glucose and insulin concentrations.[14]

The formulae used are given below

$$IR = \frac{[\text{Fasting insulin } (\mu u/ml) \times \text{Fasting glucose (mmol/l)}]}{22.5}$$

A good correlation between the FPG (a surrogate of insulin sensitivity) and HOMA-IR was seen among the normo-glycaemic subjects (r=0.97, p<0.001).

The cut-off value for normal IR was taken as 6.8, derived from the mean + 1 SD in the non-diabetic, non-obese group. Subjects with HOMA-IR >6.8 were considered to have insulin resistance.

$$\beta \text{ cell function (HOMA BF)} = \frac{20 \times \text{Fasting insulin } (\mu u/ml)}{\text{Fasting glucose (mmol/l)} - 3.5}$$

Index of insulin secretion

Insulinogenic index (ΔI / 30 min G)

The measurement of the 30 min incremental response of insulin divided by the plasma glucose at 30 min was found to be a valid surrogate of BF.[15] This was useful in demarcating subjects with deranged BF in Asian Indians.

$$\text{Insulinogenic index} = \frac{30 \text{ min insulin - fasting insulin (pM)}}{30 \text{ min glucose (mM)}}$$

The cut-off value for an abnormally low insulinogenic index was <28, which was derived from the values obtained in the non-obese, normoglycaemic group (mean-1 SD). Those having values below 28 were considered as having impaired insulin secretion.

Statistical Analysis

Mean and standard deviation of quantitative parameters are reported. Unpaired 't' test or ANOVA was used for intergroup comparisons. Paired 't' test, chi-square test, Fischer's exact probability test or Mc Nemar's test were used for intragroup comparisons as relevant. A p value < 0.05 was considered to be significant. Statistical tests were done using SPSS package version 4.01.

RESULTS

Total number recruited in the study groups was 97 and the distribution in groups 1 to 4 was 20, 25, 24 and 28 respectively. At the end of the study, at 14 weeks, 77 subjects were available for follow up as shown in Table 1. Mean ages of patients in all the groups were similar.

The baseline body weight and BMI were higher in group 1 versus other groups (Table 1). Patients treated with glimepiride had the lowest baseline body weight and showed significant increase in weight (and BMI) on follow-up.

Distribution of subjects with BMI ≥ 27 kg/m^2 at baseline in the groups 1 to 4 were: 33.3%, 22.2%, 33.3% and 30.4% respectively, and the maximum was 29.9 kg/m^2 in one subject.

Table 1 : Demographic and anthropometric characteristics of the study groups (baseline and followup)

	Control	Study Groups		
Treatment	1	2	3	4
groups	Diet + Exercise	Glimepiride	Metformin	Pioglitazone
n, M:F	15, 13:2	18, 14:4	21, 15:6	23, 17:6
Age (years)	43.5 ± 8.7	45.3 ± 10.3	44.4 ± 10.6	45.1 ± 8.5
Weight (kg)				
Baseline	71.2 ± 9.4	65.7 ± 9.1	67.7 ± 11.5	68.9 ± 9.1
Review	70.7 ± 10.7	67.5 ± 9.2	67.0 ± 11.4	67.8 ± 7.9
BMI (kg/m^2)				
Baseline	26.1 ± 1.5	24.6 ± 2.5	25.7 ± 2.6	25.5 ± 2.2
Review	25.9 ± 2.3	25.3 ± 2.5	25.5 ± 3.0	25.1 ± 2.0

Values are mean ± SD

During the study period, treatment regimen was changed in 2 patients. A 42 year old male patient treated with metformin, 250 mg bd had no improvement in glycaemic status for 2 months and could not tolerate higher doses of the drug due to gastric problems. He was prescribed glibenclamide 2.5 mg bd with which glycaemic control improved. A 30 year old female did not show glycaemic response with pioglitazone and when changed to glimepiride after a month, showed significant reduction in blood glucose.

As shown in Table 2, baseline FPG, 2h plasma glucose (2h PG) and HbA_1c values were the lowest in the control group, due to the selection criteria. Between the other three groups no significant difference was observed in these parameters. Significant improvement in glycaemic parameters were observed in all groups. Mean cholesterol values decreased significantly in groups 3 and 4. LDL cholesterol showed a significant reduction only with pioglitazone (135 ± 35 to 112 ± 23 mg/dl, $p < 0.001$). Glimepiride and pioglitazone reduced the mean TG values. HDL cholesterol showed an improvement with metformin and pioglitazone, though statistical significance was seen with pioglitazone only.

Improvement in HbA_1c, FPG, 2h PG are shown in Table 3. Patients on diet therapy showed the least improvement while the difference between the other groups was not statistically significant. HbA_1c of < 7.5% was seen in 73.3%, 50%, 52.4% and 87% of subjects in groups 1 to 4, in respective order. FPG showed improvement in 57% of patients treated with metformin while the other two groups showed improvement in significantly higher percentages.

Table 4 shows the hormonal profile in the study groups.

Table 2 : Biochemical profile of the study groups at baseline and at review visits

	Control	Study Groups		
Treatment groups	1 Diet + Exercise	2 Glimepiride	3 Metformin	4 Pioglitazone
Plasma glucose (mg/dl)				
Fasting				
Baseline	7.4 ± 1.3	10.7 ± 2.7	10.2 ± 3.3	9.3 ± 2.0
Review	7.1 ± 1.6	7.9 ± 2.6*	8.6 ± 3.7	6.8 ± 1.4*
2 hr				
Baseline	13.4 ± 1.7	18.6 ± 4.2	17.4 ± 4.2	15.9 ± 4.7
Review	11.4 ± 2.7*	11.5 ± 4.4*	12.4 ± 4.8*	9.9 ± 3.4*
HbA_{1c} (%)				
Baseline	7.5 ± 1.0	10.2 ± 2.2	9.6 ± 2.4	9.3 ± 1.8
Review	7.2 ± 1.1	7.7 ± 1.7*	8.2 ± 2.5**	6.7 ± 1.3*
Lipid profile (mg/dl)				
Cholesterol				
Baseline	5.4 ± 1.1	5.3 ± 1.4	5.1 ± 0.95	5.8 ± 1.4
Review	5.4 ± 0.9	5.5 ± 1.7	4.7 ± 0.9**	5.3 ± 1.2*
HDL-Cholesterol				
Baseline	1.0 ± 0.2	0.95 ± 0.3	1.0 ± 0.2	0.98 ± 0.15
Review	1.1 ± 0.3	1.1 ± 0.2	1.1 ± 0.3	1.1 ± 0.2*
Triglycerides				
Baseline	2.0 ± 1.1	2.2 ± 1.4	2.8 ± 2.5	2.9 ± 2.4
Review	2.1 ± 1.2	1.7 ± 0.9**	2.5 ± 1.8	2.2 ± 1.4**

Values are mean ± SD; p in comparison with the baseline values * p <0.01. ** p <0.05

A significant increase in the fasting insulin was seen with glimepiride while a significant reduction was noted with pioglitazone. The 2h insulin value showed a significant increase in controls and group 2. Fasting plasma C-peptide improved significantly in the control group. The 2h C-peptide improved in all groups. An increase in beta cell function was evident in all the study groups except in the control group and group 3 as seen by an increase in the ΔI/G values and the HOMA - BF. HOMA-IR showed significant improvement only in patients treated with metformin or pioglitazone. Patients treated with the drugs showed improvement both in the BF and insulin action.

Conclusions

Indian subjects with type 2 diabetes show several characteristic features such as high insulin resistance with low BMI and young age at diagnosis.[16] Despite these features differentiating them from several Caucasian populations, the plethora of newer oral antidiabetic agents (ODA) now available have also been used in the Indian patients. However, there has been a lack of data on the efficacy and mode of action of monotherapy with insulin secretagogue like the glimepiride and insulin sensitizers like metformin and pioglitazone in the relatively non-obese, insulin resistant Indian subjects. The present study which has focussed on the above aspects throws light both on (a) the efficacy of the drugs in comparison with the diet and physical activity modification and (b) on their effects on insulin secretion and insulin sensitivity. The drugs were used as monotherapy in newly diagnosed subjects with type 2 diabetes, > 70% of whom had a BMI below 27 kg/m^2.

Significant improvement in glycaemia was seen over a short period of 8 - 12 weeks in moderately severe, newly diagnosed diabetic patients treated with either glimepiride or metformin or pioglitazone, when compared with the diet-treated group. The improvements with glimepiride and pioglitazone were similar, while metformin produced a lower degree of reduction in HbA_1c. However, it was noted that

Table 3 : Improvement with 12 weeks of therapy by >10% of the baseline values (in percentages)

	Control	Study Groups		
Treatment groups	1 Diet + Exercise	2 Glimepiride	3 Metformin	4 Pioglitazone
Percentage of subjects showing improvement by >10% of the baseline value				
FPG	27	83	57	91
2 h PG	60	89	81	83
HbA_{1c} (%)	27	72	57	78
Improved to normal values (% in relation to baseline)				
Cholesterol	—	—	8	13
Triglycerides	—	5	16	13
HOMA - IR	—	5	38[a]	26
HOMA - BF	20	50[b]	10	26
Δ I/G	13	35[c]	15	18

McNemar's test - a, p = 0.008; b, p = 0.004; c, p = 0.03 versus baseline value

Table 4 : Hormonal profile of study groups - baseline and after 12 weeks of therapy

		Control	Study Groups		
		1	2	3	4
Treatment groups		Diet + Exercise	Glimepiride	Metformin	Pioglitazone
Plasma Insulin (mU/ml)					
Fasting -	Baseline	20.1 ± 7.9	17.1 ± 7.2	19.9 ± 7.2	19.2 ± 10.2
	Review	23.6 ± 12.7	20.8 ± 8.1**	19.1 ± 15.6	15.5 ± 7.3**
2 hr					
Baseline		82.3 ± 47.7	44.7 ± 32.5	58.1 ± 30.2	68.2 ± 38.0
Review		128.1 ± 64.4*	88.9 ± 58.8*	80.8 ± 73.8	77.7 ± 33.6
HOMA - IR					
Baseline		6.5 ± 2.7	7.8 ± 2.9	9.4 ± 5.3	7.9 ± 4.7
Review		7.0 ± 3.4	7.3 ± 3.7	7.1 ± 6.1**	4.9 ± 3.0*
HOMA - BF					
Baseline		122.4 ± 81.6	58.6 ± 43.6	70.9 ± 42.9	73.5 ± 42.9
Review		165.2 ± 142.1	121.0 ± 79.2*	99.7 ± 72.9	99.8 ± 47.0*
Δ I/G					
Baseline		24.5 ± 23.7	10.6 ± 10.4	9.5 ± 8.3	8.7 ± 7.7
Review		31.1 ± 27.2	33.5 ± 21.7*	21.6 ± 26.8	16.6 ± 11.4*
C-Peptide (pmol/ml)					
Fasting -	Baseline	0.57 ± 0.28	0.64 ± 0.38	0.59 ± 0.31	0.56 ± 0.16
	Review	0.70 ± 0.18**	0.88 ± 0.29	0.75 ± 0.39	0.64 ± 0.23
2hr	Baseline	1.4 ± 0.48	1.0 ± 0.41	1.2 ± 0.52	1.1 ± 0.39
	Review	1.4 ± 0.44	1.6 ± 0.40*	1.7 ± 0.58*	1.6 ± 0.37*

Values are mean + SD; p in comparison with the baseline values; * p <0.01, ** p <0.05

maximum number of subjects with HbA_1c of < 7.5% at review was in the pioglitazone treated group.

Modest weight gain was noted in the group on glimepiride and this was seen only in subjects who had loss of weight before diagnosis of diabetes was made. Weight gain or water retention was not observed in the subjects treated with pioglitazone in the present study. None of the cases treated with pioglitazone had pedal edema or hepatic enzyme induction during the study period.

In general, all the tested ODA were tolerated by the patients. Metformin was not tolerated by one patient. Although it was considered that metformin does not produce hypoglycaemia, we had noted that monotherapy with 500 mg of metformin twice a day had resulted in episodes of hypoglycaemic symptoms requiring a reduction in the dose of the drug. Rare hypoglycaemic episodes have been reported with metformin by Charpentier *et al* also.[17] It is worth emphasizing that metformin is effective in Asian Indian patients, in significantly lower doses (250 - 1000 mg/day) than is being used in western countries. This could be due to the lower BMI of Asian Indians and / or due to the better efficacy of the drug in this racial group perhaps related to insulin resistance.

Pioglitazone showed the most favourable effects on lipids by reducing the total cholesterol and TG levels and by improving the HDL-cholesterol values. Similar benefits of pioglitazone have been reported by other workers.[7,8] The beneficial effects were reported to be higher in comparison with rosiglitazone.[8]

Pioglitazone has been shown to decrease FPG and postprandial plasma glucose in subjects with type 2 diabetes at doses ranging from 15 - 45 mg/day, through dose-dependent enhancement of β cell function and improved whole body and hepatic insulin sensitivity.[6,18] We noted that pioglitazone treatment resulted in significant improvement in the mean values of HOMA-IR, HOMA-BF and ΔI/G in accordance with the above observations. The beneficial effects were evident with doses ranging from 15 - 30 mg/day.

In a study of French subjects, no significant difference between metformin or glimepiride monotherapy was noted with respect to the change in HbA_1c or FPG values; however, glimepiride was significantly more effective than metformin in reducing postprandial blood glucose.[17] Our findings in the relatively non-obese subjects were very similar to the above in that both the drugs produced similar reductions in the 2h PG while glimepiride produced greater lowering of FPG and HbA_1c compared with metformin.

However, it must be stressed that the dose of metformin used was very much lower (250 - 1000 mg/day) in comparison with the dose used by Charpentier *et al* (2550 mg/day).[17] Pioglitazone showed reduction in glycaemia similar to glimepiride. All the above studies had also looked at the short-term effects of the drugs.

Improvement in IR was seen in all groups treated with ODA, the maximum effect was found with metformin; pioglitazone showed significant improvement in the mean values of HOMA-IR and indices of BF. Metformin also improved IR and BF although the latter effect was not statistically significant. This perhaps was due to the small number studied. Miyazaki *et al* had also shown that pioglitazone improved both insulin sensitivity and insulin secretion in type 2 diabetes.[6,18] Glimepiride is known to

improve insulin sensitivity also in a dose-dependent manner in cultured human skeletal muscle cells.[19] Such effects may become more evident with longer treatment periods.

BF improved to some extent in all groups including the control group 1 on diet and physical activity programme, which could probably be attributed to a reduction in glucose toxicity. The maximum benefit on BF was seen with glimepiride, as expected. Glimepiride showed a beneficial effect on the first phase insulin secretion, as indicated by an improvement in ΔI/G.

Improvement in stimulated C-peptide values was observed in all the drug treated groups. The baseline 2h C-peptide in the control group was significantly higher. This was due to the inclusion of only mild diabetic subjects in this group and no further improvement was observed during the followup.

In summary, the new generation sulphonylurea, glimepiride was found to be effective in producing glycaemic control. It also reduced plasma triglyceride levels. Metformin and pioglitazone were useful in reducing postprandial hyperglycaemia; however metformin was less effective than pioglitazone in reducing FPG. Glimepiride improved insulin secretion including the early phase secretion. Metformin and pioglitazone had significant beneficial effects in improving insulin sensitivity. Both the drugs showed the benefits of improving insulin sensitivity and insulin secretion. These findings are important as they show that the insulin sensitizers are beneficial even in non-obese subjects with type 2 diabetes. Long-term efficacy of these newer agents could be assessed only by long term prospective studies.

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References

1. Viswanathan M, Mohan V, Ramachandran A, Snehalatha C, Anderson JW. Long term experience with high carbohydrate high fibre diets in Indian diabetic patients. *Diabetologia Croatica* 1984;13:163-174.
2. Anderson JW, Ward K. Long term effects of high carbohydrate, high fibre diets on glucose and lipid metabolism. A preliminary report on patients with diabetes. *Diabetes Care* 1978;1:77.
3. Clark CM. Oral therapy in type 2 diabetes : pharmacological properties and clinical use of currently available agents. *Diabetes Spectrum* 1998;11: 211-21.
4. Korytkowski M, Thomas A, Reid L, Tedesco MB, Gooding WE, Gerich J. Glimepiride improves both first and second phases of insulin secretion in type 2 diabetes. *Diabetes Care* 2002;25:1607-11.
5. Goldberg RB, Holvey SM, Schneider J. The Glimepiride protocol #201 study group: A dose-response study of glimepiride in patients with NIDDM who have previously received sulfonylurea agents. *Diabetes Care* 1996;19:849-56.
6. Miyazaki Y, Mahankali A, Matsuda M, Glass L, Mahankali S, Ferrannini E, Cusi K, Mandarino LJ, Defronzo RA. Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. *Diabetes Care* 2001; 24:710-19.
7. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL. The Pioglitazone 001 study group. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes. A 6-month randomized placebo-controlled dose - response study. *Diabetes Care* 2000;23:1605-11.
8. Khan MA, Peter JV, Xue JL. A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. *Diabetes Care* 2002;25:708-11.
9. Effect of intensive blood glucose control with metformin on complications in over weight patients with type 2 diabetes (UKPDS 34). *The Lancet* 1998;352:854-65.
10. Bailey JC, Turner RC. Metformin. *N Engl J Med* 1996 ;3:574-79.
11. Ramachandran A, Snehalatha C, Kapur A, Vijay V, Mohan V, Das AK, Rao PV, Yajnik CS, Prasanna KS, Nair JD. For the Diabetes Epidemiology Study Group in India (DESI). High Prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. *Diabetologia* 2001;44:1094-01.
12. Caulfield MT, O'Brien KD. Cardiovascular safety of oral antidiabetic agents : the insulin secretagogues. *Clinical Diabetes* 2002;20:81-84.
13. World Health Organization : Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications; Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva: Department of Non-communicable Disease Surveillance : WHO 1999.
14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RL. Homeostasis model assessment: insulin resistance and β cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412-19.
15. Wareham NJ, Phillips DIW, Byrne CD, Hales CN. The 30 minute insulin incremental response in an OGTT as a measure of insulin secretion. *Diabetic Medicine* 1995;12:931.
16. Ramachandran A, Snehalatha C : Problems specific to developing countries and the effect of westernization. Type 2 diabetes - Prediction and prevention. Ed. G.A. Hitman. John Wiley and Sons Ltd. 1999;325-48.
17. Charpentier G, Fleury F, Kabir M, Vaur L, Halimi S . Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. *Diabetic Medicine* 2001;18:828-34.
18. Miyazaki Y, Matsuda M, DeFronzo RA. Dose-response effect of pioglitazone on insulin sensitivity and insulin secretion in type 2 diabetes. *Diabetes Care* 2002;25:517-23.
19. Haupt A, Kausch C, Dahl D, Bachmann O, Stumvoll M, Haring HU, Matthaei S. Effect of glimepiride on insulin stimulated glycogen synthesis in cultured human skeletal muscle cells. *Diabetes Care* 2003;5:211-14.