International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2016.422.428

Research Article
Addition of Voglibose to Glimepiride and Metformin have Better Glucose Control in Diabetics: A Prospective, Parallel-group and Open-label Comparative Study

[1]Krishna Murti, [1]Manoj Kumar Sethi, [1]Akalanka Dey, [2]Chandra Sekhar Lal, [3]Krishna Pandey and [4]Pradeep Das

[1]Department of Pharmacy Practice, National Institute of Pharmaceutical Education and Research, Hajipur, India
[2]Department of Clinical Biochemistry, Rajendra Memorial Research Institute of Medical Sciences, Patna, India
[3]Department of Clinical Medicine, Rajendra Memorial Research Institute of Medical Sciences, Patna, India
[4]Department of Microbiology, Rajendra Memorial Research Institute of Medical Sciences, Patna, India

Abstract

This study compares the change in BMI, fasting and postprandial blood glucose, glycosylated haemoglobin (HbA1c), Glomerular Filtration Rate (GFR), serum creatinine, blood urea and lipid profile levels when two different therapies (group A = metformin+glimepiride) and group B = metformin+glimepiride+voglibose) are given to diabetic patients to compare efficacy of voglibose as an add-on therapy. This study was a 10 months prospective, open-label comparative study. Type II diabetic subjects, aged >18 years were selected and were divided into group A and B. All the parameters were evaluated before the treatment and reassessed after 3 months of treatment. Group A and B was having significant decrease in BMI with $p<0.017$ and $p<0.049$, respectively. In both of the groups glucose triad levels decreased significantly as p value found less than 0.05. There was no effect was found over blood urea level. Protective function of kidney observed when voglibose added. Evidence of controlling lipid profile also observed in triple drug therapy as p-value was <0.05. The add-on therapy using voglibose in dual therapy including glimepiride and metformin showed a very significant benefit in controlling the glucose triad levels ($HbA1_C$, fasting plasma glucose and postprandial glucose level) when compared to dual therapy. Voglibose has an effect to decrease Total Cholesterol (TC), triglycerides (TGs) and Low Density Lipoproteins (LDL) level and increase HDL significantly. There was no effect was found on blood urea level.

Key words: Voglibose, HbA1c, comparative research, glucose triad, metformin, glimepiride

Received: November 02, 2015 **Accepted:** February 20, 2016 **Published:** April 15, 2016

Citation: Krishna Murti, Manoj Kumar Sethi, Akalanka Dey, Chandra Sekhar Lal, Krishna Pandey and Pradeep Das, 2016. Addition of voglibose to glimepiride and metformin have better glucose control in diabetics: A prospective, parallel-group and open-label comparative study. Int. J. Pharmacol., 12: 422-428.

Corresponding Author: Krishna Pandey, Depertment of Clinical Medicine, Rajendra Memorial Research Institite of Medical Sciences, 800007 Agamkuan, Patna, India Tel: +91-9431042119 Fax: 0612-2634379

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Type II diabetes mellitus is one of the most common metabolic diseases with its prevalence increasing worldwide and despite the availability of newer antidiabetic drugs physician's not able to control blood glucose level satisfactorily (Nathan *et al*., 1996; IDF., 2013). For preventing macrovascular and microvascular complications in patients with type II diabetes, management of hyperglycaemia is crucial. Controlling blood-glucose levels often requires several strategies, including weight loss if needed, dietary control, increased physical activity and antidiabetic medications (Ramachandran *et al*., 2012). It is expected that if diabetes is not controlled then it may be projected to 300 million diabetic patients by 2025 (Pradeepa *et al*., 2002). This needs various strategies, such as single drug and multiple drugs from various categories of antidiabetic drugs. Risk benefit ratio must be considered, while choosing combination therapy in type II diabetic patients.

The present topic of debate is contribution of postprandial glucose levels to overall glycaemic control and the role of postprandial glucose targets in disease management (Ceriello, 2010). As a thumb rule for good glycaemic control, it has been agreed that patient is generally considered to have achieved successful disease control, when their $HbA1_C$ is <7% (American Diabetes Association, 2008; Canadian Diabetes Association, 2008; Ryden *et al*., 2007). With evidence of earlier studies, it is clear that physicians are likely to consider plasma glucose levels both after the overnight fast (pre-prandial) and after meals (postprandial) as well as the variability of glucose levels, in order to achieve optimal glycaemic control for each patient. Therefore, at the initiation of treatment physicians must need to consider the selection of agents that target both fasting and postprandial hyperglycaemia. At times it has been also observed that HbA1c goal is achieved, but both fasting and postprandial glucose levels are not adequately controlled due to inappropriate drug combinations and life style modification. International Diabetes Federation (IDF) guidelines for the management of post meal (postprandial) glucose state that the goal of diabetes therapy should be to achieve glycaemic status as near to normal as safely possible in all three measures of glycaemic control i.e., HbA1c, fasting (pre-prandial glucose) and postprandial glucose (Currie *et al*., 2010; Ceriello *et al*., 2007). Treatment of both fasting and postprandial hyperglycaemia should be initiated simultaneously at all levels of HbA1c above agreed levels.

Earlier treatment with biaguanides and thiozolidinediones has shown reduction in fasting plasma glucose level. Sulphonylureas administered in morning do lowers posprandial glucose levels during day time and also exerts reduction in fasting plasma glucose level overnight. Selective antidiabetic agents are available, which preferentially lowers postprandial glucose level, such as α-glucosidase inhibitors, incretin mimetics, dipeptidyl peptidase (DPP)-4 inhibitors and rapid acting insulin. Combination therapy seems to be justified in controlling glucose triad level. Several of the available oral agents have been studied in combination and have been shown to further improve glycaemic control when compared to monotherapy (Riddle, 2000).

Advocating the therapy combining three oral agents (sulfonylurea, metformin, α-glucosidase inhibitor or sulfonylurea, metformin and thiazolidinedione) in the management of type II diabetes seems to be a good approach (Ovalle and Bell, 1998). Thus the study was conducted to evaluate the efficacy of voglibose used as an add on therapy to glimepiride-metformin combination by comparing with glimepiride-metformin alone and its impact on glucose triad to optimise the best drug combination therapy. The goal of this comparative study will enhance physician clinical judgement to provide the right treatment at the right time.

MATERIALS AND METHODS

Study population and design: The study was carried out at out-patient department of Rajendra Memorial Research Institute of Medical sciences (RMRIMS), Indian Council of Medical Research (ICMR), Agamkuan, Patna, India. The study was a prospective, parallel-group, open-label comparative study conducted from August, 2014 to May, 2015 (10 months). The patients who were >18 years of age had diagnosed with type II diabetes of either sex and confirmed with postprandial hyperglycaemia were eligible to be included in the study design. Enrolled patients gave informed consent and were divided into two groups. Group A was taking dual therapy of glimepiride 1 mg and metformin 500 mg. Group B was taking voglibose 0.3 mg as add on to above dual therapy. Total 100 patients were included for the study i.e., 50 subjects in each group but due to loss of follow-up 30 subjects excluded from the study. Finally 70 type II diabetic patients i.e., 35 in each group were successfully enrolled during the study period.

Efficacy and safety evaluation: The primary objective was glucose triad (HbA1c, fasting glucose and post-prandial glucose level) change from baseline to 3 months after treatment. Secondary objectives were serum creatinine, blood

urea, GFR and lipid profile (TC, TGs, LDL and HDL). Other demographic details like age, sex, height, weight, Body Mass Index (BMI), duration of disease and family history also recorded. Then follow-up of all these parameters were carried out after successful completion of 3 months of treatment. The BMI was calculated by using metric imperial BMI formula.

Estimation of blood glucose both fasting and postprandial along with blood urea and serum creatinine, lipid profiles analysis were done by Merck's auto analyser instrument in clinical biochemistry laboratory of Rajendra Memorial Research Institute of Medical Sciences, Patna, India. The HbA1c was calculated by Affinion's auto analyser of HbA1c and Alere's catridge was used.

The GFR is generally considered to be the best index of renal function in health and disease. The GFR was estimated by prediction equations that take into account serum creatinine concentration and some or all of the following variables: Age, sex, race and body size. The recommended equation by the national kidney foundation is that of the Modified Diet in Renal Disease (MDRD).

Statistical methods: The analysis of all the parameters were carried out by using SPSS 22.0 and analysis done by applying paired t-test. Value of $p<0.05$ was considered significant.

RESULTS

The demographic and clinical measurements in both the groups i.e., group A and B of randomized patients are mentioned below.

Demographic characteristics of the study subjects: Age distributions of patients are summarized in Table 1. Group A was having 1 patient of age between (30-39 years), 8 patients of age between (40-49 years), 10 patients of age between (50-59 years), 15 patients of age between (60-69 years) and 1 patient of age more than 70 years. Group B were having 2 patients of age between (30-39 years), 8 patients of age between (40-49 years), 6 patients of age between (50-59 years), 15 patients of age between (60-69 years) and 4 patients of age more than 70 years. Gender distributions of patients are summarized in Table 2. Group A had 22 males and 13 females and group B had 14 males and 21 females. Percentage was calculated and it was found that group A contain 62.8% of male and 37.1% of female and group B contain 40.0% of male and 60.0% of female. Distributions according to duration of diabetes are summarized in Table 3. Group A was having 12 patients of duration of diabetes between (0-1 years), 16 patients of duration of diabetes between (1-5 years), 3 patients of duration of diabetes between (5-10 years) and 4 patients of duration of diabetes more than 10 years. Group B was having 8 patients of duration of diabetes between (0-1 year), 18 patients of duration of diabetes between (1-5 years), 4 patients of duration of diabetes between (5-10 years) and 5 patients of duration of diabetes between more than 10 years.

Table 1: Age distribution of patients

	Groups	
Age (years)	A (%)	B (%)
30-39	1 (2.8)	2 (5.7)
40-49	8 (22.8)	8 (22.8)
50-59	10 (28.6)	6 (17.1)
60-69	15 (42.8)	15 (42.8)
≥70	1 (2.8)	4 (11.4)

Table 2: Gender distribution of patients

	No. of patients in groups	
Gender	A (%)	B (%)
Male	22 (62.8)	14 (40.0)
Female	13 (37.1)	21 (60.0)
Total	35	35

Table 3: Distribution according to duration of diabetes

	Groups	
Duration of diabetes (years)	A (%)	B (%)
0-1	12 (34.3)	8 (22.9)
1-5	16 (45.7)	18 (51.4)
5-10	3 (8.6)	4 (11.4)
≥10	4 (11.4)	5 (14.3)

In this study, it has been found 46 (65.71%) patients out of 70 patients having primary relative in their family having diabetes. Figure 1 shows family history of the enrolled patients.

Physiological and biochemical measurements: The changes in all the clinical parameters evaluated are enlisted in Table 4 and 5 for group A and B, respectively.

Group A and B was having significant decrease in BMI with $p<0.017$ and $p<0.049$, respectively as shown in Fig 2. Group A was having average fasting blood glucose 183.97 mg dL^{-1} before treatment and 145.65 mg dL^{-1} at the end of the treatment ($p<0.000$). Group B was having average fasting blood glucose 186.24 mg dL^{-1} before treatment and 146.37 mg dL^{-1} at the end of the treatment ($p<0.000$) as shown in Fig. 3. Group A was having average postprandial blood glucose 266.88 mg dL^{-1} before treatment and 227.51 mg dL^{-1} at the end of the treatment ($p<0.006$). Group B was having average postprandial blood glucose 273.40 mg dL^{-1} before treatment and 176.51 mg dL^{-1} at the

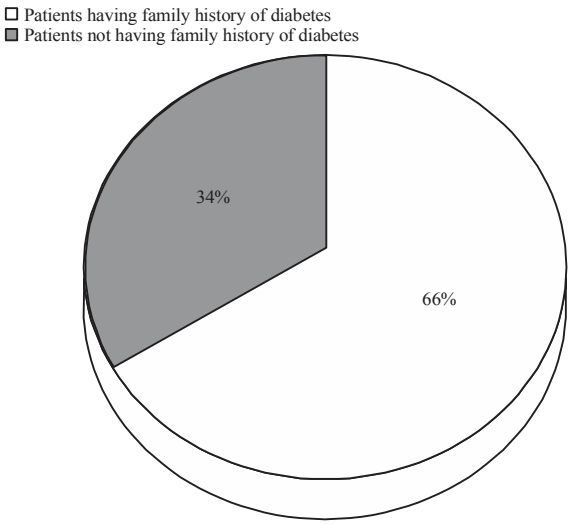

Fig. 1: Family history of diabetes, data represents that 66% of the enrolled patients were having family history of diabetes, whereas 34% were not having any family history

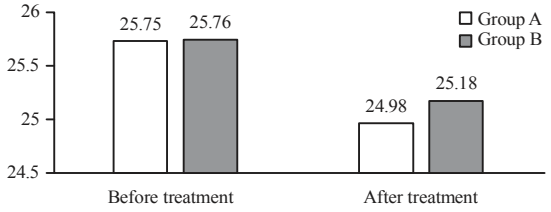

Fig. 2: Change in BMI before and after treatment, data shows that Body Mass Index (BMI) of group A and B before and after the treatment

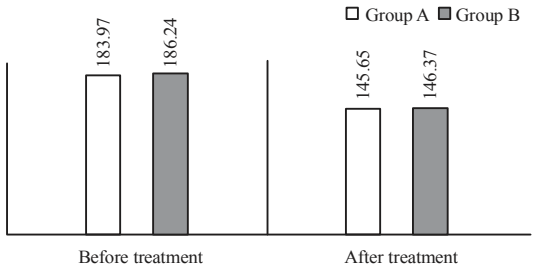

Fig. 3: Change in fasting plasma glucose before and after treatment, graphical data represents the Mean±SE in fasting blood glucose in group A and B

end of the treatment (p<0.000) as shown in Fig. 4. Group A was having average HbA1c 8.19% before treatment and 7.60% at the end of the treatment (p<0.002). Group B was having average HbA1c 9.01% before treatment and 7.81% at the end of the treatment (p<0.000) as evident in Fig. 5. Overall

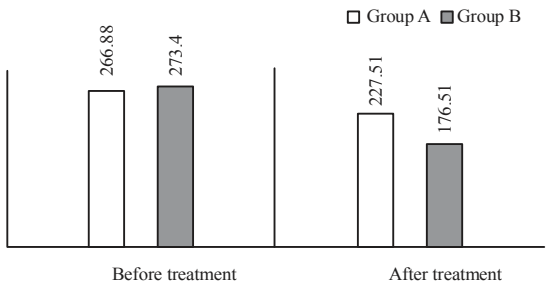

Fig. 4: Change in postprandial blood glucose before and after treatment, graphical data represents the Mean±SE in post-prandial blood glucose in group A and B

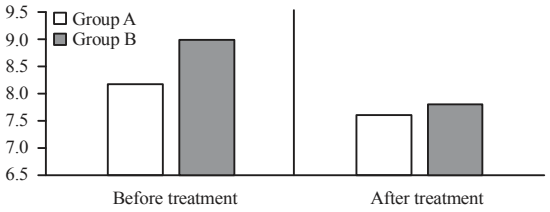

Fig. 5: Change in HbA1c before and after treatment, graphical data represents the Mean±SE in glycosylated haemoglobin (HBA1c) in group A and B

the glucose triad levels (Fasting blood glucose, post-prandial blood glucose and glycosylated haemoglobin) were better with voglibose as add on therapy in group B. There was no significant effect observed on blood urea in both the groups i.e., group A and B as data interpreted in the Table 4 and 5. In both the groups serum creatinine was increased slightly with p<0.002 and p<0.937, respectively.

The GFR was calculated by using serum creatinine level and found decreased with p<0.002, group A was having average total cholesterol 135.56 mg dL^{-1} before treatment and 129.17 mg dL^{-1} after treatment (p<0.060) and group B was having average total cholesterol 152.28 mg dL^{-1} before treatment and 141.68 mg dL^{-1} after treatment (p<0.023) and p<0.538 for group A and B, respectively. Group A was having average triglyceride 121.88 mg dL^{-1} before treatment and 111.74 mg dL^{-1} after treatment (p<0.103). Group B was having average triglyceride 132.84 mg dL^{-1} before treatment and 120.14 mg dL^{-1} after treatment (p<0.043). Group A was having average LDL 84.29 mg dL^{-1} before treatment and 70.88 mg dL^{-1} after treatment (p<0.000) and group B was having average LDL 97.52 mg dL^{-1} before treatmen and 88.18 mg dL^{-1} after treatment, which was statistically significant (p<0.011). Group A was having average HDL 36.69 mg dL^{-1} before treatment and 36.71 mg dL^{-1} after

Table 4: Changes in physiological and biochemical parameters for group A

Parameters	Before treatment (Mean±SE)	After treatment (Mean±SE)	p-value
BMI	25.75±0.68	24.98±0.58	0.017
Fasting blood glucose level	183.97±13.73	145.65±6.19	0.000
PP blood glucoselevel	266.88±21.68	227.51±14.62	0.006
HbA1c	8.19±0.35	7.60±0.28	0.002
Blood urea	29.91±0.73	28.80±0.69	0.080
Serum creatinine	0.97±0.03	1.08±0.03	0.002
GFR	79.72±2.80	71.11±2.95	0.002
Total cholesterol	135.56±6.43	129.17±4.78	0.060
Triglyceride	121.88±9.77	111.74±7.15	0.103
LDL	84.29±4.89	70.88±3.95	0.000
HDL	36.69±1.93	36.71±1.54	0.991

BMI: Body mass index, HbA1c: Glycosylated haemoglobin, GFR: Glomerular filtration rate, LDL: Low density lipoprotein and HDL: High density lipoprotein

Table 5: Changes in physiological and biochemical parameters for group B

Parameters	Before treatment (Mean±SE)	After treatment (Mean±SE)	p-value
BMI	25.76±0.66	25.18±0.67	0.049
Fasting blood glucose level	186.24±11.44	146.37±5.59	0.000
PP blood glucose level	273.40±16.23	176.51±8.38	0.000
HbA1c	9.01±0.33	7.81±0.22	0.000
Blood urea	28.54±0.60	28.37±0.61	0.750
Serum creatinine	1.01±0.03	1.02±0.02	0.937
GFR	71.13±3.49	69.46±2.61	0.538
Total cholesterol	151.28±5.60	141.68±4.44	0.023
Triglyceride	132.84±9.35	120.14±5.89	0.043
LDL	97.52±5.53	88.18±4.47	0.011
HDL	38.98±1.17	39.38±1.32	0.000

BMI: Body mass index, HbA1c: Glycosylated haemoglobin, GFR: Glomerular filtration rate, LDL: Low density lipoprotein and HDL: High density lipoprotein

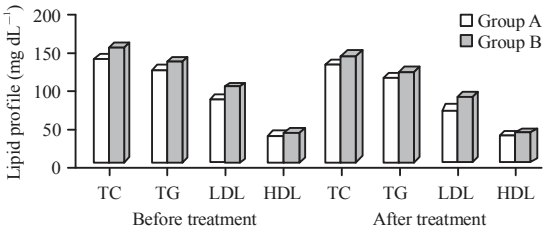

Fig. 6: Change in lipid profile before and after treatment, graphical data represents the Mean±SE in lipid profile in group A and B before and after treatment, TC: Total cholesterol, TG: Triglycerides, LDL: Low density lipoprotein, HDL: High density lipoprotein

treatment (p<0.991). Group B was having average HDL 38.98 mg dL^{-1} before treatment and 39.38 mg dL^{-1} after treatment, which was again statistically significant (p<0.000) as shown in Fig. 6.

DISCUSSION

Higher level of post-prandial and discrepancy between fasting and post-prandial glucose are significantly associated with macrovascular and microvascular complications even after control of all other factors. The patients are on the higher risk for development of cardiovascular disorder. However, higher fasting hyperglycaemia was not significantly associated with CVD risk. Post-prandial glucose, similar to post-challenge glucose was related to CVD than fasting glucose (The DECODE Study Group on Behalf of the Europe an Diabetes Epidemiology Group, 1999; DECODE Study Group on Behalf of the European Diabetes Epidemiology Group, 2001; Cavalot *et al*., 2005). On the other hand, it is evident that fasting hyperglycaemia is associated with beta cell dysfunction, whereas post-challenge hyperglycaemia is associated with insulin resistance, hypertension, obesity and dyslipidaemia (Chien *et al*., 2009). In clinical management of type II diabetes with lifestyle modifications and pharmacologic interventions, post-prandial glucose must be appreciated as a target (Yamagishi *et al*., 2005).

But in modern clinical approach, it is now recommended that for the optimal management of type II diabetes, there is the requirement to understand the relationships between glycosylated haemoglobin (HbA1c), fasting plasma glucose and post-prandial glucose (the glucose triad). When antidiabetic therapy is initiated, physicians may need to consider selection of agents that target both fasting and post-prandial hyperglycaemia.

In this study if the results of glucose triads (i.e., fasting, post-prandial and HbA1c values), a very satisfactory result was got. Group A was having average fasting blood glucose 183.97±13.73 mg dL^{-1} before treatment and was having 145.65±6.19 mg dL^{-1} at the end of the treatment, indicates significant difference. Group B was having average fasting blood glucose 186.24±11.44 mg dL^{-1} before treatment and was having 146.37±5.59 mg dL^{-1} at the end of the treatment. Group A was having average post-prandial blood glucose 266.88±21.68 mg dL^{-1} before treatment and was having 227.51±14.62 mg dL^{-1} at the end of the treatment. The $p<0.006$, which was considered significant. Group B was having average postprandial blood glucose 273.40±16.23 mg dL^{-1} before treatment and was having 176.51±8.38 mg dL^{-1} at the end of the treatment. The $p<0.000$, which was statistically significant. Reduction of post-prandial blood glucose was more in this case. Group A was having average HbA1c 8.19±0.35% before treatment and was having 7.60±0.28% at the end of the treatment. The $p<0.002$, which was considered significant. Group B was having average HbA1c 9.01±0.33% before treatment and was having 7.81±0.22% at the end of the treatment. The $p<0.000$, which was again considered significant. Observation in decrease of HbA1c was also more in case of triple drug therapy. From the above result it was confirmed that addition of voglibose has more beneficial effect on controlling post-prandial hyperglycaemia as well as very good reduction in HbA1c level.

Group A was having average blood urea 29.91 mg dL^{-1} before treatment and 28.80 mg dL^{-1} at the end of the treatment. The $p<0.080$, which was statistically non-significant. Group B was having average blood urea 28.54 mg dL^{-1} before treatment and 28.37 mg dL^{-1} at the end of the treatment. The $p = 0.750$, which was not considered significant. From this it can be concluded that there was no effect on blood urea of these two regimens. It had been seen that there was a significant decrease in GFR when the patients were on dual drug therapy, because a significant increase in serum creatinine had been seen. But in case of triple drug therapy the increase in the level of serum creatinine was not significant so, the addition of voglibose to the treatment schedule was able to prevent regular decrease in GFR, thereby protecting kidney function.

While comparing the lipid profiles a very good control with triple drug therapy was observed. In group A it was observed that the Total Cholesterol (TC), triglyceride (TG) and Low Density Lipoproteins (LDL) levels were decreased. Slight increase in HDL was also observed but p-value was not significant. But in group B it had been seen that total cholesterol, triglycerides and LDL levels were decreased significantly and HDL increased significantly. Therefore, it can be concluded with the statement that voglibose was having the efficacy to control the lipid levels also. Therefore, resultant data from group B was comparatively significant than group A in terms of reduction in glucose triad levels, lipid levels and to some extent protecting kidney functions.

CONCLUSION

The add-on therapy using voglibose in dual therapy including glimepiride and metformin showed a very significant benefit in controlling the glucose triad levels when compared to dual therapy. Voglibose has an effect to decrease TC, TG and LDL level and increase HDL significantly. No effect was found on blood urea level. Hence, this add-on therapy of voglibose to dual drug therapy of glimepiride and metformin will be the best option for managing hyperglycaemia.

ACKNOWLEDGMENTS

We are very much thankful to Director, NIPER-Hajipur for giving us permission to conduct the research work and also Mr. Naresh Kumar Sinha for giving constant technical support. We are also thankful to Ministry of Chemicals and Fertilizers, Department of Pharmaceuticals, Government of India for funding this project work.

REFERENCES

American Diabetes Association, 2008. Standards of medical care in diabetes-2008. Diabetes Care, 31: S12-S54.

Canadian Diabetes Association, 2008. Canadian diabetes association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can. J. Diabetes, 32: S1-S201.

Cavalot, F., A. Petrelli, M. Traversa, K. Bonomo and E. Fiora *et al*., 2005. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type II diabetes mellitus, particularly in women: Lessons from the San Luigi Gonzaga diabetes study. J. Clin. Endocrinol. Metab., 91: 813-819.

Ceriello, A., S. Colagiuri, J. Gerich and J. Tuomilehto, 2007. Guideline for management of postmeal glucose. International Diabetes Federation, Brussels, Belgium, October, 2007, pp: 1-29.

Ceriello, A., 2010. The glucose triad and its role in comprehensive glycaemic control: Current status, future management. Int. J. Clin. Pract., 64: 1705-1711.

Chien, K.L., B.C. Lee, H.J. Lin, H.C. Hsu and M.F. Chen, 2009. Association of fasting and post-prandial hyperglycemia on the risk of cardiovascular and all-cause death among non-diabetic Chinese. Diabetes Res. Clin. Pract., 83: e47-e50.

Currie, C.J., J.R. Peters, A. Tynan, M. Evans and R.J. Heine *et al*., 2010. Survival as a function of $HbA1_c$ in people with type II diabetes: A retrospective cohort study. Lancet, 375: 481-489.

DECODE Study Group on Behalf of the European Diabetes Epidemiology Group, 2001. Glucose tolerance and cardiovascular mortality comparison of fasting and 2-h diagnostic criteria. Arch. Internal Med., 161: 397-405.

IDF., 2013. IDF Diabetes Atlas. 6th Edn., International Diabetes Federation, Brussels, Belgium, ISBN: 2-930229-85-3, Pages: 160.

Nathan, D.M., C. McKitrick, M. Larkin, R. Schaffran and D.E. Singer, 1996. Glycemic control in diabetes mellitus: Have changes in therapy made a difference? Am. J. Med., 100: 157-163.

Ovalle, F. and D.S. Bell, 1998. Triple oral antidiabetic therapy in type 2 diabetes mellitus. Endocrine Pract., 4: 146-147.

Pradeepa, R., R. Deepa and V. Mohan, 2002. Epidemiology of diabetes in India--current perspective and future projections. J. Indian Med. Assoc., 100: 144-148.

Ramachandran, A., C. Snehalatha, A.S. Shetty and A. Nanditha, 2012. Trends in prevalence of diabetes in Asian countries. World J. Diabetes, 3: 110-117.

Riddle, M., 2000. Combining sulfonylureas and other oral agents. Am. J. Med., 108: 15-22.

Ryden, L., E. Standl, M. Bartnik, G. Van den Berghe and J. Betteridge *et al*., 2007. Guidelines on diabetes, pre-diabetes and cardiovascular diseases: Executive summary: The task force on diabetes and cardiovascular diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur. Heart J., 28: 88-136.

The DECODE Study Group on Behalf of the Europe an Diabetes Epidemiology Group, 1999. Glucose tolerance and mortality: comparison of WHO and American Diabetic Association diagnostic criteria. Lancet, 354: 617-621.

Yamagishi, S., K. Nakamura and M. Takeuchi, 2005. Inhibition of postprandial hyperglycemia by acarbose is a promising therapeutic strategy for the treatment of patients with the metabolic syndrome. Med. Hypotheses, 65: 152-154.