Chapter VI

Discussion

06. Discussion:

The type -2 diabetes mellitus (DM) is a most common chronic disease which accompanies the patient throughout the life. Since type-2 diabetes mellitus is progressive disease, its natural course may lead to late complications which clearly restrict the life span and quality of life of patient. The cost of treating complications is also high therefore early diagnosis and adequate treatment is of critical significance for type-2 diabetes patient (Davis SN 2007). Accumulating evidence shows that excessive fluctuations in post meal blood glucose levels (postprandial hyperglycemia) have adverse consequences for diabetes related morbidity and mortality.

It is now apparent that postprandial hyperglycemia plays a central role in the decline from impaired glucose tolerance (IGT) to overt diabetes and in the development and progression of diabetes complications, particularly cardiovascular disease (CVD), good glycemic control reduces the risk of vascular complications (Diabetes Control and Complications Trial Research Group, 1995; UK Prospective Diabetes Study (UKPDS) Group, 1998), and prevention of postprandial hyperglycemia decreases the risk for both type 2 diabetes and CVD in individuals with IGT (Chiasson JL et al 2002).

Consequently, postprandial glucose control in conjunction with normalization of hemoglobin HbA1c and fasting plasma glucose levels in those with manifest diabetes should be a primary goal in the prevention and management of type 2 diabetes. Effective management of postprandial hyperglycemia therefore involves not only the maintenance of normal blood glucose levels after meal but also the prevention of many other diabetic complications (Mitrakou A et al 1998).

Alpha glucosidase inhibitors reduce postprandial hyperglycemia by delaying absorption of carbohydrates such as starch, dextrin and disaccharides by inhibiting alpha glucosidase enzyme in intestinal brush orders. The inhibition of alpha glucosidase activity reliably reduces HbA1c and postprandial insulin level, also improves lipid metabolism, reduces fasting plasma glucose level and improve insulin sensitivity (Nathan DM et al 2006).

Acarbose, the first α glucosidase inhibitor to be marketed, was introduced in the early 1990s. Two another additional agents, miglitol and voglibose, have been introduced in some countries (Krentz AJ et al 2001). The efficacy of acarbose has been confirmed in more than 350 studies involving more than 30,000 patients (Bayers Healthcare 2006)

Importantly, these agents reduce blood glucose level without increasing insulin secretion so they do not cause hypoglycemia and weight gain. The α-glucosidase inhibitors do not cause weight gain, can reduce postprandial hyperinsulinaemia and have lowered plasma triglyceride concentrations in some studies (Lebovitz HE 1998). Their good safety record is a further advantage, but limited gastrointestinal tolerability has substantially limited their use (Markus R 2004).

The alpha-glucosidase inhibitor acarbose has been shown in a chronic study to reduce the risk of progression from impaired glucose tolerance to diabetes by 25%. Acarbose has also been shown to reduce the risk of myocardial infarctions and other cardiovascular events in a meta-analysis (Hanefeld, M et al 2004). Patients using acarbose had reduced HbA1c levels, reduced fasting and postprandial blood glucose levels, reduced plasma triglyceride levels, reduced body weight and BMI, reduced systolic blood pressure, and reduced insulin levels (Hanefeld, M et al 2004).

The present study investigated the effects of acarbose, miglitol alone and combination with *Salacia oblonga* and Salacia Reticutala, on lowering of FBS, PFBS, HbA1C, and weight of patient.

The postprandial lowering of blood glucose by alpha-glucosidase inhibitors such as miglitol and acarbose after a starch load is well established. The mechanism of action is the inhibition of the last step in carbohydrate digestion, namely the conversion of disaccharide to monosaccharide (glucose) and a consequent decrease in the rate of entry of glucose into the systemic circulation (Joubert PH et al 1990).

Group I treated with acarbose alone (Table No. 19) shows distribution of mean and SD values of weight, Fasting BSL, Post meal BSL, and HbA_1C parameters in group I from baseline to 6 months follow up. In present study from the table No.19, it is observed that average weight falls down from 65.86 kg at baseline to 63.42 kg at 6 months follow up.

The α-glucosidase inhibitors causes weight loss is type 2 diabetic patients (Lebovitz HE 1998). In the present study, we found, after 24 weeks intervention, the favorable decrease in body weight after acarbose monotherapy, the weight falls down from 65.86 kg at baseline to 63.42 kg at 6 months follow up i.e. 2.44 kg net weight loss i.e. 3.94% treated with acarbose 50 mg tid. This outcome is significantly greater than the results of Karen S L et al study who found net body weight loss of 0.54 ± 0.32 kg, study conducted by Santeusanio F et al found weight loss of 2.49% kg (Santeusanio F et al 1993), study conducted by Rury Holman et al (Rury RH et al 1999) found no significant weight loss (0.7 kg), The investigation of our study is greater than the change in weight in response to 12 months of treatment of acarbose group in Graydon S. Meneilly et al conducted trial (Graydon SM. et al 2000) and the outcome of The Juno Rosenstock et al (Rosenstock J.et al 1998) net weight loss by 0.98 kg (P = 0.8108). Study results are significantly greater than reviewed by Giuseppe Derosa et al P< 0.05 (1.9% net weight loss)

Our Study investigation is comparable with Fischer S et al conducted blind, placebo-controlled, multinational, five-arm European study on dose-response relationship of acarbose as a first line drug in non-insulin-dependent diabetes mellitus found 4.57% weight loss in patients treated with acarbose (Fischer S et al 1998), finding of Yuichi Shinoda et al (Yuichi S. et al 2006) acarbose treatment reduced the body weight by 3.2%, our outcome is comparable with these studies.

Regardless of dose an duration of study our study shows significant results with the studies carried for longer duration and dose higher than 50 mg.

Similarly, fasting BSL falls down from 200.9 mg% at baseline to 71.92 mg% at 6 months follow up i.e. 48.36%. Study outcome is greater than the result of study conducted by Graydon S. Meneilly et al 145.8 mg% to 145.3 mg% (Graydon SM et al 2000) (P>0.05), Markolf Hanefeld et al (Hanefeld M et al 2004) found drop in FBS by 115.92 mg% to 110.88 mg% net difference was 5.22 mg% and results reviewed by Giuseppe Derosa et al (Derosa G. et al 2012) the net drop in FBS by 10.7%. The net drop in fasting blood sugar is significantly greater than reviewed by Giuseppe Derosa et al (Derosa G et al 2012) P< 0.05 (10.7 % loss).

Tetuo Hayakawa et al found Acarbose inhibited increase of fasting blood glucose level (Tetuo H. et al 1884). Postprandial hyperglycaemia is known to contribute to the development of endothelial dysfunction (Hanefeld M et al 2004; Wascher T et al 2005), and to increase the risk of cardiovascular and all-cause mortality, even before diabetes is diagnosed (DECODE Study Group 2001; , Saydah SH et al 2001; Stamler J yet al 1993). In this study Post meal BSL is also fall down from 200.9 mg% at baseline to 107.62 mg% (-93.28) at 6 months follow up i.e. 46.43% which is greater than the findings of Fischer S et al (19.6 mg%) (Fischer S et al 1998), Hotta N, et al (11.3 mg%) (Hotta N, et al 1993) i.e. 14.0 mmol l-1 to 11.3 mmol l-1 (255 mg% to 203.4 mg%), Graydon S. Meneilly et al (Graydon SM. et al 2000) (271 ± 59 pmol/l, reduction) (P <0.01), greater than findings of The Rosenstock J. et al (Rosenstock J. et al 1998) in the study Efficacy and Safety of Acarbose in Metformin-Treated Patients With Type *2* Diabetes and found drop by 33.30 mg% the drop in post meal BSL and significantly greater than J M Gosh (J M Gosh et al 2005) who found decline in PPBS level 85.3mg% greater than the result obtained by Markolf Hanefeld et al (Hanefeld M et al 2004) (i.e. 158.58 mg% to 135.36mg %).

The Group I treated with acarbose alone the HbA1C falls down from baseline i.e. 6.77% to 5.95% at 6 months follows up, a significant reduction in glycosylated hemoglobin 0.82% is obtained. The reduction of HbA1c is comparable with the results obtained by P. Rosenbaum et al (6.4 ± 1.7 to 5.6 ± 1.9 i.e. 0.80%) (Rosenbaum et al 2002) and greater than the results obtained in UKPDS (Holman RR. et al 1999) the net drop in HbA1c was observed to 0.2% after 3 years and the study conducted by Juno Rosenstock et al (Rosenstock J et al 1998) to measure the Efficacy and Safety of Acarbose in Metformin Treated Patients With Type *2* Diabetes and found drop in HbA1C by 0.65% for 24 weeks and greater than findings of Hanefeld et al i.e. 0.57 (Hanefeld, M et al 2004) and Josse et al (Josse RG. et al. 2003) who found net drop by 0.6%. in a study Acarbose in the treatment of elderly patients with type 2 diabetes for 24 weeks, Hasche H et al (Hasche H et al 1999) found reduction in HbA1c value 6.85+/-1.7% to 6.45+/-0.82% (p=0.02). Greater than the findings of Santeusanioet al (Santeusanio F et al 1993) 0.6% and Precose product information i.e. 0.77% (P=0.0001) (NDA 20-482/S-015 Precose product information). The comparison of our findings with those of controlled studies,

either *vs* placebo or *vs* a reference drug, Karen S.L. et al found that acarbose in moderate doses resulted in beneficial effects on glycemic control 0.5% compared to placebo (Karen SL et al 1998), and showed similar reductions in glycosylated hemoglobin levels (Chiasson JL et al 2004; Hoffmann J et al 1994; Coniff RF et al 1995). In a multicenter European study, glycosylated hemoglobin dropped by 0.9% in patients on acarbose monotherapy and on acarbose treatment combined with sulfonylurea (Chiasson JL et al 2004), Chan JC et al (Chan JC et al 1998) conducted an Asian multicenter clinical trial to assess the efficacy and tolerability of acarbose compared with placebo in type 2 diabetic patients previously treated with diet he found the greater reductions in HbA1c (0.70 [-1.00 to -0.39]) which also comparable with our result, a study carried out by Hasche et al (Hasche et al 1999) concluded trial observed reduction in HbA1c value by –0.9% in a study to measure Effects of acarbose treatment in type 2 diabetic patients under dietary training: a multicentre, double-blind, placebo-controlled, 2-year study is comparable with our study.

Based on Van de Laar FA review, included 41 clinical trials, acarbose had a clear effect on glycemic control compared to placebo 0.77% our outcome is significantly comparable with the trial includes in this review (Van de Laar FA et al 2006), despite of higher dose i.e. 100 mg t.i.d and longer study period (Braun D et al 1996; Chan JC et al 1998; Coniff RF et al 1994; Coniff RF et al 1995(A); Hanefeld M et al 1991; Coniff RF et al 1995(B)). The Essen Study conducted by Juergen Hoffmann et al (Juergen Hoffmann et al 1994) treated diabetes 2 patients with acabose 100 mg tid for 24 weeks found 1.1% reduction in HbA1C value, Yuichi Shinoda et al found reduction of HbA1C by 3.5% (Yuichi Shinoda et al 2006), and it is also significantly equal with this study. Graydon S. Meneilly et al (Graydon S. Meneilly et al 2000) found a significant difference in the change in HbA1c values in response to treatment of acarbose alone after treatment of 12 months, N. Hotta et al (Hotta N, et al 1993) found the net reduction in HbA1c 11.1% to 9.7%, in a placebo controlled double blind study which is also comparable with our outcome.

Derosa et al. (Derosa et al 2009) compared acarbose and repaglinide in type 2 diabetic patients treated with a sulfonylurea-metformin combination therapy. One

hundred and three patients were randomized to receive repaglinide, 2 mg three times a day or acarbose, 100 mg three times a day with forced titration for 15 weeks. The treatment was then crossed over for a further 12 weeks until the 27th week, the acarbose treated patients experienced a significant decrease in HbA1c (–1.4%, $p < 0.05$), FPG (–10.7%, $p < 0.05$), PPG (–16.2%, $p < 0.05$), body weight (–1.9%, $p < 0.05$), BMI (–4.1%, $p < 0.05$), FPI (–16.1%, $p < 0.05$), PPI (–26.9%, $p < 0.05$), and HOMA index (–30.1%, $p < 0.05$), when compared to the baseline values. Our study outcome support results of Derosa et al study, the HbA1c value is little less but we get significant reduction of weight, FBSL, PBSL than Derosa et al study.

Fischer et al (Fischer et al 1998) found 1.0% reduction in HbA1c value in a European study on dose-response relationship of acarbose as a first-line drug in non-insulin-dependent diabetes mellitus: efficacy and safety of low and high doses for 24 weeks which is comparable with this study.

F. A. Van de Laar, reports that with acarbose dosages higher than 50 mg t.i.d., the effect on HbA1C was the same, but the occurrence of side effects increased. This suggests that 50 mg tid dose is safe recommended dose for patients and we used 50 mg tid dose in this study (Van De Laar F A et al 2005). After applying Paired 't' test and ANOVA test this falls down / decrease from baseline to 6 months for all parameters in group I shows statistically highly significant ($p<0.01$).

Group II treated with miglitol alone (Table No. 21) shows distribution of mean and SD values of weight, Fasting BSL, Post meal BSL, and HbA1C parameters in group II from baseline to 6 months follow up. It is observed that average weight falls down from 65.86 kg to 63.02 kg at 6 months follow up. Miglitol is the first pseudo monosaccharide a-glucosidase inhibitor derived from 1-deoxynojirimycin and is structurally a glucose analogue (Segal P et al 1997; Saunier B et al 1982) and efficacy in monotherapy too (Pagano G et al 1995).

Miglitol also cause weight loss in patients from base line to end of study 5.86±10.33 to 63.02±9.69 net drop by 2.84 kg i. e. 4.31%. Study outcome is significantly greater than the observed a small decrease after 6 months (62.5±11.0 to 62.1±12.3kg, $P<0.01$) by Sachiko Honjo et al (Sachiko Honjo et al 2009) and significantly greater than

results from a Cochrane systematic review and meta-analysis (Floris A. Van De Laar et al 2005) observed drop in weight by 0.27% greater than found by Segal P. et al (Segal P. et al 1997) ie 1.4 kg in the miglitol group and Van De Laar F A reviewed only 0.27 kg a small decrease in weight at end point of study (Van De Laar F A et al 2005).

The reduction in the weight observed in this study is greater than observed by Canadian University Investigator Group for Miglitol (Chiasson JL et al 2001) i.e. 0.42 kg reduction.

The fasting blood sugar level in Group II treated with Miglitol dropped by 139.28±10.57 to 71.84±9.03 i.e. 48.40% which is significantly greater than the end point values found by Segal P. et al (Segal P. et al 1997) the mean fasting blood glucose decreased from baseline to endpoint by 10 mg/dl in the miglitol group.

The end point value in this study is greater than Van De Laar F A reviewed FBSL 9.36mg/dl in Results from a Cochrane systematic review and meta-analysis, The reduction in the FBSL observed in this study is greater than observed by Canadian University Investigator Group for Miglitol (Chiasson JL et al 2001) i.e. 1.0 mg/dl reduction Canadian University Investigator Group for Miglitol (Chiasson JL et al 2001) and greater than result of the fasting blood sugar level decreases found by Drent ML et al (Drent ML et al 2002),

The decrease in the post meal blood sugar level in this study is 200.9±20.24 to 107.68±16.92 i. e. 46.40% which is significantly greater than the endpoint value found by Segal P. et al (Segal P. et al 1997) in his the reduction in PBSL was 31 mg/dl. Significantly comparable with reviewed by Van De Laar and et al 48.6 mg %. The reduction in the PBSL value observed in this study is greater than observed by Canadian University Investigator Group for Miglitol (Chiasson JL et al 2001) ie 24.1mg/dl. The study outcome is statistically significantly greater than in a one-year study in which GLYSET was evaluated as monotherapy and also as combination therapy, there was a statistically significantly smaller decrease of -39 ($p \leq 0.05$)observed in mean g PBSL over time in the miglitol 50 mg 3 times daily monotherapy arm compared to placebo (U.S. Patent No. 4,639,436).

HbA1c: The HbA1c value in this study is dropped by 6.72±0.68 to 5.63±0.64 net drop by 1.09 i.e. 16.22%, study outcome is greater than the observed by Sachiko Honjo et al (Sachiko Honjo et al 2009) the net drop he found in HbA1c value was 7.8±1.2 to 7.3±1.0% (P<0.01). The reduction in HbA1c value is significantly greater than the findings of Segal P. et al (Segal P. et al 1997) reduction in HbA1c value by 0.75%. (P = 0.0021) and Results from a Cochrane systematic review and meta-analysis reduction by 0.68% (Van De Laar F A et al 2005). Johnston PS conducted trial show reduction in HbA1c value by 0.40% (Johnston PS et al 2000) our study shows greater reduction (P < 0.05- 0.01 vs. placebo) treated with miglitol 50 mg tid. The monotherapy with miglitol with 100 mg TDI for 36 weeks University Investigator Group for Miglitol observed the 0.02 % reduction in HbA1c (Chiasson JL et al 2001) the HbA1c investigation in our study is interestingly greater. The study outcome is statistically significantly greater than in a one-year study in which GLYSET was evaluated as monotherapy and also as combination therapy, there was a statistically significantly smaller decrease of -0.58 (p≤ 0.05)observed in mean glycosylated hemoglobin (HbA1c) over time in the miglitol 50 mg 3 times daily monotherapy arm compared to placebo (U.S. Patent No. 4,639,436).

The monotherapy of miglitol in group II lowers the HbA1c greater than Standl E, (Standl E et al 2001) observed in Improved glycaemic control with miglitol in inadequately controlled type 2 diabetics trial the addition of miglitol to sulphonylureas and metformin (per protocol analysis) produced a reduction in HbA1c (-0.55%, P = 0.04), our study outcome is comparable with Johnston PS (Johnston PS et al 1998(A)) observed the chronic treatment of African-American type 2 diabetic patients with alpha-glucosidase inhibition, Miglitol treatment was associated with a mean placebo-subtracted reduction in HbA1C from baseline of 1.19% at 6 months regardless of dose of miglitol in another study Johnston PS (Johnston PS et al 1998(B)) conducted for a period of 56 weeks to assess HbA1c treatment effects (placebo-subtracted change in HbA1c from baseline) at the 1-yr endpoint was -0.40%, (P < 0.05) to measure Advantages of alpha-glucosidase inhibition as monotherapy in elderly type 2 diabetic patients, with miglitol 50mg tid, Drent ML accessed Dose-dependent efficacy of miglitol, in type 2 diabetic

patients on diet alone for 24 weeks, resulted in -0.45% decrease in HbA1c value (Drent ML et al 2002), this suggest the better results of our study.

In a double-blind, randomized study, 100 mg miglitol tds or placebo was given orally with meals for a period of 24 weeks to access Long-term effectiveness of a new alpha-glucosidase inhibitor (BAY m1099-miglitol) in insulin-treated type 2 diabetes mellitus, proved significant decrease in HbA1c value by 16% which is comparable with our study (Mitrakou A et al1998), it proved that the decrease in HbA1c Value with miglitol 50 mg tid shows similar effect observed with miglitol 100 mg tid. Our study is good example of well designed trial, Scott JL et al (Scott JL et al 2000) reviewed that well designed trials of 6 to 12 months' duration in a total of 1783 patients with type 2 diabetes mellitus insufficiently controlled by diet alone or diet plus sulphonylurea agents have demonstrated that miglitol monotherapy 50 to 100mg 3 times daily (therapeutic range) significantly improves glycaemic control and decreases postprandial serum insulin levels. With miglitol 150 to 300 mg/day, the mean absolute reduction in glycosylated haemoglobin (HbA1c) level was 0.18 to 0.75%, and the net reduction in HbA1c value in our study is significantly greater. Group II treated with Miglitol alone shows significant decrease in FBSL, PBSL, weight and HbA1c.

Group III treated with Acarbose + *Salacia oblonga*, Table No. 23 Shows distribution of mean and SD values of weight, Fasting BSL, Post meal BSL, and HbA1C parameters in group III from baseline to 6 months follow up. In present study from the table No. 23. it is observed that average weight falls down from 65.86 kg at baseline to 63.02 kg at 6 months follow up.

Similarly, fasting BSL falls down from 139.28 gm% at baseline to 71.84 gm% at 6 months follow up. Post meal BSL is also fall down from 200.9 gm% at baseline to 107.68 gm% at 6 months follow up. HbA1c is also falls down from baseline i.e. 6.83% to 5.43% at 6 months follow up. And after applying Paired 't' test and ANOVA test this falls down / decrease from baseline to 6 months for all parameters in group III shows statistically highly significant ($p<0.01$). This is first attempt to access the combined effect of acarbose with *Salacia oblonga*; author does not find any study conducted before.

Group IV treated with Miglitol 50 mg tid in combination with *Salacia oblonga* 500mg tid Table No. 25. Shows distribution of mean and SD values of weight, Fasting BSL, Post meal BSL, and HbA1C parameters in group IV from baseline to 6 months follow up. In present study from the table No.25. it is observed that average weight falls down from 67.60 kg at baseline to 64.64 kg i.e. 2.96 kg at 6 months follow up. The fasting BSL falls down from 135.53 gm% at baseline to 74.50 gm% at 6 months follow up. Post meal BSL is also fall down from 193.1 gm% at baseline to 105.42 gm% at 6 months follow up. The HbA1c value reduced from 7.03 to 5.44 there is noticeable 1.59% reduction. After applying the ANNOVA test paired 't' test the decrease from baseline to end of study for all parameter in group IV shows statistical significant ($p<0.01$).

The Distribution of mean and SD values of all parameters in Group V (Miglitol + *Salacia oblonga*) from baseline to 6 months follow up is given in table No 27. The group V is treated with Miglitol 50mg tid and *Salacia oblonga* 500mg tid. The obsolete drop in weight from base line 65.85 kg to 63.82 kg at the end of study the net reduction in weight is 2.04 kg at the end of study. The reduction in the FBSL 139.28 to 72.40, PBSL 200.9 to 107.74, and HbA1c 6.98 to 5.60 found at six month intervention. By applying Student's Paired 't' test the average values of Weight, Fasting BSL, Post meal BSL and HbA1C are highly significantly decreased from base line to after 6 months in patients with Type – 2 Diabetic Mellitus in Group V (Miglitol + *Salacia oblonga*) ($p<0.01$) Value of "F" = 1721.4, $p<0.001$, highly significant By applying Tukey-Kramer Multiple Comparison Test there is extremely highly significant difference between mean values of Weight, Fasting BSL, Post meal BSL and HbA1C are highly significantly decreased from base line to after 6 months in patients with Type – 2 Diabetic Mellitus in Group V (Miglitol + *Salacia oblonga*) ($p<0.01$)

In this study In group VI, after treatment of Miglitol + *Salacia reticulata* the six months investigation found significant decrease in Weight, FBSL, PBSL, HbA1c values, table No.29. shows means SD values of all parameter in this group from base line to six months follow up. The mean deviation of weight from baseline to end of study is 66.36 to 63.98 kg i.e. 2.38 kg net weight loss. The fasting blood sugar level reduce from base line 137.94 to 75 mg% i.e. 62.94 mg% reduction. Post-prandial blood sugar level reduce

from201.65 mg% to 109.56mg%. The HbA1c value decrease from 7.16 to 5.62, the absolute reduction is 1.54%. By applying Student's Paired 't' test the average values of Weight, Fasting BSL, Post meal BSL and HbA1C are highly significantly decreased from base line to after 6 months in patients with Type – 2 Diabetic Mellitus in Group VI (Miglitol+ *Salacia reticulata*) ($p<0.01$).

Group VII treated with *Salacia oblonga* 500mg tid Table No. 31. Shows distribution of mean and SD values of weight, Fasting BSL, Post meal BSL, and HbA_1C parameters in group VII from baseline to 6 months follow up. In present study from the table No.31. it is observed that average weight falls down from 66.44 kg at baseline to 64.94 kg i.e. 1.50 kg at 6 months follow up. The fasting BSL falls down from 129.84 mg% at baseline to 70.90 mg% at 6 months follow up. Post meal BSL is also fall down from 195.12mg% at baseline to 111.6mg% at 6 months follow up. The HbA1c value reduced from 6.67to 5.89 there is noticeable 0.78% reduction. By applying Student's Paired 't' test the average values of Weight, Fasting BSL, Post meal BSL and HbA1C are highly significantly decreased from base line to after 6 months in patients with Type – 2 Diabetic Mellitus in Group VII (*Salacia oblonga*) ($p<0.01$)

Value of "F" = 1269.20, $p<0.001$, highly significant. By applying Tukey-Kramer Multiple Comparison Test there is extremely highly significant difference between mean values of Weight, Fasting BSL, Post meal BSL and HbA1C are highly significantly decreased from base line to after 6 months in patients with Type – 2 Diabetic Mellitus in Group VII (Salacia Oblonga)) ($p<0.01$). Some short duration studies has been published previously, which focus on significant reduction of postprandial glycemia (Heacock PM et al 2005; Williams JA et al 2007; Collene AL et al 2005), postprandial insulin response (Heacock PM) with use *Salacia oblonga* extract. The greater reduction in HbA1c, FBSL, PBSL weight in this study support the published studies regardless of their short duration and dose.

William and coworkers have studied the effect of *S.oblonga* extract (240 mg and 480 mg) on postprandial glycemia and insulinemia in patients with type 2 diabetes after ingestion of a highcarbohydrate meal. Both doses of the *Salacia* extract significantly lowered the postprandial positive area under the glucose curve (14 % for the 240 mg

extract and 22 % for the 480 mg extract) and the adjusted peak glucose response (19 % for the lower dose and 27 % for the higher dose of extract) compared to the control meal. The results suggest that *Salacia* may be beneficial for postprandial glucose control (Williams JA et al 2007).

Collene and coworkers studied the postprandial glycemic, insulinemic and breath hydrogen responses to a liquid nutritional product containing *Salacia oblonga* extract (100 mg; SOE) and two insulinogenic amino acids phenylalanine and leucine. *S.oblonga* extract was found to be a promising nutraceutical ingredient as it decreased glycemia (decrease in plasma glucose level and insulin level) and breath hydrogen excretion was 60% greater in the SOE-containing meals. Supplementation with amino acids had no significant additional effect on glycemia (Collene AL et al 2005)

Group VIII treated with *Salacia reticulata* 500mg tid Table No. 33. Shows distribution of mean and SD values of weight, Fasting BSL, Post meal BSL, and HbA_1C parameters in group VIII from baseline to 6 months follow up. In present study from the table No.33. it is observed that average weight falls down from 64.28 kg at baseline to 61.90 kg i.e. 2.38 kg net weight loss at 6 months follow up. The fasting BSL falls down from 136.88 mg% at baseline to 73.16 mg% at 6 months follow up. Post meal BSL is also fall down from 203.28 mg% at baseline to 112.82mg% at 6 months follow up. The HbA1c value reduced from 6.77 to 5.76 there is significant 1.01% reduction. By applying Student's Paired 't' test the average values of Weight, Fasting BSL, Post meal BSL and HbA1C are highly significantly decreased from base line to after 6 months in patients with Type – 2 Diabetic Mellitus in Group VII (*Salacia reticulata*) ($p<0.01$)

The decoction of *S. reticulata* roots is used in the treatment of itching and swelling, asthma, thirst, amenorrhea and dysmenorrhea (Tissera and Tha-brew 2001). The roots are acrid, bitter, thermogenic, urinary, astringent, anodyne, anti-inflammatory (Nadkarni 1993). The roots and stem of *S. reticulata* have been widely used in treating diabetes and obesity (Im R. *et al*. 2008; Li Y *et al*. 2008), gonorrhea and rheumatism (Im *et al*. 2008), skin diseases (Im R *et al*. 2008; Matsuda H. *et al*. 2002) and haemorrhoids (Nadkarni 1993). In addition, the water extracts of leaves of *S. reticulata* could be beneficial for the prevention of diabetes and obesity as its multiple effects such as the

ability to increase the plasma insulin level and lower the lipid peroxide level of the kidney (Yoshino K *et al*. 2009).

Kajimoto *et al* (Kajimoto *et al*. 2000) reported that a double-blind placebo-controlled study performed in Japan resulted in significantly decreased blood sugar levels in humans with mild type II diabetes, receiving *S. reticulata* extract as part of their diet, as compared to control. In a sucrose tolerance test on human volunteers, pretreatment with the aqueous extract of *S. reticulata* prior to sucrose loading significantly sup-pressed postprandial hyperglycemia (Shimoda *et al*. 1998; Tanimura *et al*. 2005). Water extract pre-pared from *S. reticulata* leaves can also prevent diabetes and obesity similarly to that of roots and stems (Yoshino *et al*. 2009). Mangiferin, one of the main components in *Salacia* species (Li *et al*. 2004), has been reported to be potent α-glucosidase inhibitors that have been shown to inhibit increases in serum glucose levels (Yoshikawa *et al*. 1997, 1998, 2001). Aqueous extract of *S. reticulata* strongly inhibited the activities of α-glucosidase and α-amylase, but not that of β-glucosidase (Shimoda *et al*. 1998)

Jayawardena M.H.S. et al (Jayawardeda M.H.S. et al 2004) conducted a randomised single centre double blind cross over clinical trial to investigate the effects of a herbal tea containing *Salacia reticulata* (Kothala Himbutu tea) in patients with type II diabetes mellitus, a statistically significant fall in HBA1c was seen with the active drug compared to a rise in HbA1C with the placebo group (0. 54±S.D. 0.93) versus −0.3±S.D. 1.05; $P < 0.001$. The HbA1C reduction in our study is significantly greater and *Salacia reticulata* contains alpha glycosidase inhibitor kotalanol (Yoshikawa et al., 1998), which has an action similar to that of acarbose.

Our results confirm that *Salacia reticulata* in the diabetes treatment produced significant falls in HbA1C levels. Jayawardena M.H.S. et al (Jayawardeda M.H.S. et al 2004) observed a small but non significant weight gain in patients treated with *Salacia reticulata*, in contrast, our study shows noticeable reduction in weight i.e. 2.38 kg's. The drop in blood sugar level is greater than the observed by Radha R. et al (Radha R et al et al 2009) conducted trial for 90 day consisting of diabetic II patients treated with 2 gm/day *Salacia reticulata*.

Table No. 35. shows the means distribution of mean SD values of Weight (Kg) from base line to 6 months follow up in all groups under study, all group shows significant reduction in the weight base line up to end of study and unpaired 't' test applied for all group as shown in table no. 13. It shows significant difference between means values of weight at base line at 6 months follow up of study. The inter comparison of weight reduction of all groups, Group VII vs. Group VIII shows significant difference in weight reduction as compared with other groups ($p<0.05$) as reported by Jayawardena M.H.S. (Jayawardeda M.H.S. et al 2004). The Group V vs. Group VIII also shows significant difference and Group VI vs. Group VIII is too. The unpaired 't' test between Group I and Group II, Group III, Group IV, Group V Group VI shows no significant difference but show significant difference between Group I and Group VII, Group I and Group VIII, $p=1.13$ and $p=1.34$ respectively. The percentage decrease in weight by all group is listed in table No. 33, the percentage decrease by Group IV is 4.38% and it is highest decrease among all groups. It suggests that Group IV is favorable among all groups in respect to lowering of body weight. All groups' shows noticeable reduction in body weight but Group VII shows lowest drop in body weight among all group's i. e. 2.23%. When Group I shows 3.70% reduction in body weight while Group II shows 4.31% reduction in body weight. When Group I compare with Group II the percentage decrease by Group II is elevated than Group I. Group I is not superior to any other group except Group VII in lowering of body weight. The Combination of Acarbose with *Salacia oblonga* and *Salacia reticulata* shows noteworthy reduction in body weight than acarbose group, it proposes that the combination of acarbose with Salacia species is more advanced than acarbose alone, the percentage body weight fall down by Group III and Group IV is 4.31% and 4.38% respectively. The Group I shows equivalent decrease in body weight like Group VIII, but slightly greater than Group V, Group VI, Group VII.

The Group II shows 4.31% decrease in body weight, it is slightly lower than Group I. but greater than Group V, Group VI, and Group VII. The combination of miglitol with Salacia species also confirms the decrease in body weight, the miglitol alone shows significant 4.31% reduction in body weight than its combination with Salacia species and it is 3.59% for both types of combinations. It proves miglitol alone is more efficient than its combination with *Salacia oblonga* and *Salacia reticulata*. The

comparison of *Salacia oblonga* and *Salacia reticulata* vivid that the later species is more effective than previous one in respect to lowering of body weight.

Table No. 26. Distribution of mean and SD values of Fasting BSL (mg %) from baseline to 6 months follow-up in all groups under study, all Group shows significant drop in the Fasting BSL from base line up to end of study and unpaired 't' test applied for all group as shown in table No. 30. It shows significant difference between means values of FBSL at base line at 6 months follow up of study. The inter group comparison of reduction of fasting BSL of all groups group VI vs. VII shows significant difference in FBSL $p<2.54$. When Group I is compared with group III (Acarbose + *Salacia oblonga*ta) the mean difference FBSL value is $p=0.044$. The percentage decrease with both groups is 48.36% and 48.42% respectively, it suggest that the group III shows significant reduction in FBSL than Group I. In the comparison of Group I with all groups, it shows significant difference between Group I and Group VI $p=1.84$ and the percentage decrease in FBSL with these two groups is 48.36% and 45.63% respectively. These values suggest that Group I is more promising than Group VI.

When group II is compared with other groups, these is significant difference observed when Group II is compared with Group VI $p= 1.87$. The percentage decrease in FBSL value with both groups is 48.40% and 45.63% it shows greater reduction with Group II than Group VI.

The acarbose and miglitol shows almost equal reduction, the percentage decrease with these two groups is 48.36% and 48.40% respectively. The combination of acarbose with *Salacia oblonga* and *Salacia reticulata* also reduce FBSL, the percentage decrease in FBSL with these groups is 48.42% and 45.03 % respectively. The miglitol alone shows significant reduction in FBSL, the percentage decrease is 48.40%. The combination of miglitol with *Salacia oblonga* and *Salacia reticulata* also shows reduction in FBSL, the percentage reduction in FBSL with combination of miglitol with these species is 48.08% and 45.39 respectively. It suggests that miglitol alone is more effective than its combination with Salacia species.

The maximum percentage decrease is 48.42% in FBSL is found in Group III, the Group III is treated with Acarbose + *Salacia oblonga* and the decrease in FBSL from

base line to be 139.28 to 71.84 mg%, FBSL, the Group III is more promising than any other group in respect to lowering of fasting blood sugar level. The *Salacia oblonga* and *Salacia reticulata* also show significant reduction, the percentage decrease in FBSL value with these two medications is 45.39% and 46.55% respectively but this reduction not greater than acarbose alone and acarbose + *Salacia oblonga* but slightly greater than combination of acarbose with *Salacia reticulata*. When miglitol group is compared with *Salacia oblonga* and *Salacia reticulata* it is observed that miglitol shows greater reduction than both groups. Very interesting thing observed is the reduction of FBSL with combination of acarbose and miglitol with *Salacia reticulata* species, both cases shows decrease in FBSL reduction than compared with acarbose and miglitol alone, the acarbose + *Salacia reticulata* shows 45.03% net percent decrease, miglitol + *Salacia reticulata* shows 45.63% net percent decrease and acarbose and miglitol alone shows 48.36%, 48.40% decrease in FBSL respectively. It suggests that combination of *Salacia reticulata* either with acarbose or with miglitol is not effective as compared with acarbose and miglitol alone.

Table No. 27. Distribution of mean and SD values of Post meal BSL (mg %) from baseline to 6 months follow-up in all groups under study, all group shows significant drop in the Post meal BSL from base line up to end of study and unpaired 't' test applied for all group as shown in table No. 31. It shows significant difference between means values of PBSL at base line at 6 months follow up of study. Table No. 31. shows unpaired't' test, post meal BSL at 6 months follow up. The inter group comparison of reduction of PBSL of all groups, Group IV vs. Group VIII shows significant difference in FBSL $p<2.53$ and Group IV vs. Group VII $p=2.47$, the percentage decrease by these two groups is 45.41% and 44.50% respectively. The percentage decrease in post meal BSL by Group I is 46.43% the Group I is more effective than any other group in the study in respective with post meal BSL. Group II, Group III shows similar reduction, while Group VII shows lowest reduction in post meal BSL in all groups. Applying unpaired't' test when Group I compared with Group II it does not shows any significant difference, same case with Group III, but when group I compared with Group IV, Group V, Group VI, shows significant difference and when same compared with Group VII ($p=1.51$) and Group VIII shows highly significant difference especially when compared with VIII

(p=1.78). Comparison of Group II with Group I, Group III, Group V, Group VI does not shows significant difference but when compared with VII and VIII shows significant difference p= 1.02 and p=1.14 respectively.

The percentage decrease of post meal BSL of all groups showed in table No 33. Group I shows maximum 46.43% decrease in post meal BSL compared with all groups, all groups shows significant difference but Group VII shows lowest 42.80% decrease in post meal BSL among all groups. It suggests that Group I is most promising among all group in respect to lowering of post meal BSL. When Group I is compared with Group II, Group I shows slight higher value than the Group II, Group III and Group V but shows significant higher value than Group IV, Group VI and Group VIII, but shows maximum difference when compared with Group VII.

The percentage decrease in PBSL by Group II is 46.40%, the comparison of Group II with other groups, Group II shows similar decrease in PBSL like Group III but not greater than Group V and shows higher decrease in PBSL than Group VII and Group VIII.

Table No. 28. shows distribution of mean and SD values of HbA1C (in %) from baseline to 6 months follow up in all groups under study, all group shows noteworthy fall in HbA1c value from base line u to end of study and unpaired 't' test applied for all group as shown in table no. 32. The inter group comparison between Group I and Group II shows significant difference p=2.46, with other groups also shows significant difference Group I vs. Group V p= 2.69, Group I vs. Group VI p= 3.04 but higher significant difference is observed between Group I vs. Group IV p= 4.03 and Group I vs. Group III p= 4.00 and slight differentiation observed with Group I vs. Group VII and Group VIII p= 0.54 and p= 0.45 respectively. Among all groups Group I vs. group IV shows very significant difference, while Group III vs. Group IV shows negligible difference in HbA1c values.

When Group II is compared with Group III it also shows significant difference in reduced HbA1c value p= 1.53, Group II vs. Group IV p= 1.72, Group II Group V p= 0.21, Group II Group VI p= 0.07, Group II vs. Group VII 1.97 ND Group II vs. Group VIII p= 0.94. All values suggest that there is negligible difference between Group II vs.

Group VI. The percentage decrease in HbA1c value for all groups is shown in table No. 33. among all groups Group V shows highest reduction in HbA1c value by 24.64% and lowest by Group VII 11.69%. Other groups also show significant reduction in HbA1c, the reduction in HbA1c value by Acarbose group is 12.11% when it is compared with other groups it is less than any other group except Group VII all other groups shows higher reduction than Group I. The combination of acarbose with *Salacia oblonga* and *Salacia reticulata* are superior to acarbose alone in respect with lowering of HbA1c, both combination shows major reduction in HbA1c 46.40% and 45.41% respectively. The values suggest that Acarbose alone is not good for lowering of HbA1c.

HbA1c decreased by Group II is 16.22%. When it is compared with other groups does not shows any significant greater value to any other group all group shows significant higher value except Group VII and Group VIII. The combination of miglitol with *Salacia oblonga* shows very significant reduction than miglitol alone and combination with *Salacia reticulata* shows noticeable reduction too and Group V is very promising among all groups in respect to lowering of HbA1c. It suggests that combination of miglitol with Salacia species is very excellent in respect to lowering of HbA1c.