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A RETROSPECTIVE STUDY ON EVALUATION OF COMPARATIVE EFFICACY BETWEEN THREE COMBINATIONAL THERAPIES FOR TYPE 2 DIABETES MELLITUS

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ABSTRACT

Diabetes is a condition in which the body either does not produce enough, or does not properly respond to insulin - a hormone produced in the pancreas. Insulin enables cells to absorb glucose in order to turn it into energy. In diabetes, the body either fails to properly respond to its own insulin, does not make enough insulin or both. This causes glucose to accumulate in the blood often leading to various complications. This study mainly focused on Evaluation of efficasy between the combinations therapies for Type 2 Diabetes Mellitus. The aim were achieved through monitoring the blood sugar parameters, to assess the changes in glycemic control in patients with diabetes mellitus. It's a retrospective study. Overall the study results conclude that a combination of Metformin with Acarbose, Glimepiride and Sitagliptin therapy have greater impact on control of FBS, PPBS and HbA1c, on the other hand Metformin and sitagliptin combination reveals significant reduction in FBS, PPBS and HbA1c in diabetic patients compare with Metformin + Acarbose and Metformin + Glimepiride therapies. Many research articles also conclude that metformin therapy with sitagliptin have more impression on diabetic control.

Key words: Diabetes mellitus, Metformin, Sitagliptin, Acarbose and Glimepiride.

INTRODUCTION

According to FDA the treatment of type 2 diabetes mellitus (T_2DM) has included the use of metformin (particularly in the overweight patient) and sulfonylurea (SU) (in both lean and overweight patient), as first line anti-diabetic therapies world over. Prior to 1995, the use of SU was the most popular anti-diabetic therapy. SU's act by increasing insulin secretion in a glucose-independent manner, thereby risking severe unpredictable hypoglycemia, particularly if the meal is delayed or if its carbohydrate quantity reduced.[1]

The use of metformin only became popular post 1995. It only makes sense that they continue to remain mainstay therapy as despite their problems they are best suited to deal with the original pathogenic triumvirate theory for T_2DM proposed by

Ralf Defranzo, (qualitative and quantitative beta cell failure and insulin resistance at level of liver and peripheral tissue). This was particularly true since there was no agent that could help improve health of the beta cell and cause insulin release in a glucose dependent manner.[2] This all changed once it was learnt that the incretin system was involved in the pathogenesis of T_2DM. Failure of this incretin system has been implicated in progression of beta-cell failure and therefore any therapy that can augment this system has been shown to promote beta cell health and insulin release in a glucose-dependent manner.[3]
The UKPDS was the first to show that the combination of SU and metformin resulted in a progressive decline in β cell function and by 3 years up to 50% of diabetic patients can require an additional agent to maintain the HbA1c < 7.0%. Moreover, the percentage of diabetic patients classified as adequately controlled while mostly on these therapies still remains a challenge with a majority (> 50%) of the patients having a HbA1c > 7%. From the above data it seems clear that existing popular therapies are not only ineffective but are associated with a significant amount of morbidity (weight gain and hypoglycemia). [4] Diabetes is a huge problem in India affecting a large multitude of population. In India, about 50.9 million people suffer from diabetes, and this figure is likely to go up to 80 million by 2025, making it the 'Diabetes Capital' of the world.[5]
Diabetes affects people both in urban and rural India though the impact on urban India is higher. It is also becoming a growing problem in the slums of India. 1 out of 4 people living in urban slums of Chennai suffer from diabetes, which is three times higher than the national average of about 7%.[6]

- Type 1 diabetes (previously known as insulin-dependent or childhood-onset diabetes) is characterized by a lack of insulin production.
- Type 2 diabetes (formerly called non-insulin-dependent or adult-onset diabetes) is caused by the body's ineffective use of insulin. It often results from excess body weight and physical inactivity.
- Gestational diabetes is hyperglycemia that is first recognized during pregnancy.[7]

Other Diabetes causes

- There is a variety of other potential diabetes syndrome increases production of the cortisol Hormone, which serves to increased blood glucose levels. An over-abundance of cortisol can cause diabetes.
- **Glucagonoma**. Patients with Glucagonoma may experience diabetes because of a lack of equilibrium between levels of or-insulin production and glucagon production.

Steroid induced Diabetes (steroid diabetes) is a rare form of diabetes that occurs due to prolonged use of glucocorticoid therapy.[8]

Blood-glucose targets for people with Diabetes (Normal, Goal, Action suggested if)

- Parameter Normal Goal Action suggested if
- Pre-prandial Fasting Glucose <110 mg/dl, 80-120 mg/dl, <80 or >140 mg/dl
- 2h postprandial Glucose <140 mg/dl, <140 mg/dl, >180 mg/dl
- Bedtime <120 mg/dl, 100-140 mg/dl, <100 or >160 mg/dl
- HbA1c _ 6%, < 6.5 %, >8 %

Autoimmune beta cell destruction is thought to be triggered by an environmental event, such as a viral infection. Genetically determined susceptibility factors increase the risk of such autoimmune phenomena.[9]

METHODOLOGY

STUDY DESIGN

A Retrospective study was done in patients with type 2 diabetes mellitus receiving Combinational therapies in three groups to find out the glycemic control of the drug. In the study totally three groups were separated based on a combination of anti-diabetic drugs. The efficacy of the drugs compared between the groups. The details of combination drugs mentioned in the below.

S.No	Groups	Combinational Therapy
1.	Group A	Metformin + Acarbose (500 mg + 25-50 mg)
2.	Group B	Metformin + Glimepiride (500 mg + 1- 2 mg)
3.	Group C	Metformin + Sitagliptin (500 mg + 25-50 mg)

STUDY POPULATION

Based on the inclusion and exclusion criteria, 120 patients were included in the study

1. Inclusion criteria

- All the inpatients of either sex of age between 18 to 80 years for undergoing treatment in the in the hospital will be taken for the study
- Patients were to have a treatment duration of atleast 2 years and no use of a comparator regimen after the index date
- Patients with past medical and medication histories also included

2. Exclusion criteria

- Records which did not have proper lab parameters
- Deletion or addition of drugs in the combination therapy
- Patients with known surgical histories
- Known and suspected cases of allergies
- Pregnant woman's

DATA COLLECTION

Medical records of the patients from the database were analyzed to evaluate the glycemic control in patients under combinational therapy. Baseline values and follow-up values for FBG, PPBG, and HbA1C were assessed.

DESIGN OF PATIENT PROFORMA

The patient proforma was designed to include Register no., age, sex, height, weight, BMI, diagnosis, duration of diabetes and combinational therapy, family history of diabetes and personal history. The lab parameters like FBG, PPBG, HbA1C, were collected for 2 years with the dates of prescribing of combinational therapy, the data was collected according to the month intervals (initial, 6^{th} month, 12^{th} month, 18^{th} month)

DATA ANALYSIS

The comparison of Glycated hemoglobin, fasting blood sugar and post-prandial blood sugar were analyzed by using one way ANOVA test. Data analysis was done with the help of computer using by graph pad prism pad 6 and Microsoft excel. Using this software range, frequency, percentage, mean, standard deviation, p- values were calculated. A p value less than 0.05 is taken to denote significant relationship.

RESULTS

Table 1. Fasting Blood Sugar Levels between the Month Intervals

Month Interval	Group A	Group B	Group C
	Mean ± S.D	Mean ± S.D	Mean ± S.D
Initial Value	162.95 ± 5.24	150.7 ± 1.25	138.7 ± 1.25
6^{th} Month	141.14 ± 3.80	137.95 ± 3.63	129.95 ± 3.63
12^{th} Month	138.15 ± 3.94	123.52 ± 1.77	101.52 ± 1.77
18^{th} Month	126.50 ± 2.51	123.12 ± 2.92	101.12 ± 2.92
P Value	0.0017	0.0017	0.0033

Figure 1. Fasting Blood Sugar Levels between the Month Intervals for Metformin and Acarbose

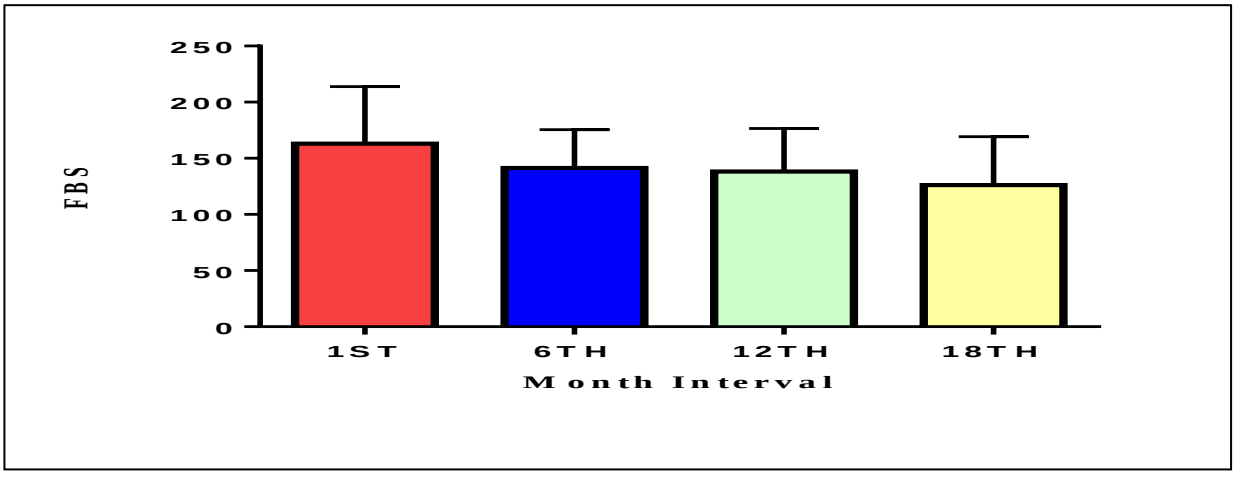


Figure 2. Fasting Blood Sugar Levels between the Month Intervals for Metformin and Glimepiride

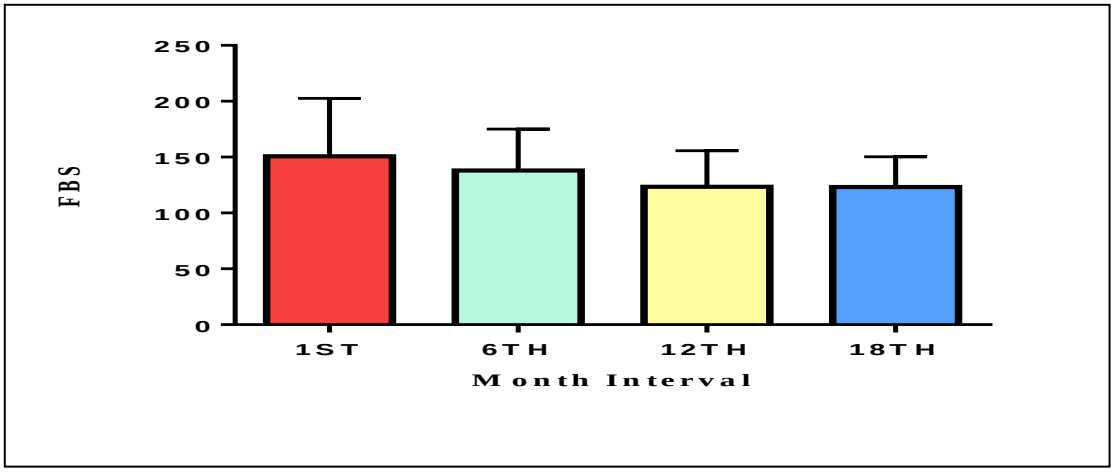


Figure 3. Fasting Blood Sugar Levels between the Month Intervals for Metformin and Sitagliptin

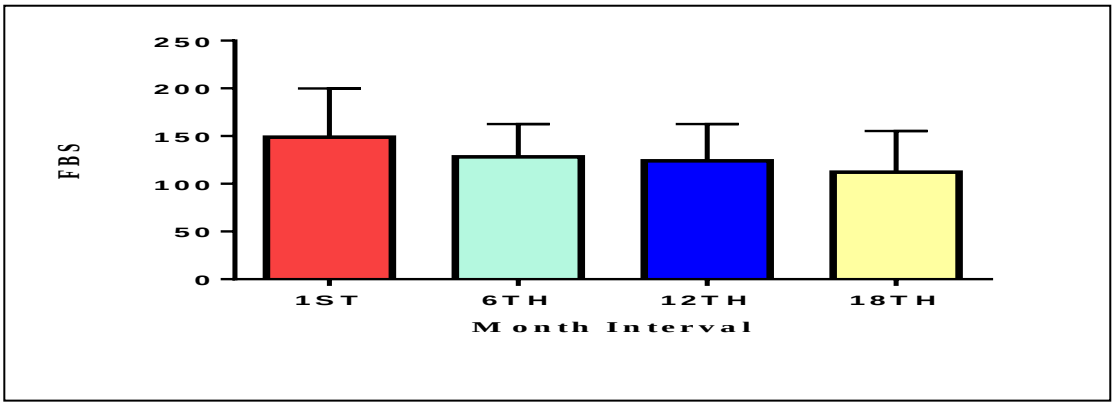


Table 2. ANOVA Comparison Fasting Blood Sugar between OHA Groups

S.no	OHA Regimen	Mean ± S.D	P Value
1	Metformin + Acarbose	142 ± 1.03	**0.0031**
2	Metformin + Glimepiride	133.82 ± 2.21	
3	Metformin + Sitagliptin	120.07 ± 2.21	

Figure 4. ANOVA-Comparison Fasting Blood Sugar Profile between three OHA regimens

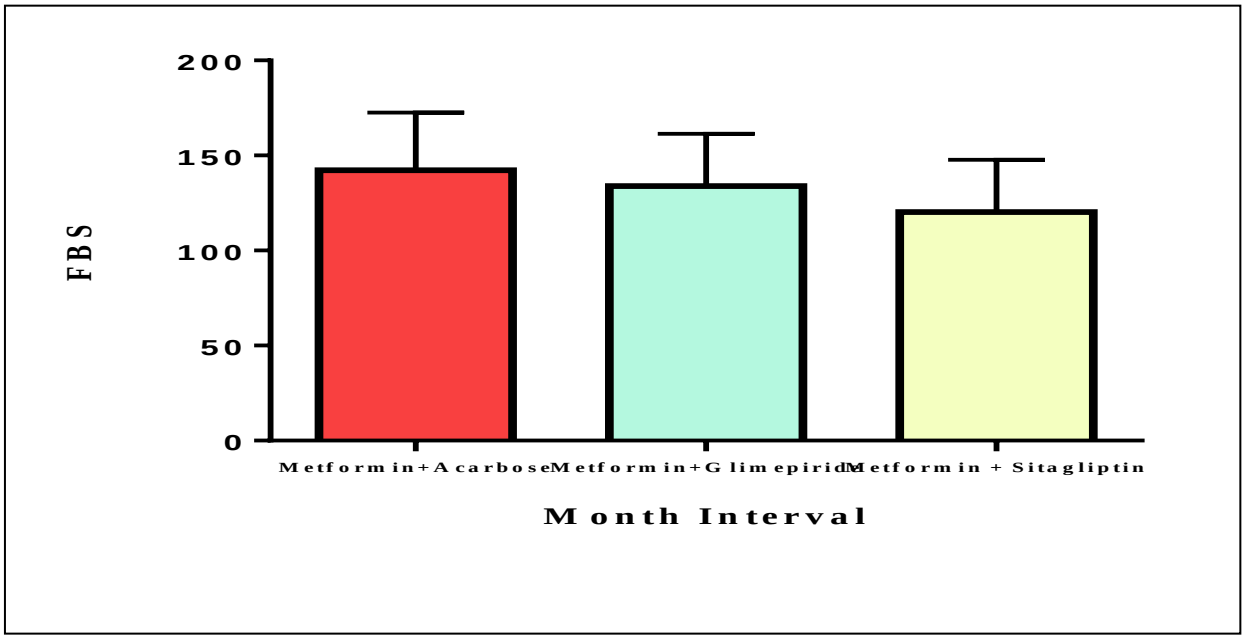


Table 3. Glycated Hemoglobin between the Month Intervals for Metformin and Acarbose

Month Interval	Group A	Group B	Group C
	Mean ± S.D	Mean ± S.D	Mean ± S.D
Initial Value	12.3 ± 2.03	7.89 ± 1.07	8.7 ± 2.18
6th Month	7.3 ± 1.18	7.14 ± 0.86	6.21 ± 2.18
12th Month	8.2 ± 1.73	7.03 ± 1.07	6.45 ± 2.2
18th Month	8.2 ± 1.36	5.83 ± 1.07	5.67 ± 1.27
P Value	<0.0001	<0.0001	<0.0001

Figure 5. Glycated Hemoglobin between the Month Intervals for Metformin and Acarbose

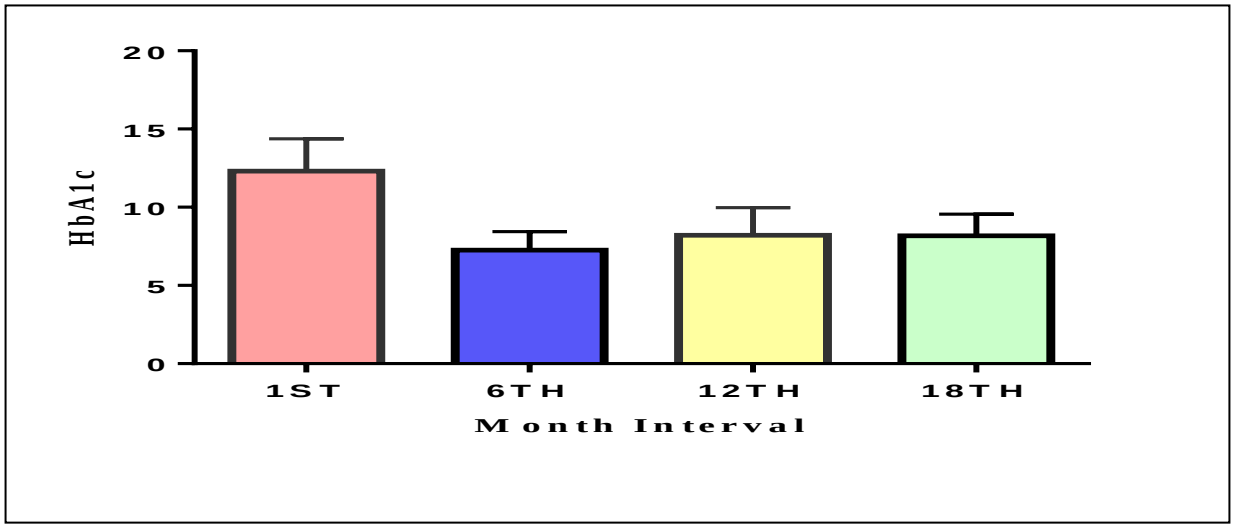


Figure 6. Glycated Hemoglobin between the Month Intervals Metformin and Glimepiride

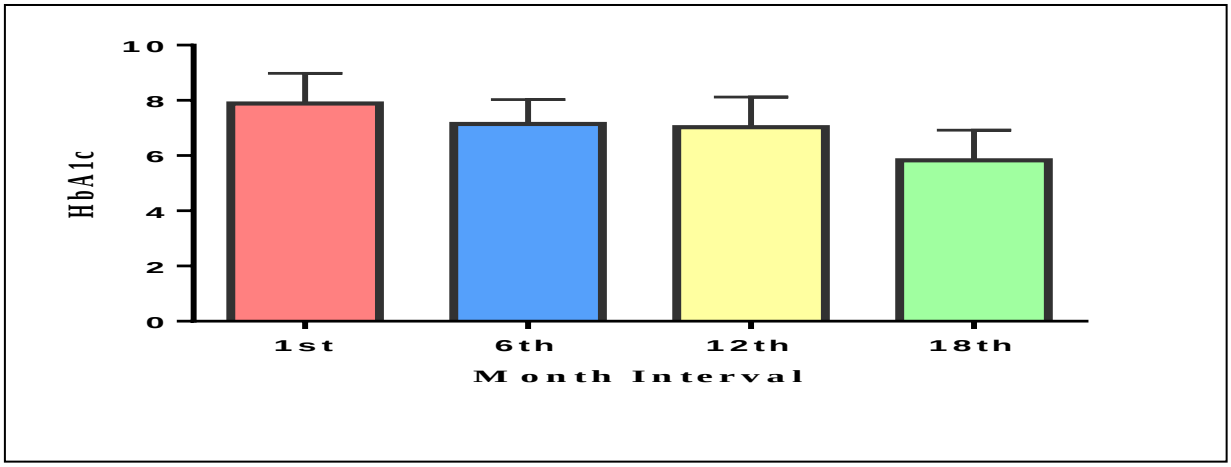


Figure 7. Glycated Hemoglobin between the Month Intervals Metformin and Sitagliptin

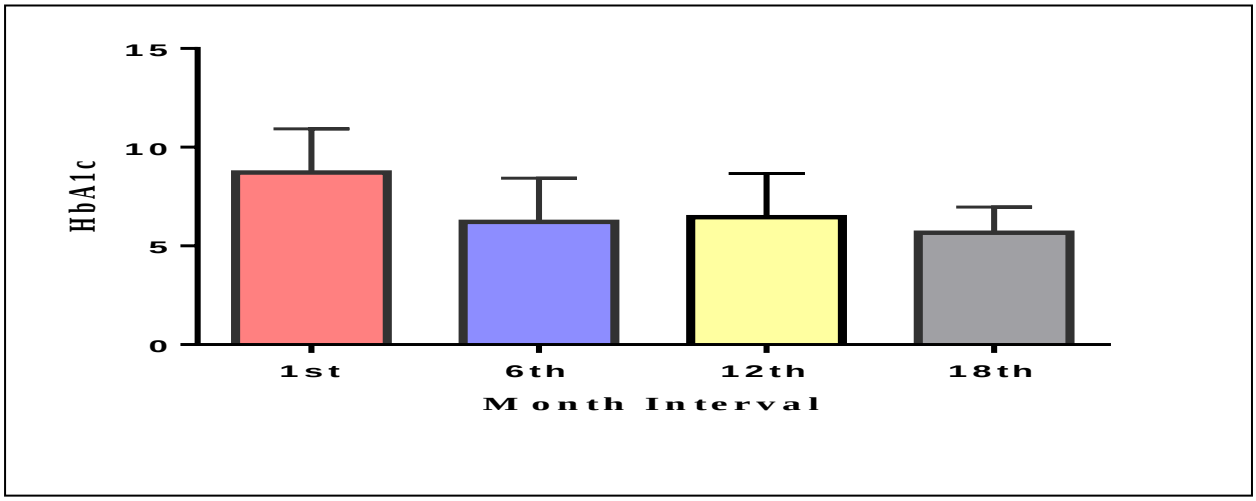
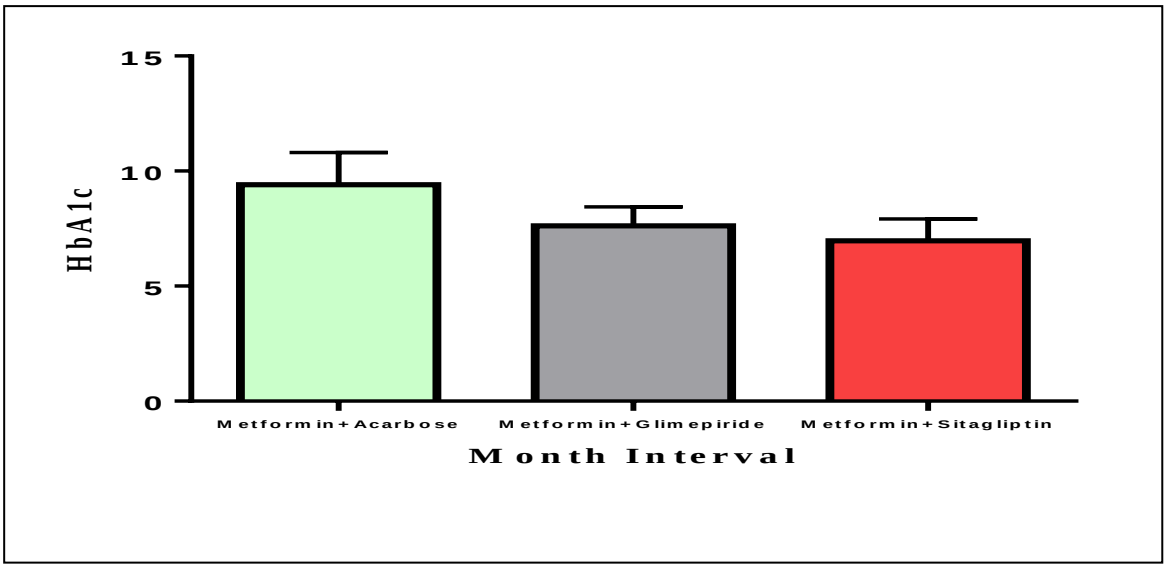


Table 4. ANOVA Comparison of Glycated Hemoglobin between OHA Groups

OHA Regimen	Mean ± S.D	P Value
Metformin + Acarbose	8.9 ± 1.42	**<0.0001**
Metformin + Glimepiride	6.97 ± 2.1	
Metformin + Sitagliptin	6.76 ± 1.8	

Figure 8. Comparison of Glycated Hemoglobin Profile between Three OHA Regimens



DISCUSSION

A total of 120 diabetic patients was included in the study. All those who were included in the study were from < 40 to > 70 years.

In the study out of 120 patients 2.52 % of patients were in age of less than 40 years, 10.83 % of patients were in the age group of 41-50 years, 26.66 % of patients were age group of 51-60 years, 35.83 % of patients were in the age group of 61-70 years and 24.16 % of patients were in the age group of more than 70 years.

Based on the combination therapies the patients were divided into three groups. Totally 40 patients in each group. Each group has a more patient ratio between the age group of 51-60 and 61-70.

Among in 40 patients in each group, 22 male patients and 18 female patients in group-A, 24 male patients and 16 female patients in group-B and 25 male patients and 15 female patients in group-C. Out of 120 patients, 55 (45.8 %) patients come across PMH interval between 11-20 years, 37 (30.8 %) patients belongs to the range of 1-10 years and 28 (23.3 %) patients have past medical histories more than 20 years.

A total of 40 patients in each group, 32 patients have PMNHs and 8 patients are having no histories for type-2 DM in group-A, a result of group-B and C shows all the 40 patients have PMNHs.

Out of 120 patients, 6 (5 %) patients with them the history of alcoholic, 4 (3 %) patients with smoking habits, and 20 (16.6 %) patients have alcoholic also smoking histories and 90 (75 %) patients are with no histories of alcohol, smoking and others. Among 40 patients in each group, 13 (32.5 %) patients in group-A, 7 (17.5b %) patients in group-B and 11 (27.5 %) patients in group-C have social histories.

In patients with genetic dispositions, 27 (67.5 %) patients have a history of DM in their father (13), mother (3), both (2) and father, mother and brothers (9) in group-A. 23 (57.5 %) patients have a history of DM in their father (7), mother (4), both (6) and father, mother and brothers (6) in group-B. 27 (67.5 %) patients have a history of DM in their father (7), mother (7), both (6) and father, mother and brothers (7) in group-C.

Out of 120 patients, 20 (16.6 %) patients are with giddiness, 2 (1.6 %) patients with weight gain, 6 patients with weight loss, 6 (5 %) patients with tiredness, 2 (1.6 %) patients with excessively hungry and 84 (70 %) patients are with free symptoms.

Attention to Diabetes Mellitus with Co- morbidities, among in 120 patients, 4 (3.3 %) patients with polyps, 34 (28.3 %) patients with HTN, 12 (10 %) patients with persistent body pain, 2 (1.6 %) patients with UTI, 5 (4.1 %) patients with non-healing wound, 10 (8.3 %) patients with skin problems and 1 (0.8 %) patient with complaints of leg swelling.

A p value of less than 0.05 indicates a significant difference between Metformin and Acarbose, Metformin + Glimepiride, Metformin + Sitagliptin groups. They're compared groups by one way analysis of variants at 95% confidence interval.

The fasting blood glucose results showed that significant reduction in all groups after 3rd, 6th and 18th month of treatment as compared to first reading

(Table: 1 & Figure: 1,2,3). OHA regimen group-C 120.07 ± 2.21 (Metformin + Sitagliptin) shows greater impact on FBS than OHA regimen Group-A (Metformin + Acarbose) and B (Metformin+ Glimepiride). Comparison between Group-A (Metformin + Acarbose) and B (Metformin+ Glimepiride) shows that Metformin+ Glimepiride (Group-B) therapy have a substantial reduction in FBS 133.82 ± 2.21 than Metformin + Acarbose (Group-A) 142 ± 1.03 (Table: 2 & Figure: 4).

Among the 40 patients in each group, Glycated Hemoglobin between the 6^{th}, 12^{th} and 18^{th} Month Intervals for Metformin and Acarbose, Metformin+ Glimepiride (6.97 ± 2.1) and Metformin + Sitagliptin (6.76 ± 1.8) reveals that p-value <0.0001. Both group B and C have a very good control in Glycated Hemoglobin compare with Metformin + Acarbose (8.9 ± 1.42) (Table: 3 & Figure: 5, 6, and 7). Comparison between the three groups shows that metformin + Sitagliptin combination have very good control in HbA1c compare with other groups (Table: 4 & Figure: 8).

CONCLUSION

Diabetes mellitus (DM) is among the most common chronic diseases in the world, affecting an estimated 180 million people in 2008. Available treatments focus on reducing hyperglycemia and improving insulin sensitivity. These modalities are attractive in theory, as they appear to target the primary defects associated with type 2 DM. The primary goal of treatment is to target glycemic control by maintaining the HbA1C level at 6- 7% decrease the incidence of microvascular and macro vascular complications without predisposing patients to hypoglycemia.

Overall the study results conclude that a combination of Metformin with Acarbose, Glimepiride and Sitagliptin therapy have greater impact on control of FBS and HbA1c, on the other hand Metformin and sitagliptin combination reveals significant reduction in FBS and HbA1c in diabetic patients compare with Metformin + Acarbose and Metformin + Glimepiride therapies. Many research articles also conclude that metformin therapy with sitagliptin have more impression on diabetic control. the study also confirmed that, Sitagliptin, a DDP-4 antagonist is as efficacious as Glimepiride in reducing HbA1C and fasting blood sugars. Sitagliptin was generally well tolerated, with a lower risk of hypoglycemia relative to Glimepiride and with significant weight loss as compared to Glimepiride.

Sitagliptin should be used to its maximum potential, started early in the disease process to maintain and preserve beta cell function [10] and preferably used in combination with Metformin in order to achieve the maximum reduction in HbA1c. [11] All recent clinical trials hint to the benefit of the early use of sitagliptin, alone or in combination, of any antidiabetic medication.

Sitagliptin, acarbose and Glimepiride to metformin monotherapy, produced significant improvement in glycemic control. The Benefits were more with combination therapy in comparison to monotherapy.[12]

Finally the Dictum is **"*Diabetics are naturally sweet and like a roller coaster. It has its ups and downs, but it's your choice to scream or enjoy the ride".***

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