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A STUDY COMPARING THE CLINICAL EFFICACY OF ORAL ANTI-DIABETIC AGENT WITH GLYCOSYLATED HAEMOGLOBIN (HbA1c) LEVELS IN TYPE II DIABETES MELLITUS

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Abstract:
Background: *Type II diabetes mellitus is a chronic metabolic disease in which there are high levels of glucose (sugar) in the blood. It is a condition characterized by high blood glucose level is caused by either a lack of insulin in the body or the body is unable to use insulin efficiently. With type II diabetes, the body either doesn't produce enough insulin, or it resists insulin.HbA1c levels are reflective of blood glucose levels over the past 6-8 weeks and don't reflect daily ups and downs of blood glucose.*
Objective: *A study was conducted to compare the clinical efficacy of oral hypoglycemic agents in type II diabetes patients by using* HbA_{1c} *as a diagnostic test to predict clinical outcome. And also to identify those with or at a higher risk for developing macro and micro-vascular disease associated with diabetes.*
Method: *A "descriptive, observational randomized& prospective study" was carried out to find the Clinical efficacy of oral hypoglycemic agents on type II diabetes patients by routinely monitoring HbA1c levels in the hospital for every 6months from Nov2012-April2016.*
Result & Conclusion: *It was found that the prevalence of type II diabetes is more common in women's that compared to men's .There was a significant reduction in glycosylated hemoglobin by considering the clinical efficacy of oral hypoglycemic agents by routinely monitoring the integrated index and changes in the baseline with the drug, which lead to decrease in HbA1c levels in Type II diabetes patients.*
Key Words: Oral Hypoglycemic Agents, Type II Diabetes Mellitus, Reduction in Glycosylated Hemoglobin & Body Mass Index.

Introduction:

Type II diabetes (Non-Insulin dependent diabetes mellitus, NIDDM) is a progressive condition and a metabolic disorder in which the body becomes resistant to the physiological effects of insulin and gradually loses the capacity to produce enough insulin by the pancreas. [2]In type II diabetes your body does not use insulin properly,this is called insulin resistance. [1]In type II diabetes thepancreas doesn't produce enough insulin (reduced insulin production) or the insulin doesn't work effectively or the cells in the body don't respond to insulin effectively (known as insulin resistance). [3]Type II diabetes represents ~85–90% of all cases of diabetes and is very common, about 10 million cases every year in India. And about 300 million people will subsequently have the disease by 2025.[6-8]

Oral hypoglycemic agents are also useful in the treatment of type II DM which includessulphonylureas, biguanides, alpha-glycosidase inhibitors,meglitinide analogs, and thiazolidinedione.The main objective of these drugs is to correct the underlying metabolic disorder, like insulin resistance or inadequate insulin secretion; and should be prescribed in combination with an appropriate non-pharmacotherapy. Diet and lifestyle strategies help to reduce weight, improve glycemic control and reduce the risk

of cardiovascular disease, which account for 70% to 80% of deaths among those with diabetes and can be managed with lifestyle modifications and medication. Type 2 diabetes is progressive disease and needs to be managed effectively to prevent macro vascular and micro vascular complications. [4] Most patients with type II diabetes are obese, and obesity itself causes some degree of insulin resistance. Patients who are overweight may have an increased percentage of body fat distribution predominantly in the abdominal region. Nevertheless, such patients are at increased risk of developing macro vascular and micro vascular complications.Having pre-diabetes is a risk factor for getting type II diabetes. Patients with pre-diabetes have to be re-tested each year.Pre-diabetic A1C range between of 5.7 to 6.4 %, the higher the A1C, the greater is the risk of developing diabetes. Those with pre-diabetes are likely to develop type II diabetes within few years, but they can take steps to prevent or delay diabetes.

To confirm the diagnosis, by using one or more of the following tests must be considered;

- ✓ Fasting blood sugar level: diagnosed if it is > 126 mg/dL at two different times.
- ✓ Hemoglobin A1C tests levels: diagnosed if the result is 6.5% or higher.
- ✓ Oral glucose tolerance test: diagnosed if the glucose level is >200 mg/dL, 2 hours after drinking a 75gms OGTT sugar drink.

American Diabetes Association (ADA) 2016 Guidelines: [1](use any one or two criteria)

- ✓ FBG(Fasting blood glucose) ≥126 mg/dL (7.0 mmol/L) ; Fasting is defined as no caloric intake for ≥8 hours
- ✓ 2-hr PG (Post prandial blood glucose) ≥200 mg/dL (11.1 mmol/L) during OGTT (oral glucose tolerance test,75-g), using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.
- ✓ A1C (Glycosylated hemoglobin)≥6.5% (48 mmol/mol)Performed in a lab using NGSP-certified method and standardized to DCCT assay
- ✓ Random PG (Post prandial blood glucose) ≥200 mg/dL(11.1 mmol/L)in individuals with symptoms of hyperglycemia or hyperglycemic crisis.

Table 1

State	Fasting Glucose (mg/dl)	2 hour Glucose (mg/dl) during a 75g OGTT	HbA1c (%)
Normal	< 100	< 140	< 5.7
Isolated Impaired Fasting Glucose	100-125	< 140	-
Isolated Impaired Glucose Tolerance	< 100	140-199	-
Combined IFG and IGT	100-125	140-199	-
Pre-diabetes or Categories of Increased Risk	100-125	140-199	5.7 - 6.4
Diabetes*	≥ 126	≥ 200	>6.5

HbA1c levels(glycated hemoglobin) are reflective of blood glucose levels over the past 6-8 weeks and do not reflect daily ups and downs of blood glucose. Because red blood cells in the human body survive for 8-12 weeks, measuring glycated hemoglobin (or HbA1c) levels are used to reflect average blood glucose levels, providing a useful

longer-term gauge of blood glucose control. HbA1c refers to glycated hemoglobin (A1C), which identifies average plasma glucose concentrations.Hemoglobin, a protein present in the red blood cells that carries oxygen throughout your body, joins with glucose in the blood and turns to be 'glycated'. By measuring glycated hemoglobin (HbA1c), clinicians are able to get an overall picture of average blood glucose levels have been present over a period of weeks/months. Firstly, HbA_{1c} gives an indication of chronic glycemia rather than being a test of glycemia at a single point in time. It gives an integrated index of glycemia over the entire 120-day lifespan of the red blood cells, but within this period of 120 days, recent glycemia has the largest influence on the HbA_{1c} value, with 50% of HbA_{1c} formed in the month prior to sampling and 25% in the month before that.[5] Therefore it's logical that such a test would be appropriate in diagnosis of a disease characterized by chronic hyperglycemia which would lead to a gradual progress of complications. Secondly, it is a relatively convenient test which does not require the patient to fast before coming for the check-up andthis test uses a single blood sample. Generally, the effects of hyperglycemia are separated into macro vascular complications (Coronary and Peripheral arterial disease and Stroke) and micro vascular complications (Diabetic nephropathy, neuropathy, and retinopathy)

Research has shown that people with type IIdiabetes, patients who try to reduces their HbA1c level even by 1% are: [1]

- ✓ 19% less likely to suffer from cataract.
- ✓ 16% less likely to suffer from heart disease.
- ✓ 43% less likely to suffer from amputation or death due to peripheral vascular disease.

Table 2

HbA1c (%)	**"eAG"(mg /dl) National institute of diabetes , digestive & kidney disease**	**mg/dl (American diabetic association)**	**mg/dl (India)**
6.0	126	135	115
7.0	154	170	150
8.0	186	204	180
9.0	212	240	215
10.0	240	275	250
11.0	269	310	280
12.0	298	345	315
13.0	326		350
14.0	355		380

Many studies hadshown that HbA1c is an index of average glucose (AG) over the preceding week-to-months. Erythrocyte (red blood cell) life span is about 120 days. The level of HbA1c at any point in time is contributed to the circulating erythrocytes, from the oldest (120 days) to the youngest. However, HbA1c is a weighted average of blood glucose levels during the preceding 120 days, means that the glucose levels in the preceding 30 days contribute substantially more to the level of HbA1c glucose levels in the earlier 90-120 days. This can explain why the level of HbA1c can increase/decrease relatively quickly with large difference in glucose, it doesn't take 120 days to detect a clinical change in HbA1c following a clinically significant change in AG. [28]Your health care provider may report your HbA1C test result as "average glucose," (eAG) which directly correlates to your A1C. Estimated average glucose (eAG) may help you to understand your A1C value because eAG is in the unit similar to what you see regularly

through self-monitoring glucose meter. A1C is reported in percentage (7% for example) and eAG uses the same units (in mg/dl) similar to your glucose meters. The American Diabetes Association has suggested an A1C of 7%, which is an eAG of 154 mg/dl, but a more or less stringent glycemic goal may be appropriate for each individual.[1] In some cases, the A1C test is used to help health care providers to confirm the results of a blood glucose test. [28]

Scope of the Study:

- ✓ To ensure the control and accuracy in blood sugar levels in pre-diabetic and in diabetic patients.
- ✓ To check the clinical efficacy of hypoglycemic agents and to find the level of reduction in HbA1c levels.
- ✓ To help patients in better control of diabetes and decrease morbidity and mortality.

Materials and Methods:

(a) Study Design, Setting and Study Population:

The present study was observational, prospective and randomized and was carried out in 'Narayana Hrudayalaya-Malla Reddy hospital in Hyderabad, Telangana, India and the study was conducted in-between November 2012 and April 2016 (42 months). Six hundred and twenty-one patients (n=621) were randomly collected who were on anti-diabetic treatment, and few were diagnosed with pre-diabetes were enrolled in the study. All the patients were advised to come after every 6 months and about 5 consecutive routine monitoring of HbA1c levels were noted, and only those patients were taken into the study.

Inclusion Criteria:

Both In-Patient's, Out-patients were taken with Type II Diabetes Mellitus , With/without Comorbidities, hospital facilities including general medicine, intensive care unit, Surgery, orthopedic, Coronary care unit, nephrology, dialysis.

Exclusion Criteria:

Pediatric, gynecology, Patients who didn't come for consecutive laboratory checkup for the HbA1c level. Parameters which alters the HbA1c levels were excluded (likeanemia, alcoholism, iron & vitb12 deficiency , hyperbilirubinemia, postsplenectomy, uremia, heavy bleeding, drugs like dapsone, high dose aspirin, chronic opiate consumption, vitamin E&C)

Instrument Used:

Micromat II & Dia STAT (HbA1c Monitoring Instrument)

(b) Data Collection:

Medical case sheets, drug charts, and their laboratory investigations were recorded in self-designed standardized performa and were analyzed .Demographics (Age, Sex), Chief complaints, Current diagnosis, medical history, medication prescribed (dose, route of administration, frequency, indication, therapy duration, marketing categories [generic/branded]) were collected.

(c) Ethical Considerations:

The study was done using WHO guidelines only after obtaining approval from institutional research and ethics committee.

(d) Statistical Analysis:

An observational study was done to view and record the data, prospective study was done to check the outcome and were applied to the study to collect the data using Microsoft excel software, and the results were applied in percentage.

Result:

Figure 1: Gender Categorization of the study population (Male=187 & Female=434)

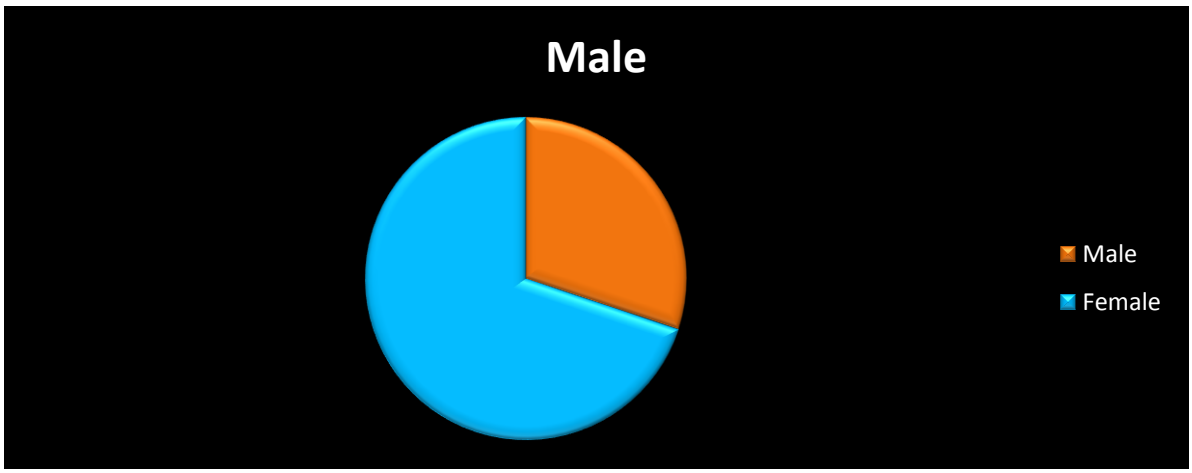

Table 3: Gender distribution in pre-diabetic patients

Gender (Pre-diabetic)	No. of Patients(n=121)	Percentage
Male	31	25.6
Female	90	74.4

Table 4: Gender distribution in Diabetic patients

Gender(Diabetic)	No. of Patients (n=500)	Percentage
Male	156	31.2%
Female	344	68.8%

Table 5: Age distribution of Diabetic and Pre-diabetic patients

Age(in years)	No. of Patients(n=621)	Percentage
Below 45 & 45	75	12.2%
46-55	98	15.7%
56-65	192	30.9%
Above 66	256	41.2%

Table 6: Duration of the disease diagnosed of diabetic patients

Duration	No. of Patients (n=500)	Percentage
Newly diagnosed	3	0.6%
2-4 years	198	39.6%
5-10 years	256	51.2%
>10 years	43	8.6%

Table 7: HbA1c level (%) on admission (Baseline) of Pre-diabetic patients

HbA1c (%)	mg/dl	No. of Patients(n=121)	Percentage (%)
5.8	115	7	5.8
5.9	119	4	3.3
6.0	122	12	9.9
6.1	125	9	7.4
6.2	128	33	27.3
6.3	131	21	17.4
6.4	134	35	28.9

Table No 8: HbA1c level (%) on admission (Baseline) of Diabetic patients

HbA1c (%)	No. of Patients (n=500)	Percentage
6.0-6.9	20	4%
7.0-7.9	101	20.2%

8.0-8.9	92	18.4%
9.0-9.9	115	23%
10.0-10.9	109	21.8%
11.0-11.9	31	6.2%
12.0-12.9	21	4.2%
13.0-13.9	4	0.8%
14.0	7	1.4%

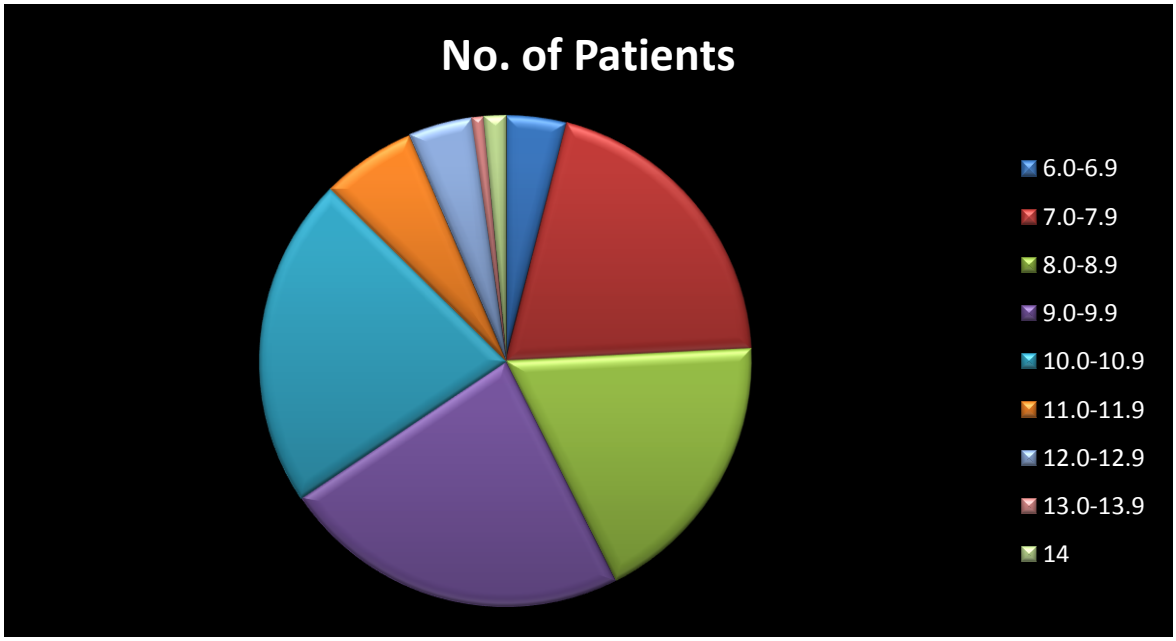

Table 9: Body mass index

BMI	Male(n=187)	Female(n=434)
Diabetic patients (n=500)		
Over weight(BMI 25-30)	53	147
Obese(BMI >30)	103	197
Pre-diabetic(n=121)		
Over weight(BMI 25-30)	7	37
Obese(BMI>30)	24	53

Table 10: Changes in clinical efficacy with integrated index of oral hypoglycemic agents (Mean of 5 consecutive values of HbA1c per patient)

Oral Hypoglycemic Agents	Reduction in HbA1c (%) or Critical difference[29]	No. of Patients (n=500)	Percentage (%)
Sulfonylurea's	0.8-2.0	48	9.6
Meglitinide's	0.5-2.0	10	2
Biguanides	1.5-2.0	292	58.4
Thiazolidinedione's	0.5-1.5	15	3
Alpha-glycosidase inhibitors	0.7-1.0	9	1.8
DPP-4 inhibitors	0.5-0.9	25	5
Sitagliptin/Metformin	0.6-0.9	61	12.2
Glibenclamide/Metformin	0.7-1.0	40	8

Table 11: Adverse drug reactions associated with oral hypoglycemic agents in the study population

ADR's	No. of Patients Affected(n=500)	Naranjo's Causality Assessment
Hypoglycemia	12	Probable
Diarrhea	17	Probable
Nausea & Vomiting	24	Probable
Abdominal pain	69	Probable
Weight gain	54	Probable

Discussion:

In diabetic patients blood glucose levels tend to rise more than usual, drop with exercise, rise after food consumption especially after canned or sweetened foods or beverages. People who do not have diabetes can make enough insulin to keep their blood sugar in a normal range. The hemoglobin A1C test is an important blood test that shows the result and how well your diabetes is being controlled. Hemoglobin A1C test provides an average levels of your blood sugar control over the previous 3 months. If your diabetes is under control (HbA1c lower than 7%), after every 3-6 months of routine monitoring, it means you are in less risk ; but if the last reading is above 7% then you will need to achieve lower levels as soon as possible. In our study, the population, female patients (n=187) with type II diabetes were high compared to male patients (n=434).Of those, n=121 patients were diagnosed as pre-diabetic (HbA1c levels=5.8%-6.4%) as their glucose levels were high but they didn't show any symptoms of diabetes. The patients newly diagnosed with diabetes were 3, 198 were diabetic from past 2-4 years ,256 patients had history diabetes type II in between 5-10 years and about 43 patients were having the history of type II diabetes since 11 years and above. And the patients in the study population were overweight (n=244) and obese (n=377).The HbA1c levels of diabetic patients in the study population were as follows 6.0-6.9=20, 7.0-7.9=101, 8.0-8.9=92, 9.0-9.9=115, 10.0-10.9=109, 11.0-11.9=31, 12.0-12.9=21, 13.0-13.9=4, 14.0=7.

The patients were treated with oral hypoglycemic agents were Biguanides (n=292), Sulfonylureas (n=48), Meglitinides (n=10), Thiazolidinedions (n=15), Alpha-glycosidase (n=9), DPP-4 inhibitor (n=25), and fixed drug combination like Sitagliptin /Metformin (n=61), Glibenclamide /Metformin (n=40) were administered to the study population and change in the reduction in HbA1c levels and clinical efficacy were found.

Conclusion:

Diabetes may be present for many years before it is diagnosed or before the presence of any symptoms related to diabetes, hence HbA1c testwill provide an accurate result of blood glucose in the body. Diabetes is a major health problem and the patients with diabetes have 2-4 times the risk of developing micro/macro vascular disease in future compared to non-diabetic patients. In our study, the female patients outnumbered the male patients. All the adverse reactions were treated and the patients were put on weight management and diet control to improve their health status accompanied by non-pharmacological treatment. The pre-diabetic patients (n=121)were given a strict glucose management chart so as to control their sugar levels to avoid development of the disease; and of those 58 patients developed type II diabetes when they came for their consecutive regular monitoring. All the 58 patients were prescribed with sulphonylureas

Patients with HbA1c levels (glycosylated hemoglobin) in between 7.0-10.9 were high in diabetic patients and levels between 6.2-6.4 were high in pre-diabetic patients. There was a significantreduction of HbA1c levels were found to be a follows with Sulfonylureas (~0.8-2.0%), Meglitinides (~0.5-2.0%), Biguanides (~1.5-2.0%), Thiazolidinediones (~0.5-1.5%), Alpha-glycosidase-inhibitors (~0.7-1.0%), DPP-4-inhibitors (~0.5-0.9%), Sitagliptin /Metformin (~0.6-1.0%), Glibenclamide /Metformin (~0.7-1.0%).

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