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# PRESCRIBING PATTERN OF ANTIDIABETIC DRUGS AMONGST PRE-OBESE DIABETIC PATIENTS IN A TERTIARY CARE HOSPITAL- AN OBSERVATIONAL STUDY

Endocrinology

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| **Sarkar S** | MBBS, MD, DM persuing, Department of Pharmacology, School of tropical Medicine, Kolkata, West Bengal |
| **Srivastava V*** | MBBS,MD, Assistant Professor, Department of Pharmacology, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha *Corresponding Author |
| **Roy A** | MBBS,MD, DM, Senior Resident, Department of Community and Family medicine, AIIMS, Bhopal |
| **Dr Manjushree Mohanty** | MBBS, MD, Head of department, Department of Pharmacology, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha |

## ABSTRACT

**Background**: In order to improve the prescription quality and rational prescription pattern promotion there is an inevitable need to investigate the factors that affect doctors' prescription patterns. Diabetes is a common non communicable disease. It leads to high morbidity and mortality due to the disease itself and its diverse complications like CAD, hypertension,renal complication,retinal damage,neurological disorders,generalised infections etc.With such multifactorial background of high prevalence,progressive nature of the disease,availability of multiple therapeutic regimens prescribed on trial and error basis, the treatment is individualised and neither complete nor satisfactory.

**Objectives:** This study was undertaken to analyse the current prescribing pattern in pre-obese patients of type 2 diabetes mellitus with regard to drug/drugs precription,dose,duration of treatment and frequency of change of drugs.

**Methods**: This is a prospective,parallel group, comparitive observational study.The enrolled pre-obese patients were divided as a)New diabetic b)Old diabetic(<3 years duration).Each category was further divided into four subgroups according to the treatment recieved a)Monotherapy-Metforminb)Combination therapy-Metformin+another antidiabetic groups,preferably sulfonylureas, alphaglucosidase inhibitors or DPP 4 inhibitors c)Triple therapy( Metformin+SU+Voglibose or Gliptins or Glitazones) d)Insulin with other oral hypoglycemic drugs.

**Results**: In the study of prescribing pattern, it was observed that most prescriptions in this tertiary care hospital were found to be in compliance with the ADA guidelines. Metformin monotherapy was prescribed as initial treatment. Sulphonylureas/Gliptins/Alpha glucosidase inhibitors/thiazolidinediones were used as second line therapy mostly anyone, in addition to metformin or as monotherapy according to patient requirement, tolerability and cost.

**Conclusions**: The antidiabetic medications prescribed in this hospital,were found to be in compliance with ADA guidelines.

## KEYWORDS

Diabetes, Obese, Pre-obese, FBS, PPBS, HbA1C

## INTRODUCTION

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long–term damage, dysfunction and failure of various organs. This disorder now is recognised as a chronic devastating progressive disease more prevalent among middle and higher economic group due to a change in their life style and food habit. The disease is spreading in an alarming rate and India, very soon(within one or two decade ) may become the capital of diabetes. Drug therapy is compulsory because of the chronic and progressive nature of the disease. The total cost of treatment in uncomplicated case is Rupees 15000 per annum and four times more in complicated cases which leads to financial burden to the individual and to the health care system as well. In order to improve the prescription quality and rational prescription pattern promotion there is an inevitable need to investigate the factors that affect doctors' prescription patterns. Studies have shown that there is a correlation between prescription patterns and gender, age, educational status, work experience, economic situation, and physician's specialty. Defining drug prescription and consumption pattern provides advantageous feedback to prescribers in order to improve their prescribing behavior. Prescription analyzing studies help the policymakers to set the priorities to promote the rational use of medicines nationwide.These numerous pharmacological interventions leaves the patients, pharmacists and doctors with an important task of selecting suitable regimen rationally from a huge armamentarium of anti-diabetic agents. This study is undertaken to analyse the different prescribing pattern in Type 2 diabetes patients in respect to number of drug/ drugs, dose, duration of treatment, frequency of change in prescription, expenditure incurred per prescription per month

## AIMS & OBJECTIVES

To analyse the current prescribing pattern in patients of type 2 diabetes mellitus with regard to drug/drugs precription, dose, duration of treatment and frequency of change of drugs amongst pre-obese patients of type 2 diabetes mellitus

### Patients and methods

This is a prospective, parallel group, comparitive observational study conducted in collaboration with department of Endocrinology KIMS, Bhubaneswar. The study was approved by the Institutional Ethical committee,KIMS,BBSR

### Inclusion Criteria

- New cases Type 2 Diabetic patients between 40 to 70 years of age
- Patients with BMI between 25-30 ( pre- obese ) and sedentary lifestyle.
- Patients already on antidiabetic medications for less than 3 years
- HbA1C levels between 6-9%
- Diabetic patients with co-morbid conditions like hypertension, obesity and dyslipidemia
- Diabetic patients presenting with microvascular complications like retinopathy, nephropathy(GFR not less than 40ml/min/ 1.73m$^2$), and neuropathy

### Exclusion Criteria

- Patient less than 30 and more than 70 years of age
- BMI<30,BMI≥40,athelets or patients whose work involves heavy exercise
- Diabetic patients with advanced nephropathy whose GFR<40ml/ min/ 1.73m2
- Untreated hypo or hyperthyroidism patients
- Patient suffering from acute metabolic disorders like diabetic ketoacidosis or hyperosmolar coma
- Patient on oral contraceptive pills
- Patients suffering from severe liver or kidney disease

### Grouping of Patients

The enrolled patients were then divided as Obese similarly divided to a) New diabetic b) Old diabetic (<3 years duration). Each category

was further divided into four subgroups according to the treatment recieved a) Monotherapy- only Metformin b) Combination therapy- Metformin + another antidiabetic groups,preferably sulfonylureas, alphaglucosidase inhibitors or DPP 4 inhibitors c) Triple therapy( Metformin+ SU+Voglibose or Gliptins or Glitazones) d) Insulin with other oral hypoglycemic drugs.

| TREATMENT RECIEVED | PREOBESE( n=168) | |
|---|---|---|
| | NEW DIABETIC CASES (n=52) | OLD DIABETIC CASES (n=116) |
| METFORMIN | 11 | 0 |
| DUAL THERAPY | 41 | 86 |
| TRIPLE THERAPY | 0 | 30 |
| INSULIN | 0 | 0 |

**Study of prescribing pattern:**

Each prescription was meticulously examined according to the WHO Drug use indicators including total Number of drugs prescribed, average number of drugs per prescription, number of drugs prescribed from the EDL, number of drugs prescribed by generic name, number of drugs prescribed by proprietary names, number of fixed dose combinations, availability of EDL, key drugs availability. Besides this, the following parameters were also recorded dose of each drug, frequency of administration , frequency of need for change in drug or dose, duration of treatment recieved in months, total expenditure incurred per prescription per month

## RESULTS

| Core Indicators | n(%) |
|---|---|
| Total Number of Drugs prescribed | 565 |
| Average Number of drugs per prescription | 4.15± 1.30 |
| Number of prescriptions with other co morbid medications | 38.21% |
| Number of drugs prescribed from the EDL | 41.8% |
| Number of drugs prescribed by generic name | 160 |
| Number of drugs prescribed by proprietary names | 405 |
| Percentage of fixed dose combinations | 5.91% |
| Availability of EDL | Yes |
| Key drugs availability | 100% |

Table 1: Showing prescribing and facility indicators as recommended by WHO, in type 2 diabetic patients pre-obese category.

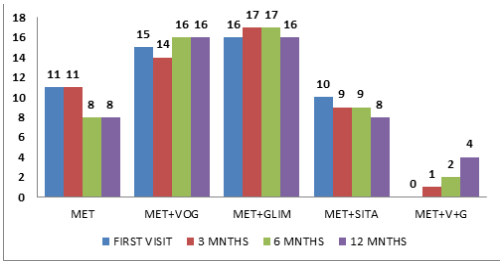


**Figure 1:** Bar diagram showing drug prescription pattern in new cases of type 2 DM (preobese) patients at their first visit, subsequent follow up at 3, 6 and 12 months of onset of treatment. MET- metformin, VOG or V - voglibose, SITA- sitagliptin, GLIM or G- glimepiride

Patients were categorised on the basis of their HbA1C levels at first visit and the medication were prescribed accordingly**.** 11 patients started with metformin monotherapy and rest 41 on dual therapy at their first visit.The dose and the regimen of the therapy was modified every 3 month interval depending on the glycemic status of each patient.At the end of 3 months, one patient from MET+VOG and one from MET+SITA combination were to be shifted to MET+GLIM combination due to inadequate glycemic control (i.e HbA1C). Another patient from MET+GLIM group was required to be changed to triple therapy i.e MET+VOG+GLIM group due to the same reason.After 6 months, three patients on metformin monotherapy required change over to MET+VOG combination, one from MET+VOG to MET+GLIM combination and one from MET+GLIM therapy to triple regimen(MET+VOG+GLIM) depending on their HbA1C levels.One patient was switched over to triple regimen(MET+ VOG+ GLIM) at 9 months from MET+GLIM therapy.After 12 months, one patient from MET+ SITA combination was changed to MET+GLIM and another patient on MET+GLIM combination was again shifted to triple therapy due to poor glycemic control.

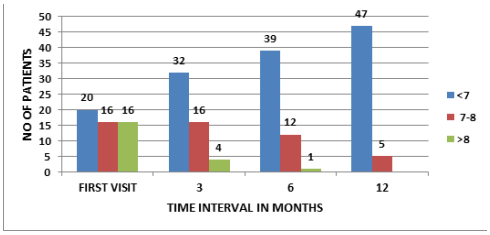


**Figure 2:** Bar diagram showing the changes in HbA1C levels in preobese new diabetic patients(n=52) at 3 , 6 and 12 months of onset of therapy in comparison to that before the initiation of treatment.

Patients were grouped into three category according to their HbA1C levels during their first visit (0 month) - a -<7%, b-7-8% and c- >8%. Amongst 52 patients, 20 had HbA1C <7%, 16 between 7 to 8% and another 16 more than 8%, at their first visit ( 0 month). After 3 months, 32 patients were effectively controlled and had HbA1C <7%, 16 were between 7 to 8% and 4 had more than 8%. After 6 months, only one patient was more than 8% , 12 were between 7 to 8% and 39 were well controlled with HbA1C levels <7 %. After 12 months of antidiabetic treatment, around 47 patients achieved controlled HbA1C levels (i.e. less than 7%) and 5 patients exhibited the same between 7 to 8% which is interpretated as good glycemic control.

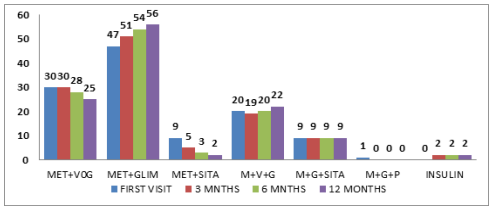


**Figure 3:** Bar diagram showing drug prescription pattern in old diabetic cases of type 2 DM (preobese) patients ( already on treatment) , at their first visit and subsequent follow up at 3, 6 and 12 months of onset of treatment . MET or M- metformin, VOG or V- voglibose, SITA- sitagliptin, GLIM or G- glimepiride, P- pioglitazone

Patients were categorised on the basis of their HbA1C levels and the medication were prescribed accordingly. At their first visit, 30 patients were maintained on MET+VOG combination, 47 on MET+GLIM, 9 on MET+SITA, 20 on M+V+G, 1 patient on M+G+P and 9 on M+G+SITA.The dose and the regimen of the therapy was modified every follow up interval depending on the glycemic status of each patient.After 3 months of the above treatment ,two patients from MET+VOG therapy and two from MET+SITA combination were shifted to MET+GLIM and MET+VOG therapy respectively, one patient from MET+SITA combination changed to MET+GLIM therapy while 2 patients were shifted to insulin, one from M+V+G group and another from M+G+P group due to inadequate glycemic control as well as associated risk factors and comorbid conditions.At the end of 6 months, 2 patients from MET+VOG combination and another two from MET+SITA were changed over to MET+GLIM therapy and one person changed to triple regimen(M+V+G) from MET+GLIM combination.At 9 months, 2 patients recieving MET+GLIM combination were shifted to triple regimen(M+V+G) , 3 patients from MET+VOG combination and one from MET+SITA were to be changed to MET+GLIM therapy.After 12 months of treatment,no further modification in treatment schedule was required.

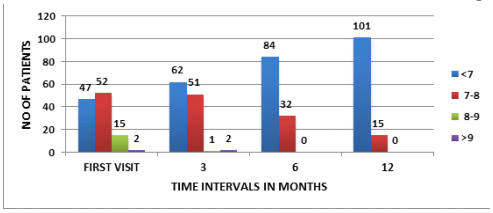


**Figure 4:** Bar diagram showing HbA1C levels in preobese old diabetic cases (n=116) at 0, 3 , 6 and 12 months of onset of therapy in comparison to that before the initiation of treatment.

Patients were categorised on the basis of their HbA1C levels as stated above into four groups- **a**-<7%, **b**-7-8%, **c**- 8-9% and **d**- >9 %.Out of total 116 patients, 47 belonged to the group 'a' (<7%), 52 to 'b' (7-8%), 15 to 'c' group (8-9%) and 2 to 'd' group (>9%) at their first visit.After

3 months, 62 patients were effectively controlled with HbA1C <7%, 51 were between 7 to 8% , 1 had between 8-9% and 2 exhibited more than 9%.After 6 months , 32 were seen in group 'b' and 84 well controlled, found to belonged to group 'a'. No patients were in group 'c' or 'd'.After 12 months of treatment , HbA1C levels of 101 patients declined below 7% and 15 patients exhibited the same between 7 to 8 % which were significant.

## DISCUSSION

The average number of drugs prescribed per patients was high in this study mostly due to association of co -morbid diseases in the study population. The observation coincide with that of Olurishe et al in 2012 in Nigeria where it was reported that more drugs are prescribed for diabetic patients, than patients suffering from other diseases and still more number of drugs are required for patients with co-morbid conditions. According to WHO prescribing indicators, all the prescriptions in the present investigation were analysed (**table no 1**). It was observed that average number of drugs per prescription was 4.15 ± 1.30. Three to seven drugs were prescribed to 36.4% of patients. A parallel study conducted in Nepal in 2011 reported similar prescribing pattern . The reason for use of more number of drugs OPD patients might be to achieve adequate glycemic control, as well as associated co morbid conditions, for which use of two or three antidiabetic agents is justified.

Infact the National Drug Policy encourages generic prescribing which allows flexibility of stocking thereby increasing accessibility, availability and affordability of various brands of a particular drug. Essential drugs are selected on the basis of public health relevance, evidence on efficacy, safety and cost. Adaption of essential drug list has resulted in improved availability of medicines with in economic range and more rational use of drugs.Most of the drugs in the present study were prescribed by proprietary names and very few by generic names. Almost all antidiabetic , antihypertensives and hypolipidemic drugs were precribed by their proprietary names. Only some multivitamins and metformin were prescribed generically. This might be due to availability of effective combination of antidiabetics by reputed pharmaceutical companies and good socioeconomic status of patients attending thos hospital. About 48.21% patients were suffering from co-morbid illness and hence recieved additional medications. Essential drug list and fixed dose combinations were available in this hospital like insulins (regular, intermediate), metformin, glimepiride, enalapril, atorvastatin etc.

In Odisha , including KIMS, Bhubaneswar, the diabetic patient has to pay about 48% of the total health care cost on drug prescription, followed by transportation and laboratory tests, which amounts to about 7% of the 15 total cost to the individual . The cost of medications is therefore very important for the diabetic patients. In addition to their glycemic status, these patients incur other healthcare costs including treatment of comorbid diseases. In order to ensure medication adherence, the economic status of the individual patient must be taken into consideration

The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommend early initiation of metformin montherapy as a first-line drug and as combination therapy for T2DM patients if necessary. This recommendation is based primarily on metformin's glucose-lowering effects, relatively low cost, and generally less of side effects, including the absence of weight gain .[7] In the present study, the same principle with metformin was followed.

In the present study, metformin was the most common and first prescribed medication. Out of 168 patients , 100% were recieving metformin either as montherapy or combination with other medications. This is in accordance with the recent ADA guidelines 2014. Patients having HbA1C less than 6.5 were given metformin as monotherapy in varying doses of 500mg,1000mg or 1500mg. For further increase in glycosylated Hb levels, it was mostly prescribed either as dual or triple regimen with other OHAs.

A sulphonylurea preferred as an alternative to metformin for certain patients (non-obese, higher HbA1c) or when metformin is not tolerated. Sulphonylureas offer a more aggressive treatment option and thus may be given to patients presenting with a higher HbA1c to facilitate a more rapid reduction in blood glucose levels .The combination of metformin and sulfonylurea (SU) is one of the most commonly used regimen and can attain a greater reduction in HbA1c (0.8–1.5%) than either drug alone[8]. The glimepiride/metformin combination results in a lower HbA1c concentration and fewer hypoglycemic events, compared to the glibenclamide/metformin combination . Metformin and sulfonylurea combination therapy was associated with reduced all-cause mortality. Epidemiological investigations suggest that patients on SUs have a higher cardiovascular disease event than those on metformin In the present study, around 63.7% patients from preobese category were prescribed metformin, in combination with Glimepiride . None of the patients were on glibenclamide combination because glimepiride has minimal adverse events and chances of hypoglycemia is less compared to glibenclamide. New diabetics in both preobese and obese category having HbA1C between 7.5- 9 were prescribed with this combination. These patients showed significant reduction in HbA1C levels and required very less number of alterations in prescription. Most of the old diabetic patients were also put on this combination and showed optimum glycemic control.

The third commonly used oral hypoglygemic agents at present is alphaglucosidase inhibitors preferred mostly in preobese group.They play an important role in digestion of complex carbohydrates by cleaving oligosaccharides into monosaccharides. AGIs compete with the oligosaccharides for the binding site. They are classic competitive inhibitors. The mechanisms of action of the different AGIs are similar though not identical. Acarbose is also an inhibitor of intestinal sucrase and pancreatic amylase. Voglibose inhibits most alpha glucosidase enzyme but is weaker than Acarbose at inhibiting sucrase and has little effect on pancreatic amylase. In general, literature review reveal beneficial effects on glycemic control. A met analysis study, by calculating the mean effect from 13 trials with voglibose, showed significant reduction in HbA1C BY 0.9%, FBS by 1.3mmol/l and PPBS around 3 mmol/l.

In this study, Voglibose was the third most commonly prescribed antidiabetic as combination therapy either with metformin or as triple drug regimen with metformin and sulfonylureas.In pre-obese category around 39.88% patients recieved the same . Since the pre-obese patients had higher mean age group, the chances of postprandial hypoglycemia tends to increase, hence Voglibose was less prescribed to them. Furthermore most of the new diabetic patients obese category, with HbA1C between 6.5 to 7.5 were prescribed with this drug as it causes a reduction upto 0.8 of HbA1C with minimal chances of hypoglycemia and weight loss as an additional advantage. There was significant reduction of both FBS and PPBS seen after 12 months of therapy.

The next preferred antidiabetic agent in current therapeutics is DPP4 (dipeptidyl peptidase 4) inhibitors. They were designed for the treatment of the disease based on prior knowledge of the physiology of the incretin hormone GLP-1 (Glucagon like peptide) and an understanding of the target (DPP-4). Contrasting with the development of other antidiabetic agents whose blood glucose-lowering effects were discovered more by srendipity than by suitable drug design study without fully knowing the underlying mechanisms (e.g. metformin, sulphonylureas and glitazones). DPP-4 inhibitors are a new class of medicine that work to potentiate the effect of incretin hormones. Incretin hormones are secreted from the gastrointestinal tract(the enteroendocrine cells), into the bloodstream in response to food intake. The two most well-characterised incretin hormones are the GLP-1 and glucose-dependent insulinotopic polypeptide, also known as gastric inhibitory peptide (GIP). Circulating levels of GLP-1 are low in the fasting state, and rise quickly following a meal. However, GLP-1 has a very short half-life and is rapidly degraded by the enzyme, DPP-4. In an attempt to hasten the beneficial effects of GLP-1, GLP-1 agonists, e.g. exanetide and liraglutide, as well as the DPP-4 inhibitors are combined together.

The DPP-4 inhibitors include sitagliptin, vildagliptin, alogliptin, saxagliptin, linagliptin, and teneligliptin. These drugs have modest efficacy i.e. reduces HbA1C levels by 0.5 to 0.8 mg/dl. They offer the potential advantage of a low risk of hypoglycaemia and weight gain. As there is a low risk of hypoglycaemia developing with their use, they may be advantageous in patients who are close to achieving their target HbA1c, but who continually experience elevated glucose levels following a meal.

In the present study , DPP4 inhibitors like sitagliptin, vildagliptin and teneligliptin were prescribed. Some of the patients were effectively controlled but in 5% cases, therapy had to be changed due to increase financial burden or inadequate glycaemic control. Around 11.03% patients from pre-obese group were prescribed gliptins in combination with metfomin. Those patients having HbA1C levels between 6.5 to 7.5 mg/dl were given this therapy. The combination of 50mg gliptins was prescribed with either 500mg or 1000mg of metformin.

The addition of thiazolidinediones to metformin in a 24-week randomized, double-blind, parallel-group study significantly decreased HbA1c concentration and improved insulin sensitivity as well as HOMA ß cell function . However, in spite of preventing diabetes incidence, the natural course of declining insulin resistance may not be modified by a low dose of the metformin- thiazolidinediones combination . The ADOPT study (A Diabetes Outcome Progression Trial) assessed the efficacy of thiazolidinediones, as compared to metformin or glibenclamide, in maintaining long-term glycemic control in patients with recently diagnosed type 2 diabetes. Thiazolidinediones was associated with more weight gain, edema, and greater durability of glycemic control; metformin was associated with a higher incidence of gastrointestinal events and glimepiride with a higher risk of hypoglycaemia.. According to a meta-analysis done by Ferwana et al in 2010, it was observed that patients on pioglitazone have increased risk of bladder cancer than general population. In the present study, pioglitazone was prescribed to very few patients because of the risk of bladder carcinoma.

In the present study, insulin was added to either dual and triple regimen when the HbA1C was uncontrolled with OHAs.Metformin as added to insulin-based regimens has been shown to improve glycemic control, limit changes in body weight, reduce hypoglycemia incidence, and to reduce insulin requirements (sparing effect), allowing a 15–25% reduction in total insulin dosage[5]. The addition of metformin to insulin therapy in type 1 diabetes is also associated with reductions in insulin-dose requirement and HbA1c levels [6].

Insulin was given to those patients whose HbA1C was above 9mg/dl even after giving triple drug therapy. 1.92% patients from obese category were given insulin and were effectively controlled by the end of 12 months. This treatment regimen is in agreement with ADA guidelines 2014. Thiazolidinediones was given as triple regimen combined with metformin and sulfonylureas in 1.19% cases in pre-obese category and the patients were adequately controlled by the end of 12 months.

## CONCLUSION

In the current scenario, prescribing study becomes very important in management of diseases particulary type 2 DM where a large number of ways are available to attack the cardinal metabolic defects(insulin resistance and beta cell failure). In this study of prescribing pattern, it was observed that most prescriptions in this tertiary care hospital were found to be in compliance with the ADA guidelines. Metformin monotherapy was prescribed as initial treatment. Sulphonylureas/ Gliptins / Alpha glucosidase inhibitors/ thiazolidinediones were used as second line therapy mostly anyone, in addition to metformin or as monotherapy according to patient requirement, tolerability and cost. Use of sulphonylureas dominated over other classes of second line drugs. Insulin was prescribed to some obese diabetic with HbA1C level >9% and uncontrolled FBS as well as PPBS.

The majority of patients, particularly those with a high blood glucose levels at the beginning of treatment, were unlikely to achieve full glycaemic control and reach therapeutic target goals on the monotherapy alone. Hence, majority of the patients having HbA1C (7-8%) were started with dual or triple therapy considering in addition the comorbid conditions.

All the antidiabetics prescribed were from the essential drug list and available in this facility of KIMS. With proper evaluation of glycaemic status and suitable rational prescription, significant reduction in all the three glycemic parameters i.e FBS, PPBS, HbA1C, both in new and old diabetic patients, of pre-obese category was noticed starting from third month of post treatment onwards. Hence the antidiabetic medications prescribed in this tertiary care hospital, were effective in improving the glycaemic status to near normal.

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