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DRUG UTILISATION PATTERN OF ANTIDIABETIC DRUGS AMONGST OBESE DIABETIC PATIENTS IN A TERTIARY CARE HOAPITAL- AN OBSERVATIONAL STUDY

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ABSTRACT

Background: The principal aim of drug utilisation studies (DUS) is to facilitate the rational use of drug in a population.DUS is an essential part of pharmacoepidemiology and pharmacoeconomic as it describes the extent,nature and determinants of drug exposure. Diabetes at present appears as a common non communicable disease. It leads to high morbidity and mortality due to the disease itself and its diverse complications like coronary artery disease, hypertension, renal complication, retinal damage, neurological disorders, incidence of stroke at different sites, 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 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 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-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.

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 with metformin being the first line of treatment followed by sulfonylureas and alphaglucosidase inhibitors

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

Introduction

Diabetes at present appears as a common non communicable disease spreading rapidly all over the world. It leads to high morbidity and mortality due to the disease itself and its diverse complications like coronary artery disease, hypertension, renal complication, retinal damage, neurological disorders, incidence of stroke at different sites, generalised infections etc. Drug utilisation is defined as marketing ,distribution, prescription and use of drugs in a society ,with emphasis on the resulting medical and social consequences. The principal aim of drug utilisation studies (DUS) is to facilitate the rational use of drug in a population.DUS is an essential part of pharmacoepidemiology and pharmacoeconomic as it describes the extent,nature and determinants of drug exposure and it is used to identify treatment adherence problems as well. In the current scenario, drug utilisation 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).These numerous pharmacological interventions leaves the patients,pharmacists and doctors with an important task of selecting suitable regimen rationally from a huge armameterium 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 incurrred 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 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 30-39.99(obese class 1 and 2) 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	OBESE(n=52)	
	NEW DIABETIC CASES (n=12)	OLD DIABETIC CASES (n=40)
METFORMIN	3	2
DUAL THERAPY	9	27
TRIPLE THERAPY	0	11
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	256
Average Number of drugs per prescription	4.15± 1.30
Number of prescriptions with other co morbid medications	48.21%
Number of drugs prescribed from the EDL	41.8%
Number of drugs prescribed by generic name	80
Number of drugs prescribed by proprietary names	176
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 both preobese and obese category.

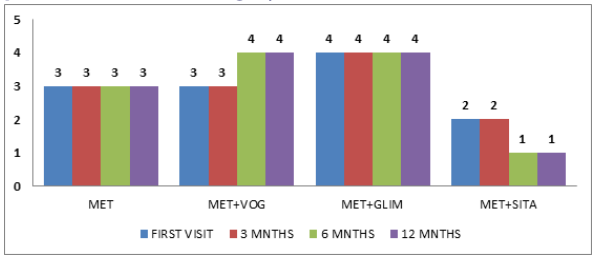

Figure 1: Bar diagram showing drug prescription pattern in new cases of type 2 DM (obese) patients at their first visit and subsequent follow up at 3, 6 and 12 months of onset of treatment. MET- metformin, VOG- voglibose, SITA- sitagliptin, GLIM or G- glimepiride

- Patients were categorised on the basis of their HbA1C levels at their first visit and the medication were prescribed accordingly
- Three patients were put on metformin monotherapy and rest nine on dual therapy out of total 12 patients.
- The dose and the regimen of the therapy was modified every interval depending on the glycemic status of each patient.
- Number and drug brand was not altered within first 3 months duration, only dose was increased in one patient i.e MET 1000mg+GLIM 1g shifted to MET 1000mg+GLIM 2g
- One patient was shifted from MET+SITA combination to MET+VOG combination at 6 month due to financial burden
- No change in prescription was seen at 12 months. Almost all patients were found to have well controlled glycemic status.

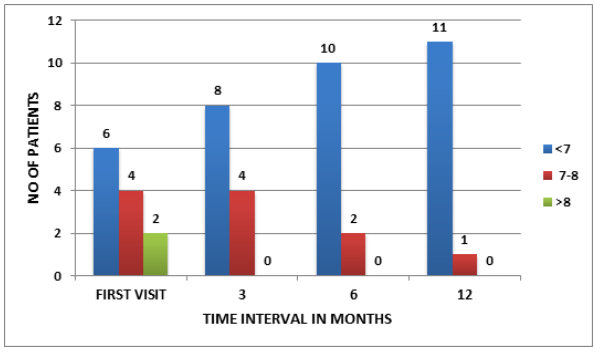

Figure 2: Bar diagram showing HbA1C levels in obese new diabetic patients(n=12) at 3 , 6 and 12 months of onset of therapy in comparison to that before the initiation of treatment. It is depicted as number of patients who achieved HbA1C target within this period after antidiabetic medications

- 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 the total 12 patients, 6 had HbA1C <7%, 4 between 7 to 8% and 2 exhibited more than 8%, at the baseline.
- After 3 months, 8 patients were effectively controlled with HbA1C <7%, 4 were between 7 to 8% .
- After 6 months, only one patient had HbA1C more than 8% , 2 between 7 to 8% and 10 achieved the levels <7 %.
- After 12 months, 11 cases achieved a controlled HbA1C levels i.e less than 7 % while only one exhibited the same between 7 to 8 %

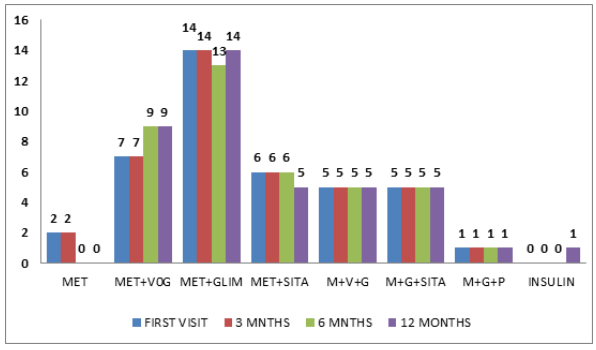

Figure 3: Bar diagram showing drug prescription pattern in old diabetic cases of type 2 DM (obese) patients, (already on treatment) at their first visit and subsequent follow up at 3, 6 and 12 months of onset of treatment. MET or M- metformin, VOG or V- voglibose, SITA- sitagliptin, GLIM or G- glimepiride,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

- Patients were categorised on the basis of their HbA1C levels and the medication were prescribed accordingly
- 7 patients were put on MET+VOG combination, 14 on MET+GLIM, 6 on MET+SITA, 5 on M+V+G, 1 on M+G+P and 5 on M+G+SITA regimen.
- The dose and the regimen of the therapy was modified at every follow up intervals depending on the glycemic status of each patient.
- No modifications in prescriptions was done at 3 months and 9

months

- At 6 months, 2 patients recieving metformin monotherapy were changed to MET+VOG combination while one patient on MET+GLIM therapy was changed to triple regimen i.e M+V+G. One patient on triple regimen (M+V+G) was switched over to insulin therapy due to inadequate glycemic control.
- At 12 months, one patient from MET+VOG and one from MET+SITA combination were shifted to MET+GLIM and MET+VOG therapy respectively. Rest of the patients were well controlled.

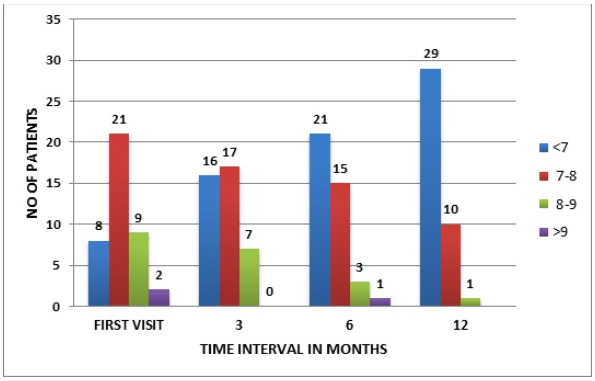

Figure 4: Bar diagram showing HbA1C levels in obese old diabetic cases (n=116) who were already on treatment at 0, 3 , 6 and 12 months of onset of therapy in comparison to that before the initiation of treatment.

- 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 %.
- Among a total of 40 patients, 8 belonged to the group 'a' , 21 to group 'b' , 9 to group 'c' and 2 to fouth group 'd' .
- After 3 months, 16 patients were effectively controlled with their HbA1C <7%, 17 were between 7 to 8% , and 7 had between 8-9%. No patients belonged to group 'd'.
- After 6 months , 15 were in group 'b' , 21 found well controlled and belonged to group 'a' , 3 to group 'c' and one to group 'd'.
- Around 29 patients achieved a controlled HbA1C levels i.e less than 7mg/dl while ten patients had the same between 7 to 8mg/dl and one patient showed an uncontrolled HbA1C (>9%) due to poor prescription compliance.

Utilisation Of Antidiabetic Medications In T2 DM Patients		
Drugs Prescribed	**Obese (N = 52)**	
	No of patients	**%**
1. Metformin	52	100%
2. Glimepiride	29	55.78%
3. Voglibose	18	34.62%
4. Sitagliptin , Vidagliptin	11	21.16%
5. Pioglitazone	1	1.92%
6. Insulin Therapy	1	1.92%

Table 2: Showing the utilisation pattern of antidiabetic medications in T2DM patients over the period of 12 months in preobese and obese category.

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 [179]. 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 encorages 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 [.] 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 52 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[c]. 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. Patients who started SUs first and added metformin later also had higher rates of cardiovascular disease compared with those who started metformin first and added SUs later. These investigations are

ofcourse potentially affected by unmeasured confounding variables.

The third commonly used oral hypoglygemic agents at present is alphaglucosidase inhibitors preferred mostly in obese and 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 obese category around 34.62% patients recieved the same . Since the 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 21.16% patients from 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[6]. The addition of metformin to insulin therapy in type 1 diabetes is also associated with reductions in insulin-dose requirement and HbA1c levels[7].

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 1.92% cases in obese category and the patients were adequately controlled by the end of 12 months.

Conclusion

Diabetes mellitus at present is encountered as an epidemic in India. The morbidity and mortality due to diabetes and its potential complications are enormous, which impose significant healthcare burdens on both the family and society. Constant migration of people from rural to urban areas, the economic boom, and corresponding change in life-style are all contributing to the steady rise of the disease.The disease is chronic and progressive inspite of the treatment. Drug therapy is not satisfactory yet. Hence research is on all over the world to find out the most suitable cost effective medication. As a result of ongoing research, a variety of regimen has come up for diabetes management which again created a problem for the physician of choosing the best suitable one for a particular patient.

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. 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 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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