DRUG UTILIZATION PATTERN OF ANTI-DIABETIC DRUGS

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Abstract:
Background: *Diabetes is a metabolic disorder characterized by high glucose level as a result of pancreatic β cells dysfunction and/or insulin resistance. Diabetes is one of the significant causes of morbidity and mortality. Obesity has direct relationship with insulin resistance, enhancing the burden by synthesis of inflammatory mediators and activating JNK pathway. Oxidative stress induces endothelial dysfunction and altered metabolism rate in hyperglycemic condition resulting in complications. Progress of these complications worsens the disease condition and patients' quality of life. Higher rate of hospitalization is due to severity of disease and complications which increases the economic burden. Early diagnosis and appropriate treatment helps to alleviate the severity and hospitalization. Drug utilization studies remain the effective tool for evaluating prescriptions and promote rational use of drugs. Rational use of drugs helps in maximising therapeutic outcome and minimise the economic burden. Lifestyle chances, patient education on disease and medication aids in improving positive outcome of therapy.*
Objective: *To evaluate drug utilization pattern of anti-diabetic drugs in hospitalized patients and compare the choice of therapy.*
Method: *This is retrospective observational study done by observing and reviewing case sheets of 130 diabetic in-patients.*
Result: *Oral Hypoglycemic agents and insulin were prescribed as both monotherapy as well as combination therapy based on severity of disease and complications. Metformin was the most commonly utilized oral Hypoglycemic drug. Human Actrapid Insulin was preferred next to metformin. Metformin + Glimepiride was utilized the most in combination therapy.*
Key words: *Diabetes, Drug utilization, Metformin, Monotherapy, Combination therapy.*

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INTRODUCTION:

Diabetes mellitus is a chronic metabolic disorder resulting from the deficiency of insulin secretion and insulin resistance. It is one of the major global health problems and leading to an increased rate of morbidity and mortality.[1] Hospitalization was the major concern among diabetic patients due to the severity of the disease. People with diabetes are more likely to be hospitalized because of both micro vascular complications especially neuropathy, nephropathy and macro vascular complications involving stroke, cardiac failure. Rational use of Oral Hypoglycemic Agents and insulin help in decreasing hospitalization.[2] A rise in diabetic population was increased by 62% in past 10 years.[3] There are reports that more than 463 million people were with diabetes as of 2019 and it will rise to about 700 million by 2045.[4] Diabetes was the cause for 1.5 million deaths. The prevalence rate of diabetes among worldwide was estimated to be 2.6% in 2000 and 4.4% in 2030.[5] Type 1 diabetes also known as "Insulin-dependent diabetes is a chronic autoimmune condition characterised by depletion of beta cells of pancreas resulting in insulin insufficiency. This results in the marked inability of the beta cells to produce insulin leading to hyperglycemia.[6] Type 2 diabetes is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production and eventual pancreatic beta-cell failure. It is associated with lifestyle risk factors.[7] Obesity is directly associated with progression of diabetes mellitus. Excess adipose mass in obese condition results in increased production of cytokines, pro inflammatory mediators which activate various pathway inducing insulin resistance. In obese individuals, increased adipose tissue mass introduce hypoxia which in turn causes cellular stress. The increased stress to cells activates pro inflammatory cytokines and JNK pathway resulting in PI3K pathway impairment.[8] Inflammatory responses are increased in hyperglycemic condition which serves as a key factor in progress of diabetes complications and worsening of conditions. Oxidative stress is predominant among diabetic patients which is the major factor for induction of vascular complication.[9] In diabetic patients, insulin therapy is considered alone or in combination with oral agents when HbA1c is $\geq$ 7.5% and is essential for patients with HbA1c $\geq$ 10%. The Insulin initiation is to begin by adding a long-acting which is either once-daily or twice-daily formulation, alone or in combination with oral hypoglycemic agents. Rapid-acting or short-insulin can be added at mealtime to control the expected postprandial raise in glucose.[10] Drug utilization studies are the most effective tool for evaluating healthcare systems as well as to promote rational prescriptions.[11] The rational drug prescribing reduces the mortality and morbidity rate and also reduces the financial burden for patients. The need for drug prescribing pattern studies is to bring out an ideal tool in the development of quality prescribing and therapeutic care. Irrational prescribing not only leads to failure in treatment but also makes way for burden, distress, anxiety and increased costs.[12] Irrational prescribing leads to an increase in mortality and morbidity rates. Accessing the essential medicines from the essential drug list helps the prescriber to ensure rational drug therapy and also it helps the patients to achieve better therapeutic management.

AIM & OBJECTIVE

Aim

The aim of this study is to evaluate the drug utilization pattern of anti-diabetic drugs prescribed for hospitalized diabetic patients.

Objective

➢ To analyze the drug utilization pattern of diabetes patients (DUR).
➢ Compare and contrast the demographic characteristics among diabetes patients.
➢ Compare and contrast the choice of therapy used in patients with diabetes.

METHODOLOGY:

Study Design

The retrospective observational study

Study Site

This study was conducted by observing case sheet of inpatients in a tertiary care hospital.

Eligibility criteria

Inclusion criteria

➢ Patients admitted in the hospital of both genders.
➢ Diabetic patient of age group between 30 and 85 years.
➢ Patients with associated complications related to diabetes.
➢ Patients who are willing to cooperate.

Exclusion criteria

➢ Patients with pregnancy (Gestational diabetes).
➢ Patients with drug abuse or addict.
➢ Patients who are mentally ill.

Sample population and Data collection

Data collection

- ➤ Diabetes mellitus patients who visited and admitted in the Medicine and Surgery wards of hospital were the subjects for the study.
- ➤ Their population were obtained from inpatients case sheets from respective wards.
- ➤ The size of the sample was 130.
- ➤ The patient details were collected from the case sheets and reviewed.
- ➤ The first step in the study was designing of data collection form.
- ➤ The patient data collection form was used to collect the details like patient name, age, sex, provisional diagnosis, history of present illness, surgical history, personal habits serving as risk factor for diabetes, complications, current therapeutic management of diabetes.

Analysis
- ➤ The documented data were imputed into worksheet of Microsoft Excel 2007 to obtain statistical analysis.

Conclusion
- ➤ The study was conducted to establish Drug utilization pattern of anti-diabetic drugs in particular setup.
- ➤ Hence monotherapy with oral hypoglycemic agents and insulin, combination therapy of oral hypoglycemic agents with insulin and combination therapy of two oral hypoglycemic agents were focused and observed from the case sheets.
- ➤ The obtained results were discussed and concluded.

## RESULTS & DISCUSSION:

Characteristics of patients

The demographic characteristics of the patients in the current study are described in Table 1. Figure 1 represents gender distribution of patients. Figure 2 gives the grouping of study population based on age. Figure 3 represents complications found among the study population.

### Table 1: Demographic Characteristics

| S.No.	Characteristics	No. of patient N=130	Percentage
1	**Gender**		
	Male	77	59.2%
	Female	53	40.7%
2	**Age**		
	30- 40 years	08	6.1 %
	41- 60 years	71	54.6 %
	61-75 years	40	30.7 %
	76- 85 years	11	8.4 %
3	**Duration since first diagnosed**		
	1-5 years	21	16.1 %
	6-10 years	65	50 %
	11-20 years	44	33.8 %
4	**Complications**		
	Neuropathy	14	10.7 %
	Nephropathy	22	17 %
	Hypertension	34	26.1 %
	Stroke	8	6.1 %
	CAD	14	10.7 %

CAD = coronary artery disease

Figure 1: Gender distribution of patients
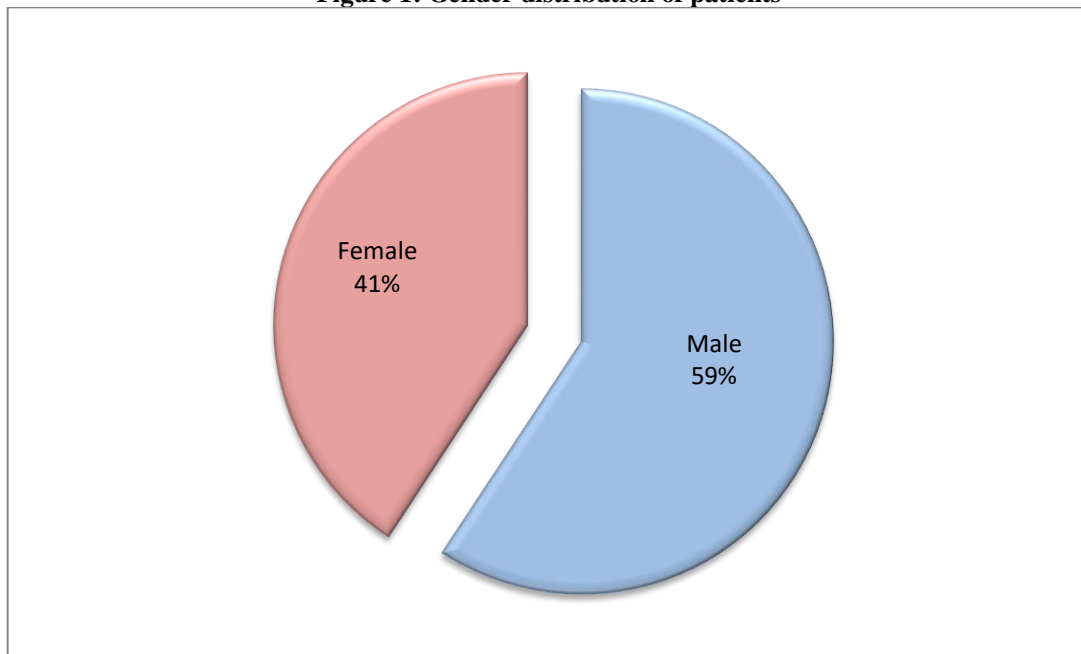
Figure 2: Age group of study population
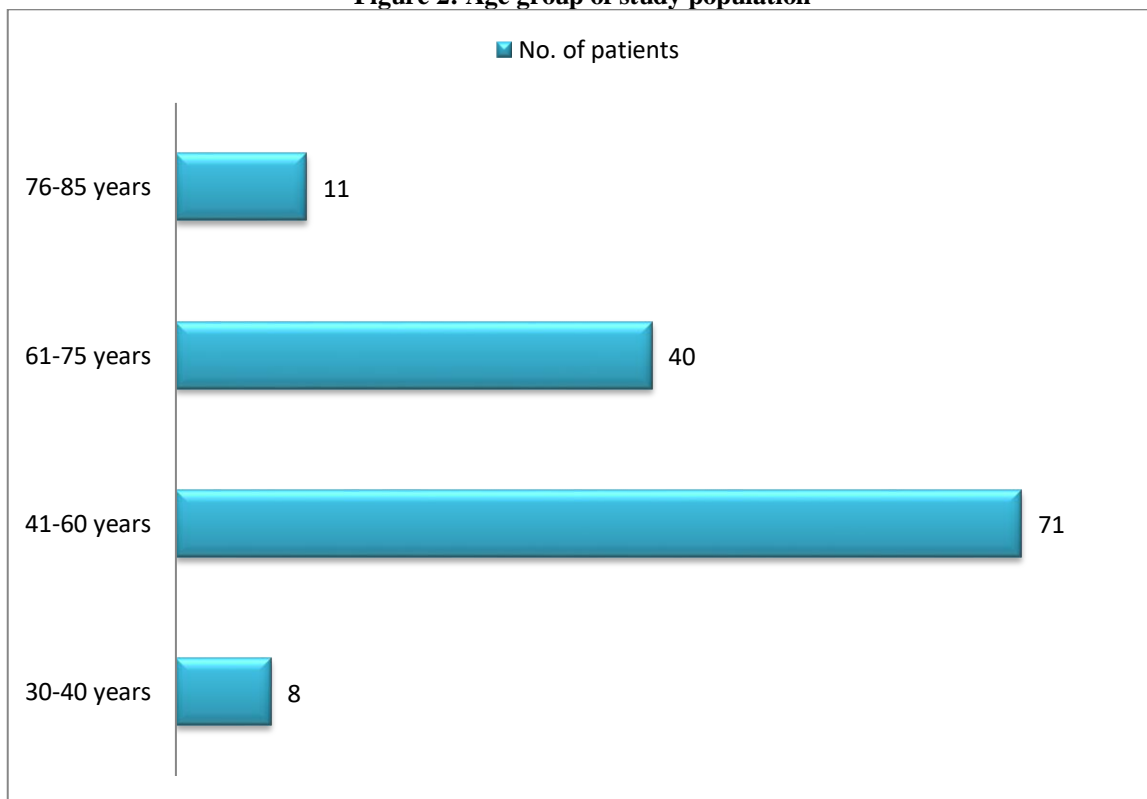
Figure 3: Complications among observed patients
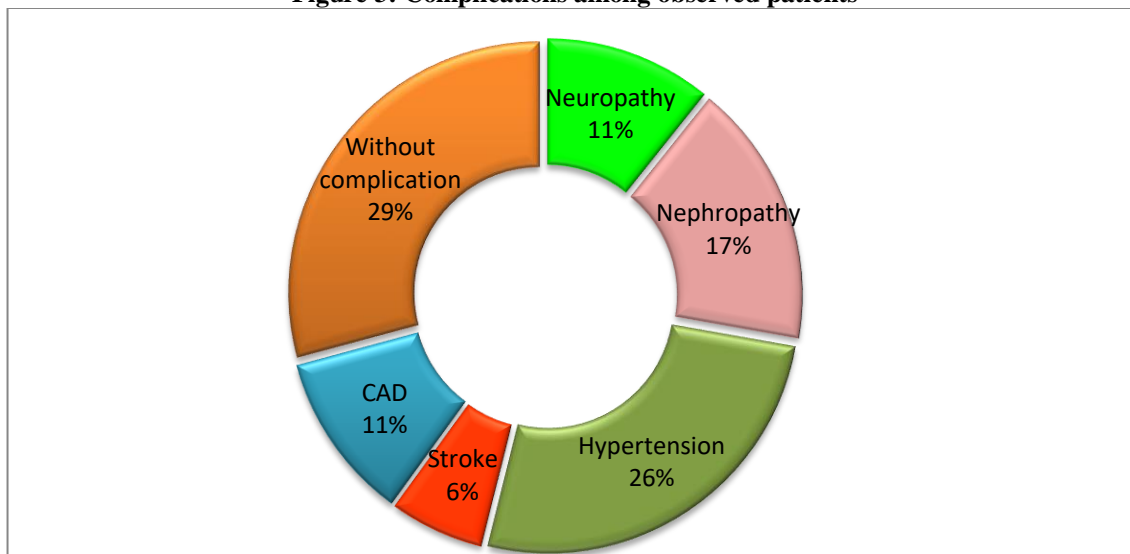
Types of therapy

Type of therapy and distribution of anti-diabetic agents according to prescribed therapy is given in Table 2.

Table 2: Anti-diabetic agents according to therapy

| Therapy	Drugs	No. of patients N=130	Percentage	Total N=130
Monotherapy	Metformin	32	24.6 %	65 patients
	Glimepiride	02	1.5 %	
	Glipizide	03	2.3 %	
	Sitagliptin	10	7.7 %	
	Vildagliptin	02	1.5 %	
	Human Actrapid insulin	10	7.7 %	
	Human monotard insulin	06	4.6 %	
Combination therapy OHA+OHA	Metformin + Glimepiride	21	16.2 %	39 patients
	Metformin + Glipizide	09	6.9 %	
	Metformin + Sitagliptin	09	6.9 %	
Combination therapy OHA+Insulin	Metformin + Human Actrapid insulin	13	10 %	26 patients
	Metformin + Human Monotard insulin	03	2.3%	
	Sitagliptin + Human Actrapid insulin	10	7.7 %	

OHA= Oral Hypoglycemic Agent

Therapy adopted according to complication
Therapeutic regimen according to severity of disease and complication was described in Table 3. Figure 4 describes the anti-diabetic therapy on basis of complications and severity.

Table 3: Therapy adopted according to complication

| Complications	Type of therapy		
	Monotherapy	Combination therapy	
		OHA + OHA	OHA + Insulin
Neuropathy		Metformin + Sitagliptin Metformin + Glimepiride	Sitagliptin + Human Actrapid insulin
Nephropathy	Human Actrapid insulin Human Monotard insulin		Sitagliptin + Human Actrapid insulin Metformin + Human Actrapid insulin
Hypertension	Metformin	Metformin + Sitagliptin Metformin + Glimepiride Metformin + Glipizide	
Stroke	Human Actrapid insulin Human Monotard insulin		Metformin + Human Actrapid insulin
CAD	Human Actrapid insulin	Metformin + Glimepiride Metformin + Glipizide	Metformin + Human Actrapid insulin Metformin + Human Monotard insulin
Without complication	Metformin Glimepiride Glipizide Sitagliptin Vildagliptin		

Figure 4: Hypoglycemic therapy for patients based on complication
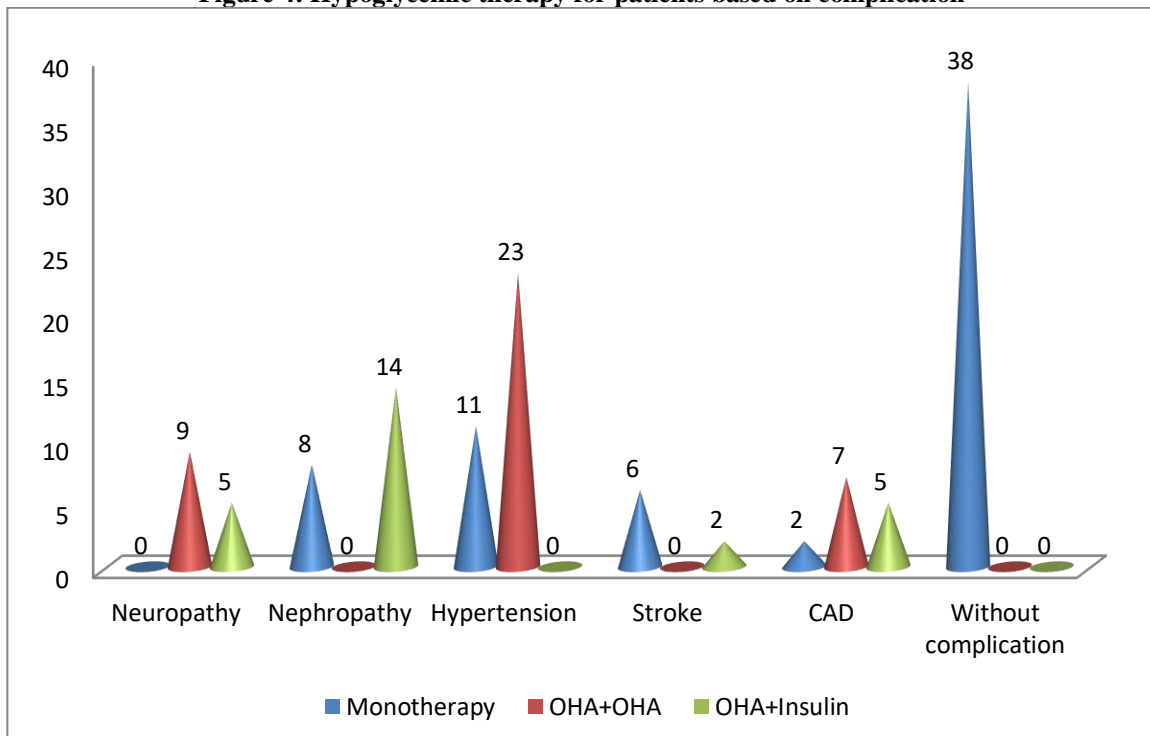
Utilization pattern

Drug utilization of each anti-diabetic agent was analysed from the study. Each drug used alone as well as in combination was calculated from which utilization of each drug was obtained. Total utilization of anti-diabetic agents from the case sheets studied are described in Table 4. Figure 5 represents the utilization percentage of all the drugs studied.

Table 4: Utilization pattern of anti-diabetic agents

S. No.	Drug	No. of Utilization N=130		Total Utilization	Percentage of utilization
		Mono therapy	**Combination therapy**		
1	Metformin	32	55	87	44.6 %
2	Human Actrapid insulin	10	23	33	17 %
3	Sitagliptin	10	19	29	14.9 %
4	Glimepiride	2	21	23	11.7 %
5	Glipizide	3	9	12	6.1 %
6	Human monotard insulin	6	3	9	4.6 %
7	Vildagliptin	2	-	2	1 %

Figure 5: Anti-diabetic drugs and their utilization
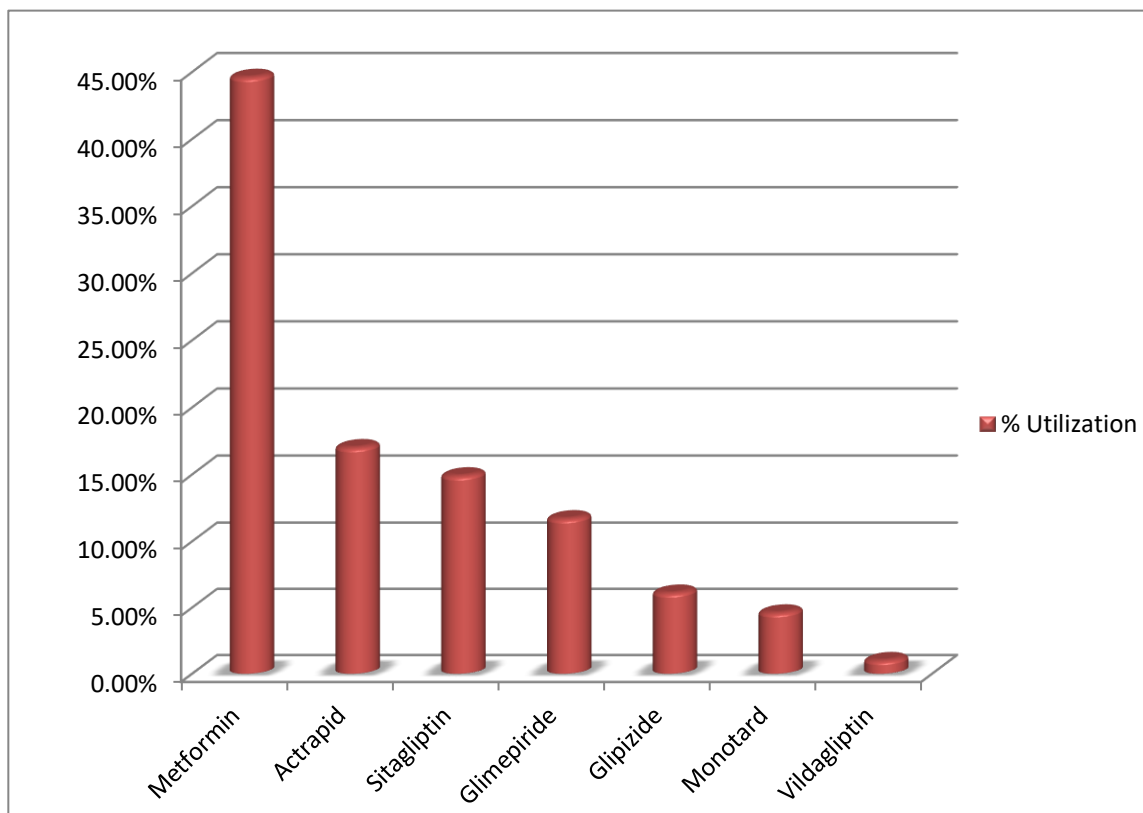
In this study most of the hospitalized diabetic cases had severe uncontrolled blood glucose level. Because of that, Insulin was seen in most of the prescriptions. Based on **American Diabetes Association guidelines**, Insulin treatment was recommended for diabetic patients under hospitalization. It is given in the form of bolus to achieve blood glucose level under control. We observed that Insulin is the drug of choice for hospitalized uncontrolled type 2 diabetes patients and for therapeutic failure to oral hypoglycemic agents. Combination of oral anti-diabetic agents was also preferred after the patient achieves good glycemic control.

During the period of study, in a total of 130 patients, 77 patients were male contributing 59.2% of total cases observed and 53 female patients which is 40.7%. In this study, male patients were higher than female. Most of the patients were between age group 41 to 60 years and that is about 54.6% followed by patients of age 61 to 70 contributing 30.7% of total observed case sheets. 65 patients (50%) were diagnosed with diabetes since 6 to 10 years and on regular medication which is close to those diagnosed with diabetes since 11 to 20 years as they were 44 in number (33.8%). 34 patients were found to be hypertensive which conclude that hypertension was most prevalent among diabetic patients accounting for 26.1%. 22 patients out of 130 patients were suffering from nephropathy and 14 patients from neuropathy followed by coronary artery disease contributing to 14 patients. Stroke was diagnosed in 8 patients among the reviewed 130 diabetic patients.

The studies related to diabetes were usually performed in middle aged people as the data availability in younger and elder people were limited.[14] Hypertension was the most common co morbidity in diabetic patients.[15] Poor glycemic control leads to life threatening complications. Almost one fourth of diabetic population suffer from foot problems.[16] About 20% of diabetic people were suffering from Diabetic Kidney which is associated with higher risk of end stage renal failure. DKD accounts for major morbidity and mortality rate of diabetic population.[17]

The study showed that oral hypoglycemic agents of Biguanide, Sulphonylureas and Dipeptidyl Peptidase-4 inhibitors classes were widely used. Among that Metformin, Glimepiride, Glipizide, Sitagliptin and Vildagliptin are commonly with Human Actrapid and Monotard insulin falling under insulin category which were used in addition with oral hypoglycemic agents.[18]

Both monotherapy and combination therapy were adopted equally in treating hyperglycemic condition. Patients prescribed with monotherapy with either oral hypoglycemic drug or insulin were 50%. Remaining 50% patients were under combination therapy of which 30% were prescribed with combination therapy consisting of two oral hypoglycemic agents. Remaining 20% of observed subjects were prescribed with combination of one oral hypoglycemic agent and insulin as the treatment for diabetes.

Combination therapy is recommended only when HbA1c level is more than 1.5%. Combination therapies are recommended in patients who are unable to achieve therapeutic goals with first line oral hypoglycaemic agents as monotherapy.[19]

Drug Utilization Pattern also known as Drug Utilization Review help in promoting appropriate prescribing of drugs and aid in rational use of drugs which has potential benefit in public health.[20] Irrational use of drugs leads to increase in drug prescribing pattern, patients are potent to adverse effects, failure of expected therapeutic goal and increase burden of healthcare.[21] Regarding insulin administration, the initial step is the combination of insulin together with the already administered oral hypoglycemic agents for uncontrolled type 2 diabetic patients.[22] As per **American Diabetes Association,** Blood Glucose targets below 140 mg/dL were considered as the most appropriate for all hospitalized patients.

Drug utilization pattern of anti-diabetic agents analysed by calculating usage of each drug in both monotherapy and combination therapy. Metformin was found to be most frequently used anti-diabetic agent with 44.6% of utilization. Metformin is the first line drug for type 2 diabetes and it is used as both singlet therapy and combination therapy in this study. It is preferred the most because of better glucose lowering effects than other oral hypoglycemic medications and easy affordability at cheaper price. Human Actrapid insulin falls next to metformin in utilization with a total of 17 %. Sitagliptin was used by 14.9% of patients as observed followed by Glimepiride. Glimepiride was utilized by 11.7% of selected patients. Glipizide had total usage of 6.1% followed by Human Monotard insulin which was found to be used in 4.6% patients. Vildagliptin was least prescribed among the reviewed case sheets. It was used by 2 patients only as monotherapy and not preferred in combination therapy. The percentage of Vildagliptin utilization was 1%.

From 2006 to 2013, use of metformin was increased from 47.6% to 53.5%, dipeptidyl peptidase 4 inhibitors utilization raised from 0.5% to 14.9% and insulin usage increased from 17.1% to 23.0%. Use of Sulfonylureas slightly declined from 38.8% to 30.8% while thiazolidinediones utilization met deep decline in usage from 28.5% to 5.6%.[24] Antibiotics were commonly seen in case sheets of in patients with diabetes to treat foot infections. Third generation cephalosporin's were preferred for foot infection cases. Lincomycin in intravenous route and oral Metronidazole plays an important role in infected foot.[25]

CONCLUSION:

Irregular diagnosis, poor adherence to therapy and uncontrolled diabetes is associated with serious outcomes progressing to complications, worsening of disease. From the study, we conclude that oral hypoglycemic drugs were predominant in prescriptions dominating the diabetic therapy. Metformin remains the first line drug of choice. Insulin was used only in severe glycemic levels and is found to be more effective in achieving target in hospitalized patients. Patients lack awareness on severity of disease and hence were not concern about drug usage. Patient education on management of disease and importance of adherence to therapy will have potential benefits in improving patient's quality of life. Rational use of anti-diabetic drugs as monotherapy or in combination when necessary will minimize the dosage of drugs and thereby eliminating avoidable adverse effects.

Author Contributions

The work was done by M. Dheepthi, S.U. Mohamed Afreeth and S. Suba Dhanisha. Mrs. M. Fathima Basheera contributed to the research study design, data collection and writing of this paper. Mr. M. Santhanakumar guided in research work. Dr.C. Sowmya contributed to the editing of this paper.

Conflict of interest

The authors declare that there is no conflicts of interest.

REFERENCES:

1. Sriram A, Dhanapal CK and Junior Sundresh N. Drug use pattern involved in diabetic with hypertension patents in a tertiary care teaching hospital. The Pharma Innovation Journal 2018; 7(7): 535-538 .
2. Tamoghna Maiti, Sourav Chakrabarty, Sonai Mandal, Amrita Panda, Tanmoy Gangopadhyay, Satrajit Dan ,A Study On Drug Utilization Pattern In Patients Of Type II Diabetes Mellitus Attending Referral Diabetic Clinic At A Tertiary Care Teaching Hospital In Rural Bengal. European Journal of Pharmaceutical and Medical Research, 2016:3(9):641-64.
3. Pouya Saeedi, Inga Petersohn, Paraskevi Salpea, Belma Malanda, Suvi Karuranga, Nigel Unwin, Stephen Colagiuri, Leonor Guariguata, Ayesha A Motala, Katherine Ogurtsova, Jonathan E Shaw, Dominic Bright, Rhys Williams, IDF Diabetes Atlas Committee. Global and regional diabetes estimates for 2019 and projection for 2030, International diabetes federation, Diabetes atlas, 2019; edition 9. Diabetes Research and Clinical Practice, 2019;157:107843. DOI: 10.1016/j.diabres.2019.107843. PMID: 31518657.
4. The IDF Diabetes Atlas Ninth edition 2019.
5. WHO. Home/ Newsroom/ Fact sheets/ Detail/ Diabetes.
6. Anastasia Katsarou, Soffia Gudbjornsdottir, Araz Rawshani, Dana Dabelea, Ezio Bonifacio, Barbara J. Anderson, Laura M. Jacobsen, Desmond A. Schatz and Ake Lernmark. Type 1 diabetes mellitus. Nature Reviews Disease Primers, 2017; 3: Article number: 17016.
7. Abdulfatai B. Olokoba, Olusegun A. Obateru and Lateefat B. Olokoba. Type 2 Diabetes Mellitus: A Review of Current Trends. Oman Medical Journal, 2012; 27(4): 269–273. DOI: 10.5001/omj.2012.68. PMID: 23071876.
8. M. Dheepthi, S.U. Mohamed Afreeth, S. Suba Dhanisha, C. Sowmya. Targetting inflammatory pathway in diabetes mellitus. World journal of pharmacy and pharmaceutical sciences, 2021; 10(8):1488-1498.
9. S.U. Mohamed Afreeth, M. Dheepthi, S. Suba Dhanisha, C. Sowmya. Antioxidants And Their Potential Role In Diabetes. Research Journal of Pharmaceutical, Biological and Chemical Sciences,2021; 12(4):43-50.
10. Bahendeka Silver, Kaushik Ramaiya, Swai Babu Andrew, Otieno Fredrick, Sarita Bajaj, Sanjay Kalra, Bavuma M. Charlotte, Karigire Claudine, Anthony Makhoba. EADSG Guidelines: Insulin Therapy in Diabetes. Diabetes Therapy, 2018;9(2):449-492. DOI: 10.1007/s13300-018-0384-6. PMID: 29508275.
11. Bela Patel, Bhavit Oza, Kamlesh P. Patel, Supriya D. Malhotra, Varsha J. Patel. Pattern of anti-diabetics drugs use in type-2 diabetic patients in a medicine outpatient clinic of a tertiary care teaching Hospital. International

Journal of Basic& Clinical Pharmacology,2013;2: 485-491.

12. Akshay A. Agarwal, Pradeep R. Jadhav and Yeshwant A. Deshmukh. Prescribing pattern and efficacy of anti-diabetic drugs in maintaining optimal glycemic levels in diabetic patients. Journal of Basic and Clinical Pharmacology, 2014; 5(3): 79–83. DOI:10.4103/0976-0105.139731. PMID: 25278671.

13. American Diabetes Association. Diabetes Care, Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes, 2021;44(1):111-124. DOI: 10.2337/dc21-S009.

14. Rani J and Reddy S. Prescribing pattern of anti-diabetic drugs in urban population of Hyderabad. National Journal of Physiology Pharmacy and Pharmacology, 2015;5:5-9.

15. Paul W. Lofholm and Bertram G. Katzung. Rational prescribing and Prescription writing. Basic and Clinical Pharmacology, 11th edition. McGraw Hill, 2009: 1127-1136.

16. Aikaterini Trikkalinou, Athanasia K Papazafiropoulou and Andreas Melidonis. Type 2 diabetes and quality of life. World Journal of Diabetes, 2017;8(4):120–129. DOI:10.4239/wjd.v8.i4.120. PMID: 28465788.

17. Kathryn McGrath. Diabetic Kidney Disease. American Family Physician, 2019; 99(12): 751-759.

18. Arun Chaudhury, Chitharanjan Duvoor, Vijaya Sena Reddy Dendi, Shashank Kraleti, Aditya Chada, Rahul Ravilla, Asween Marco, Nawal Singh Shekhawat, Maria Theresa Montales, Kevin Kuriakose, Appalanaidu Sasapu, Alexandria Beebe, Naveen Patil, Chaitanya K. Musham, Govinda Prasad Lohani and Wasique Mirza. Clinical Review of Anti-diabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. Frontaries in Endocrinology, 2017;8. Article 6. DOI:10.3389/fendo.2017.00006. PMID: 28167928.

19. Santwana Padhi, Amit Kumar Nayak, AninditaBehera. Type II diabetes mellitus: a review on recent drug based therapeutics. Biomedicine & Pharmacotherapy, 2020; 131: 110708.

20. Purnima Ashok and Vijeesh Tholur Subramanian. Importance of Drug Utilization Evaluation Studies In Patient Health Care. Journal of Pharmacy Practice, 2017; 10(3):157-159. DOI: 10.5530/ijopp.10.3.34.

21. Naresh Karki, Ruban Raj Joshi, Buddhi Kumar Shrestha and Pravin Prasad. Drug Utilization Pattern by Using WHO Core Prescribing Indicators in Orthopedics and Obstetrics / Gynecology Departments of a Tertiary Care Hospital. Journal of Lumbini Medical College,2019;7. Article 1. DOI: 10.22502/jlmc.v7i1.280.

22. Emmanouil M Pagkalos. Combinations of insulin and oral hypoglycemic agents in diabetes mellitus type 2. Diabetes Research and Clinical Practice, 2011;93(1): 100-101. DOI: 10.1016/S0168-8227(11)70022-5. PMID: 21864738.

23. American Diabetes Association. Diabetes Care, Diabetes Care in the Hospital: Standards of Medical Care in Diabetes,2020;43(1):193-202. DOI:10.2337/dc20-S015.

24. Kasia J. Lipska, Xiaoxi Yao, Jeph Herrin, Rozalina G. McCoy, Joseph S. Ross, Michael A. Steinman, Silvio E. Inzucch,Thomas M. Gill, Harlan M. Krumholz and Nilay D. Shah. Trends in Drug Utilization, Glycemic Control, and Rates of Severe Hypoglycemia, 2006–2013. Diabetes Care, 2017; 40(4): 468-475. DOI: 10.2337/dc16-0985.

25. Adil Hassan Aliakbar, Malath Azeez Alsaadi and Abbas Abd Zaid Barrak. Evaluation of the Surgical and Pharmacological Treatment of Diabetic Foot Infection: A Retrospective Study. Open Access Macedonian Journal of Medical Science, 2019; 7(9): 1499–1504. DOI:10.3889/oamjms.2019.298. PMID: 31198462.