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DRUG UTILIZATION REVIEW OF ORAL HYPOGLYCEMIC DRUGS: A RETROPROSPECTIVE STUDY

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Abstract:

A drug utilization review of a population's drug use to determine effectiveness, potential risks, drug interaction issues, and other issues. It aims to give doctors recommendations for the rational use of drugs, reducing side effects, polypharmacy, and exposure to potent drugs. With this study, we hope to provide a basic understanding of the illness and draw attention to the fact that improper use of anti-diabetic medications can result in poor patient outcomes and significant wastage of money and resources. ***Background:*** *In recent years, India has seen a rapidly exploding epidemic of diabetes, and it presently holds the world record for having the most diabetic people in one nation. In view of this situation, drug utilization review of anti-diabetic medicines in the Indian healthcare environment has a valid significance to promote rational drug use in diabetics.* ***Objective:*** *This study aimed to identify the demographic information about the patients and to examine prescription trends for antidiabetic medications, as well as the distribution of adverse drug reactions, diabetes complications, and co-occurring diseases.* ***Methodology:*** *A retrospective observational study was conducted.* ***Conclusion:*** *The use of anti-diabetic drugs was almost found to be rational. The Pharmacist is the key person for improved therapeutic management based on the stage and condition of the patient.*

Keywords: *Drug Utilization, Prescription Pattern, Insulin, Hypertension, Anti-diabetic drugs.*

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INTRODUCTION:

In recent years, India has experienced a rapidly increasing diabetes epidemic, and it now has the highest number of diabetic people in a single country. According to the World Health Organization, diabetes affected 31.7 million people in India in 2000, and this figure is expected to rise to 79.4 million by 2030. In view of the above situation, drug utilization review of anti-diabetic medications in Indian healthcare settings has the potential to promote rational drug use in diabetics.

Diabetes Mellitus: It is a metabolic disorder characterized by hyperglycemia (high blood sugar level), glycosuria (sugar in urine), hyperlipaemia (high blood levels of bad fat), negative nitrogen balance (overall low nitrogen content), and sometimes ketonaemia (high level of ketone bodies in blood). These conditions can be caused by insulin deficiency.[1]

Hyperglycemia and Glycosuria:

1. Insulin facilitates glucose transport across cell membranes (the entry of glucose from the blood into a cell) in nearly every cell, particularly skeletal muscle and fat. After entering a cell, the first step in intracellular glucose utilization is glucokinase phosphorylation to form glucose-6-phosphate. Insulin promotes phosphorylation by increasing the production of glucokinase enzymes. Following this important step, glucose is committed to subsequent metabolic cycles, i.e. glucose is consumed.
2. Insulin promotes glycogen synthesis from glucose in the liver, muscle, and fat by stimulating the enzyme glycogen synthase. Another way by which insulin lowers blood glucose levels is by inhibiting the enzyme phosphorylase which is responsible for glycogenolysis (glycogen to glucose conversion) in the liver.
3. Lastly, insulin inhibits gluconeogenesis (glucose synthesis from non-carbohydrate sources like protein, free fatty acids, and glycerol) in the liver by decreasing the synthesis of phosphoenolpyruvate carboxykinase. Later is an essential enzyme of gluconeogenesis.

Thus, in diabetes, when insulin is not working, there is underutilization production of glucose leading to hyperglycemia and glycosuria.

Hyperlipidemia, Ketonemia, and Ketonuria: Insulin inhibits lipolysis and promotes triglyceride synthesis. In diabetics, the opposite happens; fat is broken down due to the unchecked action of lipolytic hormones like glucagon. This increases free fatty acid and glycerol levels in the blood.

The liver then absorbs these free fatty acids and glycerol to produce Acetyl-CoA. Under normal conditions, Acetyl-CoA is resynthesized to fatty acids and triglycerides, but in diabetics, this process is inhibited, and Acetyl-CoA is converted into ketone bodies (acetone, acetoacetate, β-hydroxy-butyrate). Ketone bodies can be used as an energy source by muscles and the heart, but when their capacity is exceeded, ketonemia and ketonuria occur.

Negative Nitrogen Balance: Insulin promotes protein synthesis from amino acids and inhibits protein breakdown in muscle and most other cells. Insulin deficiency causes protein breakdown into amino acids, which are released into the bloodstream and taken up by the liver, where they are converted into pyruvate, glucose, and urea. The excess urea produced is excreted in the urine, resulting in a negative nitrogen balance.[1]

Hypertension: Hypertension, also referred to as high or raised blood pressure, is a condition where the blood vessels have persistently increased blood pressure. The vessels carry blood from the heart to every part of the body. When the heart beats, blood is pumped into the vessels.[2]

Table 1: Clinical Classification of Hypertension

CATEGORY	SYSTOLIC (mmHg)	DIASTOLIC (mmHg)
Normal	**< 120**	**and < 80**
Prehypertension	**120-139**	**or 80-89**
Hypertension		
Stage 1	**140-159**	**or 90-99**
Stage 2	**>160**	**or >100**
Isolated systolic hypertension	**≥140**	**and < 90**
Malignant hypertension	**>200 (sudden onset)**	**≥140 (sudden onset)**

- High blood pressure (hypertension) can cause or worsen many diabetic complications, such as diabetic eye disease and kidney disease. Most diabetics eventually develop high blood pressure in addition to other heart and circulation issues.
- Diabetes damages arteries and makes them targets for hardening, a condition known as atherosclerosis. That may result in high blood pressure, and if it is not treated, it may damage blood vessels and cause heart attacks and kidney failure.
- People with hypertension are more likely to have the following symptoms than those with normal blood pressure readings:
  1. Heart disease or coronary artery disease
  2. Strokes
  3. Peripheral vascular disease or hardening of arteries in the legs and feet
  4. Cardiomyopathy (heart failure) [3] [9] [10] [11]

Table 2: Etiological Classification of Hypertension

A. ESSENTIAL HYPERTENSION (90%)
1. Genetic factors 2. Racial and environmental factors 3. Risk factors modifying the course
B. SECONDARY HYPERTENSION (10%)
1. Renal i. Renovascular ii. Renal parenchymal diseases
2. Endocrine i. Adrenocortical hyperfunction ii. Hyperparathyroidism iii. Oral contraceptives
3. Coarctation of Aorta
4. Neurogenic

Types of Diabetes Mellitus:

Type 1: Insulin-dependent diabetes mellitus (IDDM), juvenile onset diabetes mellitus:

1. As the name indicates, this type of DM is due to a deficiency of insulin (insulin dependence), which is due to the destruction of β cells in pancreatic islets.
- This destruction of β cells in the majority of cases is due to autoimmune disorders (type IA). In such cases, antibodies that destroy β cells are detectable in blood.
- Destruction of β cells in some cases is because of unknown reasons; idiopathic (type IB) and no β cell antibody is found.
2. Overall, in all type I cases circulating insulin levels are low or very low.
3. This type is less common (autoimmune disorders are not very common).
4. This type has a low degree of genetic predisposition. [4]
5. Risk factors include family history, environmental factors (such as exposure to a viral illness), and also the presence of damaging immune system cells (autoantibodies).

Type 2: Non-Insulin-dependent diabetes mellitus (NIDDM), maturity onset diabetes mellitus:

1. There is no loss or moderate reduction in β cell mass. No anti-β-cell antibody is demonstrable.
2. Insulin in circulation is low, normal, or even high.
3. More commonly, over 90% cases of DM are type 2.
4. Type 2 DM has a high degree of genetic predisposition (chances of developing diabetes are high if parents/grandparents have this type of diabetes).
5. This type of DM generally has a late onset (past middle age). [5]
6. Risk factors for type 2 DM are high blood pressure, obesity, abnormal cholesterol and triglyceride levels, age, inactivity, race or ethnicity, family history, polycystic ovary syndrome, and gestational diabetes. [6] [7] [8]

Pathophysiology:

Patients with diabetes mellitus have a 1.5-2.0 times higher rate of hypertension than a nondiabetic population that is appropriately matched. Hypertension is usually absent at the time of diagnosis in people with insulin-dependent diabetes mellitus (IDDM). Blood pressure increases as renal insufficiency progresses and may hasten the development of end-stage renal failure. Numerous non-insulin-dependent diabetes mellitus (NIDDM) patients have hypertension at the time of their diagnosis. The extent of obesity, advanced age, and extensive atherosclerosis that are typically present are all related to the incidence of hypertension in NIDDM, which likely includes many patients with essential hypertension. A number of additional pathophysiologic mechanisms also play a role in the development and maintenance of hypertension in diabetic patient. An increase in total body exchangeable sodium and hyperglycemia can cause extracellular fluid to build up and the plasma volume to increase. In some patients, alteration in the renin-angiotensin-aldosterone system's functionality and vascular sensitivity to vasoactive hormones may also be involved. Recently, it has been suggested that

insulin resistance and hyperinsulinemia, which are known to stimulate sodium retention and increase sympathetic nervous system activity, may also be involved in the maintenance of elevated blood pressure.

ORAL HYPOGLYCEMIC DRUGS:

The main disadvantage of insulin is that it must be administered intravenously. Oral hypoglycemic medications lower blood glucose levels and are effective orally.

I. SULFONYLUREAS: This is the class of sulfa drug.
   1. First generation: Tolbutamide, Glibenclamide
   2. Second generation: Chlorpropamide (Glyburide), Glipizide, Gliclazide, Glimepiride.

   Sulfonylureas have a similar mechanism of action to insulin, except they act on different sets of receptors. They act on the "sulfonylurea receptors" (SUR1) on the pancreatic β cell membrane, causing depolarization by reducing the conductance of ATP sensitive K+ channels. This enhances Ca 2+ influx, leading to degranulation. (Note: Everything is similar to insulin except receptors).

   Chorpropamides are not recommended because of associated drawbacks like a very long duration of action, higher risk of hypoglycemia, jaundice, alcohol flush, etc.

   Glimepiride is a newer sulfonylurea, claimed to exert stringer extrapancreatic action by enhancing GLUT4 translocation to the plasma membrane, thus causing lesser hyperinsulinemia.

II. BIGUANIDES: Metformin, Phenformin

   Mechanism of action:
   1. Suppress hepatic gluconeogenesis as its major action.
   2. Though they do not alter the translocation of the major glucose transporter GLUT4, they enhance GLUT1 transport from the intracellular site to the plasma membrane.
   3. Retard intestinal absorption of glucose, other hexoses, amino acids, and Vit B12.
   4. Interfere with the mitochondrial respiratory chain while encouraging anaerobic glycolysis to increase peripheral glucose uptake.

   Drawbacks:
   1. Lactic acidosis: Small increase in blood lactate occurs with metformin.
   2. Vit B12 deficiency due to interference with its absorption can occur with a high dose of metformin.

   Metformin is preferred in obese type 2 patients because of its anorectic and because of its potential to lower the risk of myocardial infarction and stroke.

III. MEGLITINIDE / PHENYLALANINE ANALOGUES: Repaglinide, Nateglinide

   It acts in an analogous manner by binding to the sulfonylurea receptor as well as to other distinct receptors causing the closure of ATP dependent K+ channels followed by depolarization and insulin release (similar to insulin and sulfonylureas).

   Repaglinide, if given half an hour before the meal, can prevent postprandial hyperglycemia.

IV. THIAZOLIDINEDIONES: Rosiglitazone, Pioglitazone

   This class of antidiabetic drugs are selective agonists for the nuclear peroxisome proliferator-activated receptor (PPARY) which enhances the transcription of several insulin responsive genes leading to enhanced synthesis of GLUT4. This class of drugs has the potential to reverse insulin resistance.

   Rosiglitazone doesn't cause hypoglycemia but is contraindicated in liver and heart disease.

   Pioglitazone has a similar profile and additionally, it can improve lipid profile.

V. α-GLUCOSIDASE INHIBITORS: Acarbose, Miglitol

   Acarbose is a complex oligosaccharide that reversibly inhibits α-glucosidases, enzymes involved in the digestion of carbohydrates g.i.t. Acarbose is antihyperglycemic (doesn't allow blood sugar to raise) and nit hypoglycemic (doesn't lower the already raised blood sugar).

   This may also be used as an adjuvant to diet (with or without sulfonylurea) in obese diabetics.

VI. MISCELLANEOUS:

Guar Gum is a dietary fiber obtained from Indian cluster beans (Guar). It forms a viscous gel when in contact with water. Administered just before or mixed with food, it slows gastric emptying, and delays carbohydrate absorption. This results in the suppression of postprandial glycemia. It also reduces serum cholesterol by about 10%.

NEWER APPROACHES IN DIABETES:

1. Exenatide: The glucagon-like peptide-1 (GLP-1) is an important incretin i.e. released from the gut in response to orally administered glucose.

It has limited clinical use because of rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4).

Exenatide is a synthetic GLP-1 analogue which is resistant to DPP-4, and acts by enhancing postprandial insulin release, suppressing glucagon release, and slowing gastric emptying.

2. Sitagliptin: This orally active drug inhibits DPP-4 thereby preventing the degradation of endogenous GLP-1 and other incretins.
3. Pramlintide: This synthetic amylin is a polypeptide produced by pancreatic β cells which acts by reducing glucagon secretion from cells and also delays gastric emptying.
4. Dopamine D2 agonist: Circadian rhythm of hormone (GH, prolactin, ACTH, etc.) release and reset it to reduce Dapagliflozin Insulin resistance.
5. Sodium-glucose co-transport-2 (SGLT-2) inhibitor: Dapagliflozin
   Almost all the glucose filtered at the glomerulus is reabsorbed in the proximal tubules. The major transporter which is responsible for the absorption of glucose is SGLT-2. Inhibition of this transporter lowers blood glucose (by reducing glucosuria) in type 2 DM, as well as causes weight loss. Side effects arise due to glycosuria which can predispose to uro-genital infections, electrolyte imbalance and increased urinary frequency.

Use of insulin and oral hypoglycemic agents in specific conditions:

- Insulin and sulfonylureas reduced microvascular complications in type 2 DM, but did not have a significant effect on macrovascular complications.
- Metformin could reduce macrovascular complications as well; it decreased the risk of death and other diabetes-related endpoints in overweight patients.
- When a diabetic on oral hypoglycemic presents with infection, severe trauma or stress, pregnancy, ketoacidosis or any other complication or has to be operated upon- switch over to insulin.

METHODOLOGY:

This study was carried out at the Apollo Hospital, a reputable hospital in Hyderabad, Telangana. Additionally, a pharmacy is also present there. Here, a lot of patients come from Telangana and the surrounding areas. The study took place at Apollo Hospital over the course of a month. A survey of about 100 patients has been conducted, and their case records were carefully examined. Retrospective analyses of treatment records are part of the study. We focused on a number of factors, including the patient's gender, age, and various classes of drugs that were administered along with their route of administration. Documented information was collected from the case sheet of respective wards, only in the presence of delegated neurologist and his assistants. Although the patient's identity was kept confidential, an ID number was assigned to each patient. The review of 100 cases in total, along with the analysis of forms was carried out in accordance with neurologist recommendations. The information gathered for the study included: Patient ID no., date of admission and date of discharge, age, and sex of the patient, history of illness, provisional diagnosis, names, dose, and route of administration of the prescribed drugs.

Diabetes complications develop gradually over time. The longer you have diabetes and the less well you control your blood sugar, the more likely complications are. Over time, complications from diabetes could become incapacitating or even fatal. Complications could include:

1. Cardiovascular disease: Diabetes significantly raises the risk of a variety of cardiovascular problems, such as coronary artery disease with chest pain (angina), heart attack, stroke, and artery narrowing (atherosclerosis).
2. Nerve damage (neuropathy): Too much sugar can harm the walls of the tiny blood vessels (capillaries) that nourish your nerves, particularly in the legs. This can result in tingling, numbness, burning, or pain that usually starts at the tips of the toes or fingers and gradually spreads upward. If left untreated, the patient may lose all feeling in the affected limbs. Damage to the digestive nerves can result in nausea, vomiting, diarrhea, or constipation. It may cause erectile dysfunction in men.
3. Kidney damage (Nephropathy): The kidneys contain millions of tiny blood vessel clusters (glomeruli) that filter waste from the blood. Diabetes can harm this delicate filtering system. Severe damage can result in kidney failure or irreversible end-stage kidney disease, which may necessitate dialysis or a kidney transplant.
4. Eye damage (Retinopathy): Diabetes can damage the retina's blood vessels (diabetic retinopathy), potentially leading to blindness. Diabetes also increases the risk of other serious vision conditions such as cataracts and glaucoma.

5. Foot damage: Nerve damage in the feet or poor blood flow to the feet increases the risk of various foot complications. If cuts and blisters are not treated, they can develop serious infections and often heal poorly. These infections may eventually necessitate amputation of a toe, foot, or leg.
6. Skin problems: Diabetes can make you more prone to skin problems such as bacterial and fungal infections.
7. Hearing impairment: Diabetes patients are more likely to have hearing impairments.
8. Alzheimer's disease: Type 2 diabetes has been linked to an increased risk of dementia, including Alzheimer's disease. The worse is the blood sugar control, the higher is the risk appears to be. Although there are theories about how these disorders are related, none of them have been proven.
9. Depression: People with type 1 and type 2 diabetes frequently
10. experience depression symptoms. Diabetes management can be hampered by depression. [9] [10] [11]

Diagnosis of Diabetes Mellitus:

	HbA1c (percent)	Fasting Plasma Glucose (mg/dL)	Oral Glucose Tolerance Test (mg/dL)
Diabetes	≥ 6.5	≥ 126	≥ 200
Prediabetes	5.7 – 6.4	100 - 125	140 – 199
Normal	~ 5.7	≤ 99	≤ 139

Fig1: Blood test levels for diagnosis of Diabetes and Prediabetes

RESULTS:

Demographic details of Patients:

Fig2: Based on Age.

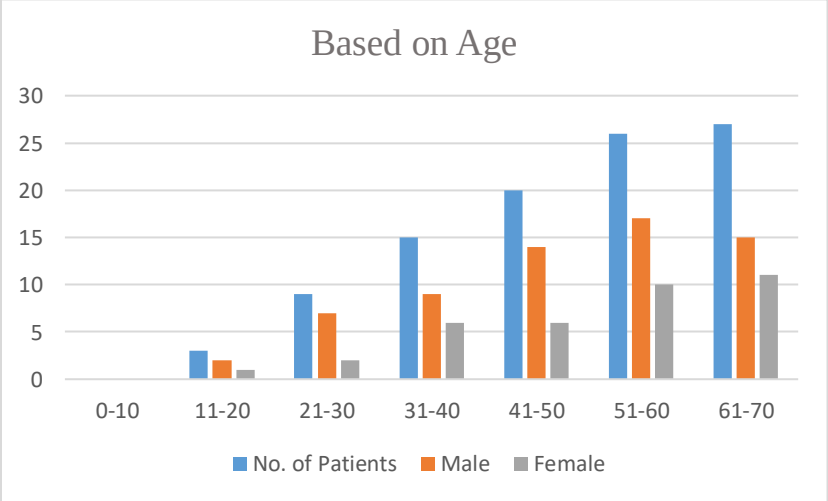


Fig3: Based on Gender & Route of Administration.

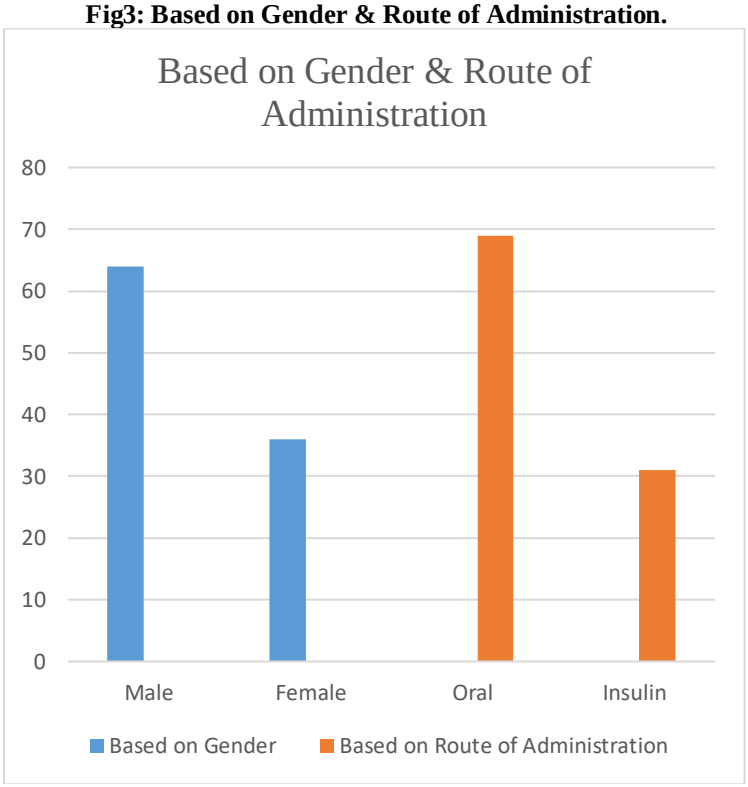


Fig4: Based on prescribing frequencies of other drugs.

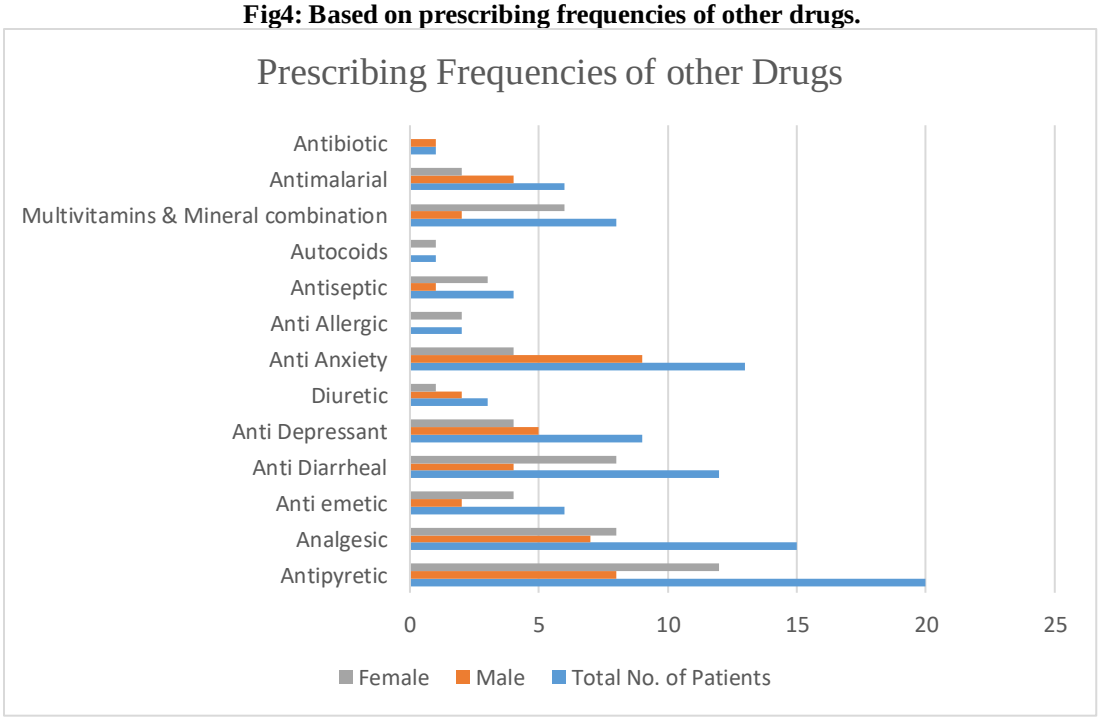


Fig 5: Based on Etiology.

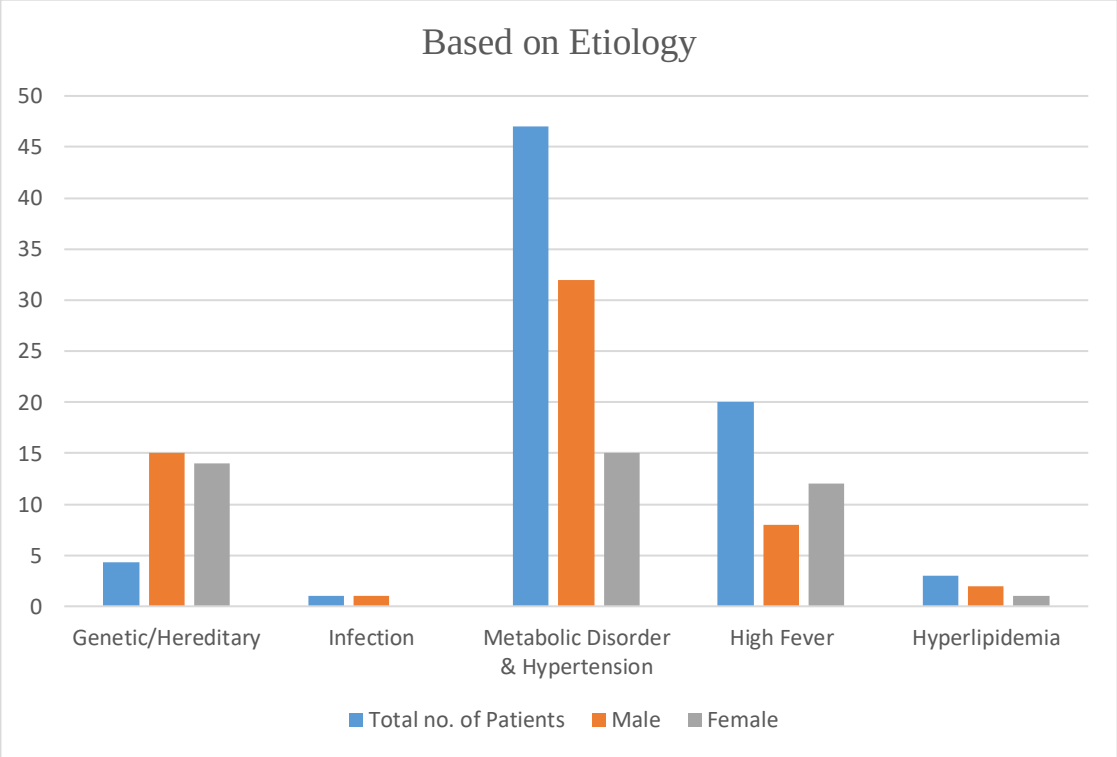
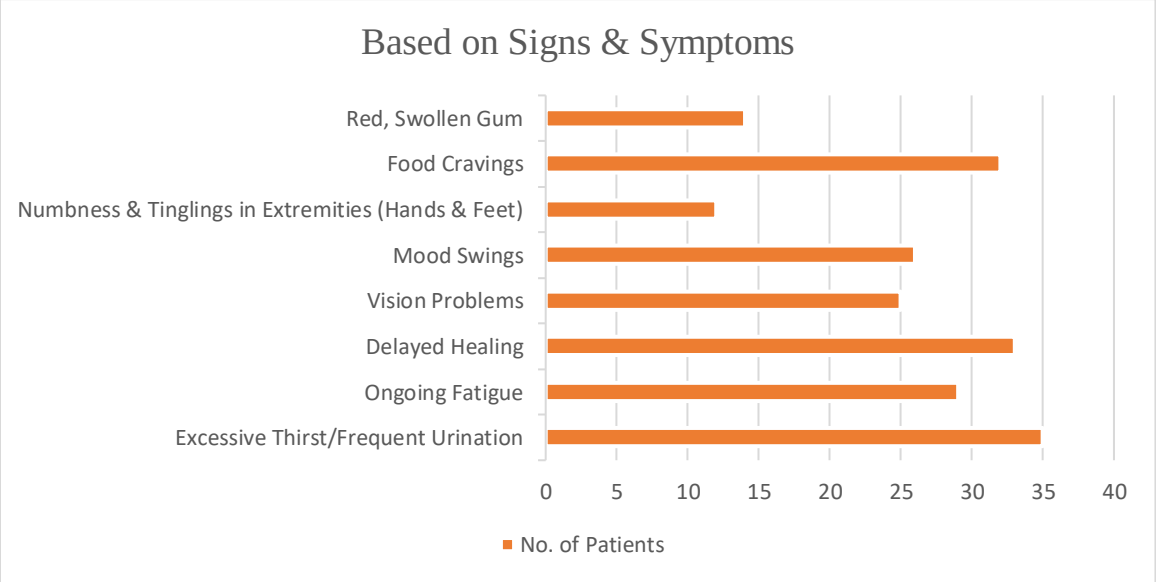


Fig 6: Based on signs & symptoms.



This study emphasizes the importance of patient education or counseling regarding the use of antidiabetic and concomitant drugs, blood glucose and glycosylated hemoglobin (HbA1c) levels, diet control, and the correction of diabetic complications. HbA1c monitoring of patients' adherence to prescribed treatments is recommended, and measures to improve it should be taken.

DISCUSSION:

We assess the utility of these studies in determining true drug consumption, assessing comorbidity in diabetic patients, and determining the prevalence of diabetes. International comparisons of antidiabetic drug utilization, which were also reviewed and

analyzed, show wide variations in the use of hypoglycemic agents, which have arisen for unknown reasons. The lack of studies linking these variations in antidiabetic drug use to particular clinical outcomes has prevented drug utilization research from being as thorough as it could be. There is a need to broaden the applications of research on the use of antidiabetic agents, including assessment of morbidity patterns.

CONCLUSION:

The patients in this study had poor hypertension awareness and control. Diabetes mellitus, on the other hand, was associated with both greater awareness and better control of hypertension than hypertension alone. This may be due to the higher use of antihypertensive medications by patients with diabetes mellitus, as type 2 diabetic patients in this setting were treated with multiple antidiabetic drug therapy. Biguanides (metformin) were the most commonly prescribed diabetes drug class, followed by sulphonylureas (glimepiride), thiazolidinediones (pioglitazone), insulin, alpha-glucosidase inhibitors (miglitol). Insulin was the most commonly used multiple therapy. In our study, we found that while more than half of type 2 diabetic patients showed poor adherence (compliance) to prescribed therapy increases and greater utilization of newly developed medications, there were no concurrent improvements in overall glycemic control or rates of severe hypoglycemia. Although the use of newer and more expensive agents may have additional benefits, more research is needed to determine the value and cost-effectiveness of current treatment options.

Hypertension is a significant, modifiable risk factor for diabetes's macrovascular and microvascular complications. The clinical efficacy of lowering blood pressure is well documented, with cardiovascular and microvascular benefits demonstrated for multiple classes of antihypertensive medications.

Treatment should be individualized to the specific patient based on their comorbidities; their anticipated benefit for the reduction in ASCVD, heart failure, progressive diabetic kidney disease, and retinopathy events; and their risk of adverse events.

Pharmacists are the key persons for better management of therapy based on the stage and condition of the patient. The pharmacist is thus a "DRUG EXPERT who performs valuable, knowledge-based duties and serves the community in a very dutiful manner."

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