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DIABETES MELLITUS -MONITORING OF ADVERSE DRUG REACTIONS

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ABSTRACT

Diabetes mellitus is an endocrinological and/or metabolic disorder with an increasing global prevalence and incidence. Diabetes Mellitus is a group of physiological dysfunctions characterized by hyperglycaemia resulting directly from insulin resistance, inadequate insulin secretion or excessive glucagon secretion. It has many sub-classifications including Type-1, Type-2, Gestational Diabetes and Steroid-Induced Diabetes. Type-1 and Type-2 Diabetes Mellitus are the main sub-types each with different pathophysiology, management but both have a potential for hyperglycaemia. The risk of Adverse Drug Reactions (ADRs) was especially high for patients with diabetes undergoing chemotherapy. It important to learn about Adverse Drug Reactions, because ADRs are one of the leading causes of morbidity and mortality in healthcare. One-third of people with diabetes experience at least one Adverse Drug Reaction. Biguanides, peptide hormones and sulphonyl urea are the classes of Antidiabetics drugs and amongst them most commonly used drugs are "Metformin and Insulin". Mostly ADRs were related to the endocrine and gastrointestinal system. In this article we aimed to evaluate the Adverse Drug Reaction incidence in patients suffering with Diabetes Mellitus.

Keywords: Diabetes mellitus, Endocrinological, Hyperglycemia, Juvenile diabetes, Gestational diabetes

1. INTRODUCTION

Diabetes is a multi-factorial, chronic and progressive metabolic disorder characterized by chronic hyperglycaemia due to defects in the metabolism of carbohydrate, fat and protein **[1, 36]**. Diabetes is either due to the pancreas not

producing enough insulin or the cells of the body not responding properly to the insulin produced **[2]**.

1.1 **Types of diabetes**

Diabetes is referred as an elevated blood sugar level which may be due to many causes. Based on these various causes, diabetes is classified into different types. Depending on what causes the problem, treatment for the problem vary. There are three main types of diabetes mellitus namely Type 1, Type 2 and Gestational diabetes mellitus **[3]**.

1.2 **Type 1 diabetes** is an auto-immune condition, characterized by failure of the pancreas to secrete enough insulin due to idiopathic attack or autoimmune destruction of insulin secreting beta-cells of the islets of Langerhans in the pancreas **[4]**. In simpler words, beta cells of the pancreas that produce insulin are mistakenly destroyed by the immune system. This leads to an absolute deficiency of insulin. Earlier this form was termed as insulin dependent diabetes mellitus also known as juvenile diabetes.

Causes: It is mainly due to genetic causes. Some people also get affected due to environmental factors. Certain researches also prove that, it can be due to some chronic low grade enter-o-virus infection present in the pancreas **[5]**.

Symptoms:

Frequent urination, Increased appetite, Frequent thirst, Weight loss, Mood swings

Treatment and management:

Type 1 diabetes can be managed with medications and life-style modifications.

1. Insulin

   Type 1 diabetes can be treated by taking artificial insulin every day, either through injection or an insulin pump **[6, 37]**.

2. Metformin

   It has an oral medication that helps to manage blood sugar levels by improving body's ability to utilize insulin. Previously, it was prescribed to the patients only with type 2 diabetes but presently it also used in the patients with type 1 who are experiencing insulin-resistance.

3. Other medications

   If diabetes leads to other problems like hypertension or renal diseases, doctor may prescribe other medications to help and manage those conditions.

4. Diet and exercise

   - Monitoring and counting carbs
   - Maintaining healthy diet
   - Reducing stress

Being physically active can also lower the blood sugar levels.

Curing type 1 diabetes:

Scientists of diabetes research institute are working on a biological cure that would restore the body's ability to produce insulin. One approach includes a method known as islet transplantation. In this method, cells from pancreas of a healthy person are transplanted into a patient with type 1 diabetes.

1.3 Type 2 diabetes is globally the most commonly occurring. Previously, adults above 30 years were mostly affected, but according to the recent cases, it is also observed amongst obese children. It begins with insulin resistance, a condition in which cells fail to respond to insulin properly. Lack of insulin development is observed as the disease progresses. Earlier, this form was known as non-insulin dependent diabetes mellitus or adult-onset diabetes or late onset diabetes. It may be treated with oral anti-diabetic medications, with or without insulin. Gestational diabetes mellitus occurs when glucose intolerance is first observed during pregnancy. It usually resolves after the birth of the baby.

According to the World Health Organization, diabetes resulted in 1.6 million deaths, thus, becoming the 9th leading cause of death globally. The raise of diabetes in India is expected to be over 134 million by 2045 according to 019 estimates. Largely influenced risk factors for diabetes may include age, family history, obesity, unhealthy diet and physical inactivity **[7]**.

2. ADVERSE DRUG REACTIONS:

A prospective study was undergone in India to report the adverse drug reactions (ADRs) in patients with type 2 diabetes mellitus (T2DM) using anti-diabetic drugs. A total of 220 patients (121 males, 99 females) were enlisted. Severity and causality assessment was done using modified Hart-wing and Siegal's scale and Naranjo's probability scale, respectively. Commonly prescribed drugs were peptide hormone, sulphonylurea and biguanides. Most commonly observed ADRs were related to gastrointestinal system and endocrine system. Severity assessment of ADRs showed 26.9% as moderate, 73.1% as mild for 26 patients (16-males, 10-females). No severe reactions were observed **[8]**.

The prevalence of type 2 diabetes mellitus(T2DM) is increasing worldwide and has reached epidemic proportions in many countries. Worldwide, 420 million people have diabetes and the number of people with the disease will rise up to 645 million by 2040 **[9]**. In India, more than 65.1 million cases were confirmed as T2DM and it is estimated that by 2030 there will be almost 89 million patients. Similar to other countries, the aetiology of diabetes includes genetic factors, environmental influences such as obesity, life style changes **[10]**.

All the patients (>=25 yr), with T2DM, attending medicine outpatient department, emergency department, admitted to

Intensive Care Unit and medical wards during the study and willing to share the disease history were included in the study **[11]**. The details of ADRs were taken and collected from the patients as per the requirements specified in pharmacovigilance programme of India (PvPI) prescribed genuine reporting form. Patients below 25 yr, and patients taking herbal drugs or drugs of abuse are excluded from the study.

The ADRs were classified on the basis of drug class and System organ class (SOS). Causality assessment was done on the basis of Naranjo's scale and severity assessment using Modified Hart-wig and Siegel's scale **[12]**.

A total of 220 patients with T2DM were observed for the study, of whom 121 were males. 156 patients were in the age of 25 and 64 patients were elderly patients. During this study, 26 ADRs were observed and maximum were observed from elderly patients **[13]**. As per SOS commonly seen ADRs were related to gastrointestinal system, particularly loss of appetite & epigastric pain and in endocrine system, particularly hypoglycaemia was observed and also ADRs related to skin and appendages, musculoskeletal, cardiovascular and respiratory system were also seen **[14]**.

Classification of ADRs according to drug class showed that four of 21 patients treated with sulphonylureas, nine of 70 patients treated with biguanides, three of 35 patients treated with peptide hormone, four of 34 patients were among combination drugs such as sulphonylurea + biguanide combination experienced ADRs **[15]**.

Of the 26 ADRs, 8 were considered as probable when evaluated at Naranjo's scale of probability and remaining 18 were considered as possible **[16]**. On severity assessment 7 ADRs were moderate and 19 were mild, no severe reactions were observed **[17]**.

2.1 Dose-Dosage form-

2.1.1 Metformin- (Brand Name- Glucophage, Glucophage XR, Glumetza, Riomet, Riomet ER)

Table 1: Metformin dose and dosage form [18]

Age group	Dosage forms	Dose Strength
Adults	Tablets (immediate release)	500mg, 850mg, 1000mg
	Tablet (extended release)	500mg, 750mg, 1000mg
	Oral solution	100mg/ml
	Oral suspension (Extended release)	• 47.31g/473mL per bottle Reconstituted suspension is 500mg/5mL
Paediatrics	Tablet (immediate release)	500mg, 850mg, 1000mg
	Oral solution	100mg/ml
	Oral suspension (Extended release)	• 47.31g/473mL per bottle Reconstituted suspension is 500mg/5mL

2.1.2 Insulin- (brand name- Humulin R, Novolin R, Humulin R U-500, Myxredlin)

Table 2: Insulin Dose and dosage form [19]

Age group	OTC	Rx-
Adult	100units/mL (3mL vial) 100units/mL (10mL vial)	500units/mL (20mL vial); prescribe with U-500 syringes to avoid conversion for U-100 tuberculin syringes ii. 500units/mL (3mL pen) iii. 100units/100mL 0.9% NaCl
Paediatric	100units/mL (3mL vial) 100units/mL (10mL vial)	500units/mL (20mL vial); prescribe with U-500 syringes to avoid conversion for U-100 tuberculin syringes ii. 500units/mL (3mL pen) iii. 100units/100mL 0.9% NaCl

Insulin delivery technology-

i. Insulin syringes
ii. Insulin pens or shots
iii. Insulin pumps and artificial pancreas technology **[20, 21]**

2.2 Use of metformin in diabetes patients-

Type 2 diabetes mellitus is primarily treated with metformin, especially in obese people. Comparing metformin to insulin, glibenclamide, and chlorpropamide, it has been demonstrated that metformin reduces diabetes mortality and complications by 30% **[22]**.

Metformin lowers serum glucose levels via a number of various mechanisms, most notably non-pancreatic ones that don't result in an increase in insulin secretion, metformin lowers serum glucose levels. It is known as an "insulin sensitizer" because it makes insulin work more effectively. The liver's endogenous glucose synthesis is suppressed by metformin, primarily as a result of a decrease in the rate of gluconeogenesis and a minor impact on glycogenolysis. Furthermore, metformin stimulates insulin signalling and glucose transport in muscles while inhibiting key enzymes involved in gluconeogenesis and glycogen production in the liver. When the enzyme adenosine monophosphate kinase (AMPK) is activated., the AMPK regulates the cellular and organ metabolism and any decrease in hepatic energy, leads to the activation of AMPK **[23]**.

It helps bring down your N

level in three ways:

- Your liver is instructed to produce less glucose.
- It reduces insulin resistance, which improves the way your muscles use insulin and allows glucose to enter your muscles rather than just remain in your blood.
- It aids in reducing the amount of glucose your intestines absorb from food.

It can lower your A1c, the "average" of your blood sugar control over a few months. It can also delay pre-diabetes from becoming diabetes **[24]**.

Usually when we use medication for diabetes, we can observe that there are lot of drugs which increase your weight but in case of metformin a recent study shows that patient using metformin has gained weight of around 1kg after 10yrs of treatment, but the patients treated with glibenclamide gained about 3kgs and patients treated with insulin gained over 6kgs **[22]**.

Metformin is often prescribed for polycystic ovary syndrome (PCOS), but FDA hasn't approved it **[25]**.

Metformin has been reported very useful in various conditions and has been effectively used for certain disease or disorder though years such as- Gestational diabetes, Polycystic ovary syndrome, Cancer protection, associated diabetes, Nephrotoxicity prevention

2.2.1 Major side effects seen in patients using metformin as their primary treatment are classified into 3 types –

1. Common adverse effects-
   Heartburn, stomach pain, nausea or vomiting, bloating, diarrhoea, constipation, weight loss, headache, unpleasant metallic taste in the mouth.
2. Rare adverse effects-
   Some people (less that 5%) reported heartburn, headache, upper respiratory infection, and bad taste in their mouth especially when extended-release metformin is taken and also 12% people reported flu-like symptoms, sweating, flushing, heart palpitations, rashes **[26]**.
3. Serious adverse effects-
   i. Lactic acidosis ii. Anaemia iii. Hypoglycaemia

i. Lactic acidosis-

It is a dangerous condition caused by build-up of lactic acid, a chemical which is made naturally by our muscles and red blood cells. When this happens while taking with metformin, it's called metformin-associated lactic acidosis (MALA).

Although it is very rare, this condition has a "black box" warning regarding its risk. A boxed warning is the most severe warning given by Food and Drug Administration (FDA).

It usually occurs due to metformin build-up in the body. The build-up causes pH imbalance in the body. It's a medical emergency that should be treated immediately.

The death rate of metformin-associated lactic acidosis is about 30-50% but its only reported per every 100,000 patients a year.

Metformin-associated lactic acidosis is more likely to happen if-

- Have kidney or liver disease

- Drinking a lot of alcohol
- Have severe congestive heart failure
- Are sick with fever, diarrhoea, or vomiting
- Are dehydrated

If any symptoms of lactic acidosis are seen consult doctor immediately and also if,

Extreme tiredness, weakness, decreased appetite, nausea, vomiting, dizziness, trouble breathing, light headedness, fast or slow heart rate, feeling cold, muscle pain, flushing or sudden reddening and warmth, stomach pain with any of these other symptoms **[27]**

ii. Vitamin B12 deficiency-

- Metformin can decrease the levels of vitamin b12 in the body.
- It rarely causes anaemia (low red blood cells)
- Lack of vitamin b12 causes peripheral neuropathy.
- It's also a good idea to add foods naturally high in B12 to your diet. Beef liver and clams have the most. Chicken, beef, eggs, dairy products, and fortified cereals are good sources. Supplements can also bring your levels back to normal.

The more common symptoms of anaemia include: Tiredness, dizziness, light headedness

iii. Hypoglycaemia-

Metformin usually doesn't cause hypoglycaemia, but in rare cases it might develop when combined with- Poor diet, Strenuous exercise, Excessive alcohol intake **[28]**, Other diabetes medications (Insulin and insulin secretagogues) **[29]**, Have hormone disorder, Fasting, Kidney or liver problems

Early signs of hypoglycaemia include- Feeling hungry, trembling and shaking, sweating, confusion **[30]**.

4. Serious side effects-

These are very rarely seen in less than 1 in 10,000 people. Severe tiredness, fast or shallow breathing, being cold, slow heartbeat, sclera of eye turns yellow, skin turns yellow.

5. Serious allergic reactions-
   i. In rare cases anaphylaxis
   ii. Leukocytoclastic vasculitis
   iii. Psoriasiform drug eruption **[31]**

2.3 Use of Insulin in diabetes mellitus-

The medication insulin regular (human) is a member of the insulin drug class. Your body produces the hormone insulin to aid in the transfer of glucose (sugar) from the bloodstream to your cells. The sugar is used by your cells to fuel your body. In those with type 1 diabetes, the pancreas cannot produce insulin. If you have type 2 diabetes, your body either produces insufficient insulin or uses it improperly. High blood sugar levels

result from the sugar staying in your system in the absence of enough insulin (hyperglycemia).

Short-acting human insulin normal is a synthetic form of the hormone that your pancreas produces. It mimics the insulin your body produces in reaction to meals. This additional insulin aids in blood sugar regulation and guards against diabetic complications.

Insulin regular (human) can cause minor or significant adverse effects. Some of the most significant negative effects are listed below-

a) Swelling of your arms and legs

b) Weight gain

c) Low blood sugar (hypoglycaemia). This needs to be treated.

Symptoms can include:

Sweating, dizziness or light headedness, shakiness, hunger, tachycardia, tingling in your hands, feet, lips, or tongue, trouble concentrating or confusion, blurred vision, slurred speech, anxiety, irritability, or mood changes

- Injection site reactions-

  If you keep having skin reactions or they're serious, don't inject insulin into skin that is red, swollen, or itchy. Symptoms at the injection site can include: Redness, swelling, itching.
- Skin changes at the injection site (lipodystrophy)- Change (rotate) the site on your skin where you inject your insulin to help reduce the chance of developing these skin changes. If you have these skin changes, don't inject insulin into this type of skin.

Symptoms can include- shrinking or thickening skin at the injection sites **[32]**

2.3.1 Serious side effects-

- Hypoglycaemia-

  The most prevalent and dangerous adverse effect of insulin, occurring in roughly 16% of type 1 and 10% of type II diabetes patients, is hypoglycemia (the incidence varies greatly depending on the populations studied, types of insulin therapy, etc). Despite the endocrinologic counterregulatory responses to hypoglycemia, some responses are diminished, ineffective, or non-existent in some cases.

  Patients receiving intense or ongoing insulin infusion therapy have an increased chance of experiencing hypoglycaemia.

  Symptoms include: mood changes, confusion, including delirium, light-headedness or dizziness, Sleepiness, blurred or impaired vision, tingling or numbness in your lips or tongue, headaches, fatigue, lack of coordination, seizure, loss of consciousness **[33]**
- Hypokalaemia-

  Symptoms include: tiredness, weakness, muscle cramps, constipation, breathing problems (at a severe stage without medical

attention), heart rhythm problems (at a severe stage without medical attention)

- Hypersensitivity –

  Because more pure forms of porcine insulin or synthetic human insulin are being used, hypersensitivity reactions, whether local or systemic, are becoming less common (less than 1% of patients). Subcutaneous nodules, erythema, oedema, or heat are some examples of local responses. They typically arise during the first two weeks of therapy before going away. True insulin allergies are uncommon, and sensitization is typically linked to particular animal proteins in bovine and less pure forms of porcine insulin.

  Desensitization is an option for diabetes patients who have a real allergy to insulin. Some insulin manufacturers sell desensitisation kits and procedures. Symptoms include: a rash all over your body, trouble breathing, fast heart rate, sweating, feeling faint, swelling of your hands and feet.

- Cardiovascular-

  The effects of hyperinsulinemia on the cardiovascular system are being assessed. Some specialists are considering insulin as a potential atherogenic drug because diabetic individuals frequently have microvascular and macrovascular disorders. The idea that hyperinsulinemia serves as the prelude of hypertension is controversial and the subject of ongoing research. Aside from hypertension and carbohydrate tolerance, other cardiovascular risk factors that are increased in those with these conditions include dyslipidaemia, impaired platelet function, clotting factors, and the fibrinolytic system. Currently, research is being done to determine how these illnesses relate to diabetes and insulin. By boosting renal salt retention, encouraging vascular smooth muscle hypertrophy, and/or stimulating the sympathetic nervous system, insulin may contribute to the aetiology of hypertension. It might cause dyslipidemia by encouraging the production of very low-density lipoproteins in the liver (VLDLs).

  Symptoms include: shortness of breath, swelling of your ankles or feet, sudden weight gain.

- Immunologic-

Immunologic Anaphylaxis to various insulin preparations has occasionally been characterised by considerably raised serum

levels of IgE and IgG to protamine, but not by anaphylaxis to ordinary insulin.

Anti-insulin antibodies can develop as a result of immunologic reactions to insulin, especially animal insulin formulations. The elimination half-life of insulin lengthens in the presence of these antibodies.

- Ocular-

Bilateral presbyopia at the start of therapy is a rare ocular condition (blurry vision). This is often self-limited and is considered to be caused by changes in the osmotic equilibrium between the lens and the ocular fluids.

- Gastrointestinal-

  Occasionally, insulin has been linked to gastrointestinal upset. With dose reduction, GI distress usually goes away **[32, 34]**.

3. OVERCOMING THE ADVERSE EFFECTS-

- Take metformin with meal
- Switch to extended-release metformin
- Be careful with dietary changes and supplements **[35]**
- Choosing right type of insulin
- If ADRs are severe use non-insulin medication or alternative treatment.
- If severe hypoglycemia is seen patient can have a quick release glucose drink, a piece of hard candy, a sugar lump, etc.

4. CONCLUSION

Evaluation of ADRs is important for the analysis of risk factors to ensure maximum benefits of drug therapy. More data on prescribed drugs and their effects will help in reducing and elimination of ADRs and ensure patient safety.

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