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A STUDY ON EFFECT OF DRUG DURING IN CLINICAL MANAGEMENT OF DIABETES

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ABSTRACT:
Diabetes is defined as a state in which homeostasis of carbohydrate, protein and lipid metabolism is improperly regulated as a consequence of a relative or absolute deficiency of insulin secretion, resistance to insulin action or both at one or more center in tedious pathways of hormones activity. Diabetes is deadly disease in both developed and developing countries. In 2000, there were a probable 175 million people with diabetes universal and by 2030, the projected estimate of diabetes is 354 million. The most widely recognized unfavorable responses to insulin are weight addition and hypoglycaemia (Henry et al, 1993; Kudlacek et al, 1992). Weight increase in the wake of beginning insulin treatment for uncontrolled diabetes is an inescapable outcome and is the consequence of expanded truncal fat and muscle mass and severe side effects of biguanides include diarrhoea, abdominal discomfort, nausea, metallic taste, and anorexia.
Keywords: Diabetes, Insulin, Biguanides and Hypoglycaemia.

1. INTRODUCTION:

The word *diabetes* is Greek for a draw off, referring to the ejection of a more quantity of urine; and *mellitus* is Latin used for sugar. Consequently diabetes mellitus means the passage of huge amounts of sweet urine. This is derived from the information that excess glucose in the blood spills over into the urine, absorbing fluids with it. Diabetes mellitus is a clinically and hereditarily heterogeneous group of disorders characterized by abnormally elevated levels of glucose in the blood. The hyperglycemia is due to lack of insulin secretion or to resistance of the body's cells to the action of insulin, or to a combination of these. Frequently there are also disturbances of carbohydrate, fat, and protein metabolism. Glucose metabolism involves small intestine, pancreas, muscle cell and liver. If there are, some problem with any of this diabetes organ leads to defect in glucose metabolism and can develop diabetes (The expert committee on the diagnosis and classification of diabetes mellitus, 2002). The classical symptoms of diabetes are Polydipsia, Polyuria and Polyphagia; Polydipsia or excessive thirst is a method of restoring the water content of the tissues lost by Polyuria (Tiwari et al, 2002). The mechanism responsible for Polyuria or increased volume of urine output is based on the amount of glucose in circulating blood and accumulation of ketone bodies in blood acts as diuretics (Tierney et al, 2002). Symptoms may develop quite rapidly in insulin dependent diabetes, mainly in children; in type 2 diabetes symptoms usually develop much more slowly and may be subtle or completely absent (Tierney et al, 2002)

1.1 Diabetes Mellitus Scenario in World

The occurrence of diabetes is hastily rising all over the world at a frightening rate (Huizinga and Rothman, 2006). Over the past 30 years, the status of diabetes has changed from being measured as a kind disorder of the old to one of the main causes of morbidity and mortality disturbing the childhood and middle aged people. It is essential to note that the increase in prevalence is seen in all six populated continents of the globe. Diabetes is deadly disease in both developed and developing countries. In 2000, there were a probable 175 million people with diabetes universal and by 2030, the projected estimate of diabetes is 354 million (Wild et al., 2004). The worldwide increase in the popularity of diabetes is owed to population growth, aging, urbanization and an augment of obesity and physical inactivity. The prime determinants of the epidemic are the rapid epidemiological transition associated with alteration in dietetic patterns and reduced physical activity. Unlike in the West, wherever older populations are mainly affected, the burden of diabetes in Asian countries is excessively high in young to middle-aged adults (Chan et al, 2009; Ramachandran et al, 2010). Healthcare expenditures on diabetes are expected to account for 11.6% of the total healthcare expenditure in the world in 2010. Expected global healthcare

expenditures to treat and avert diabetes and its complications are expected to total as a minimum 376 billion U.S. Dollars (USD) in 2010. By 2030, this number is expected to go above some USD490 billion (IDF Diabetes Atlas, 2009).

1.2 Diabetes Mellitus Scenario in India

India goes in front the world with leading number of diabetic patients earning the doubtful distinction of being termed the "diabetes capital of the earth". In India simply, the occurrence of diabetes is expected to rise from 31.7 million in 2000 to 79.4 million in 2030 (Wild et al, 2004). The World Health Organization guess that death from diabetes as well as heart disease cost India about $210 billion each year and is likely to increase to $335 billion in the subsequently ten years (Bjork, 2003). In the national investigation 54.1% of diabetes developed it in the mainly productive years of their life specifically prior to the age of 50 years and they also had a high threat of developing chronic complications of diabetes (Ramaiya et al., 1990; Ramachandran et al., 1992). The incidence of non-insulin-dependent diabetes is 4-6 times higher in the urban areas as compared to rustic areas. The pervasiveness of impaired glucose tolerance (IGT) in the rural inhabitants is also high at 7-8%, which indicates existence of a genetic basis for Type 2 diabetes in tribal Indian population (Viswanathan et al, 1996).

Diabetes is a costly disease for the health care sector, at communal and at individual level. Expenditure of diabetes care is extremely high. The cost of concern increases a lot of folds when complications occur or when access to hospital, operation or insulin treatment is needed. A study by the authors has shown that the yearly median expenses by patients on diabetes care are Rs 10,000 in city and Rs 6,300 in rustic areas (Ramachandran et al, 2007). A low-income person spends nearly 25–35% of their yearly income on diabetes concern. Due to the high financial burden on the patients as well as their families, people are likely to neglect health care causing severe morbidities and early death.

2. PATHOPHYSIOLOGY

2.1. Pancreatic Islet Hormones

Islets of Langerhans are cell clusters (often hundreds of cells) that are spread throughout the pancreas and perform the endocrine function (Henderson, 1969). Islets constitute about 2% by weight of the adult human pancreas and are multicellular microorgans (Bonner-Weir, 2005; Klöppel and Veld, 1997). The islets consist of five major cell types which are characterized by different hormone secretion profiles (Fig- 1.01): β-cells secrete insulin (to decrease blood glucose); α-cells secrete glucagon (to increase hepatic glucose production and blood glucose); δ-cells secrete somatostatin (to regulate α and/or β-cell hormonal secretion); PP cells secrete pancreatic peptide (to inhibit gall bladder contraction, increase gastrointestinal motility and self regulate pancreatic exocrine and endocrine secretion), and Epsilon cells secrete ghrelin (to increase hunger before a meal, stimulate growth hormone secretion and inhibit fat utilization in adipose tissue) (Wierup et al, 2002).

2.2 Insulin:

Insulin, the most important hormonal regulator of glucose metabolism, was earliest isolated from pancreatic tissue and it is a quite small protein, with a molecular weight of around 6000 Daltons. (Banting and Best, 1922). Insulin is a 51 amino acid anabolic peptide-hormone that is secreted by the β-cells in the Islets of Langerhans. Insulin made up of two chains (A and B) linked by disulfide bonds. One of its principal functions is the stimulation of glucose uptake from the systemic circulation, in addition to the restraint of hepatic gluconeogenesis, thus serving a main role in glucose homeostasis and preventing the metabolic disorder diabetes mellitus (Scott, 1912; Duville et al, 1997).

3. CATEGORIZATION OF DIABETES MELLITUS

Diabetes mellitus emerges in two diversities, everyone with its individual cause: diabetes mellitus type I (previously known as juvenile onset diabetes), caused by lack of the pancreatic hormone insulin (whose principal function is to encourage the entry of glucose into cells); and diabetes mellitus type II (previously known as maturity onset diabetes), in which insulin is accessible but cannot be appropriately utilized (The expert committee on the diagnosis and classification of diabetes mellitus, 2002). The third group consists of other less common types of diabetes that are caused or associated with certain specific conditions and/or syndromes. The very last group comprises diabetes diagnosed during pregnancy, called gestational diabetes (GDM) (Tuomilehto et al, 2001).

3.1. Type 1 Diabetes Mellitus (β-cell destruction, frequently leading to absolute insulin deficiency)

This usually leads to a type of diabetes in which insulin is required for survival. Individuals with type 1 diabetes are metabolically normal before the disease is clinically manifest, but the process of β-cell destruction can be detected earlier by the presence of certain autoantibodies. Type 1 is normally recognized by the nearness of against GAD, islet cell or insulin antibodies which find the immune system forms that lead to beta–cell demolition. This type of diabetes recently incorporated by the terms Type I diabetes, Insulin subordinate diabetes or adolescent beginning diabetes

results from immune system interceded obliteration of beta cells of pancreas (Atkinson and Maclaren, 1994).

3.2. Type 2 Diabetes Mellitus (**ranging from primarily insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance)**

This type of diabetes consists of heterogeneous conditions responsible for approximately 90% of all individuals with diabetes. . It is often associated with central or visceral obesity, as well as other cardiovascular risk factors such as hypertension, and abnormalities of lipoprotein metabolism with the characteristic dyslipidemia of elevated triglycerides and low high-density lipoprotein cholesterol. Type 2 diabetes (T2D) is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature. Both are usually present at the time that diabetes becomes clinically manifest (Kolterman et al, 1985).

4. MEDICATION OR CHEMICAL-INDUCED DIABETES

Drug-induced diabetes occurs due to a variety of drugs and mechanisms (Comi, 2004). An underlying and often unsuspected abnormality in carbohydrate metabolism in the patient or a family history of diabetes greatly increases the risk for developing drug induced diabetes. A lot of drugs can damage insulin secretion. These drugs can not cause diabetes by themselves, except they may impulsive diabetes in individuals with insulin resistance.

These offending drugs are collected according to the mechanism by which they stimulate diabetes. The foremost group interferes with insulin production or secretion (e.g. Beta Blockers), the second group blocks insulin action (e.g. Steroids), the third group interferes with both insulin secretion and action (e.g. Thiazides), and the final group increases blood glucose using mechanisms independent of insulin's actions (for example Nicotinic corrosive) (Pandit et al, 1993). Weight lifters who take enormous portions of anabolic androgens have the option to create debilitated glucose resilience. Various medications including Pentamidine, nicotinic corrosive, asprin, glucocorticoids and nalidixic corrosive can cause transient hyperglycemia in overdoses (Ferner, 1992).

5. PHARMACOLOGICAL INVOLVEMENTS IN THE TREATMENT OF DIABETES MELLITUS

5.1. Insulin Treatment in Diabetes Mellitus:

The acquaintance of insulin with treat diabetes has spared an expected 5 million years of life for patients with type 1 diabetes during the year 2000 (Owens, 2001). Significant advancement has been made, lately, in the generation, definition and conveyance of insulin arrangements, just as the improvement of insulin treatment regimens which keeps up long haul normoglycaemia, with a generally safe of hypoglycaemia (Bolli, 1997, Bolli, 1992). Insulin is the most strong glucose-bringing down operator, with hypoglycaemia being the main significant portion restricting element.Insulin therapy should aim to mimic nature, which is remarkably successful both in limiting postprandial hyperglycaemia and preventing hypoglycaemia between meals (Ciofeta et al, 1999), but unfortunately pharmacological problems complicate insulin therapy. Insulin analogues have an alteration in the amino acid sequence of human insulin, which change the rate of insulin absorption, or some other structural change like being linked to a fatty acid chain, that alters the insulin time action curve (Bethel and Feinglos, 2002). Insulin is arranged either from human, or porcine, or ox-like or a blend of cow-like and porcine. Human insulin (Humulin, Novolin) is presently broadly accessible arranged by recombinant DNA systems. The physicochemical properties of human, porcine and ox-like insulins contrast inferable from their distinctive amino corrosive arrangements. Insulin is the backbone for treatment of for all intents and purposes all sort 1 DM and many sort 2 DM patients. Insulin might be directed intravenously (IV), or intramuscularly (IM); anyway for long haul treatment, subcutaneous (SC) course is liked.

5.2 Complications of Insulin Therapy:

The most widely recognized unfavorable responses to insulin are weight addition and hypoglycaemia (Henry et al, 1993; Kudlacek et al, 1992). Weight increase in the wake of beginning insulin treatment for uncontrolled diabetes is an inescapable outcome and is the consequence of expanded truncal fat and muscle mass (Diabetes Control and Complications Trial Research Group, 1993; Yki et al, 1999). This is likewise because of diminished vitality misfortunes through glycosuria. Hypoglycaemia may result from an improperly enormous portion, from befuddle between the pinnacle conveyance of insulin and nourishment admission or from superimposition of extra factors that expansion affectability to insulin (adrenal inadequacy, pituitary deficiency) or that increment insulin-free glucose take-up (work out). Utilization of physiological insulin regimens joined with training can really diminish the recurrence of hypoglycaemia (Pampanelli et al, 2002; Bott et al, 1997) and lessen the danger of hypoglycaemia (Lalli et al, 1999; Cryer, 2002).

5.3. Oral Hypoglycemic Agents:

Sulfonylureas: Sulphonylureas are basically identified with sulphenamides and were found unintentionally, in 1942 when it was noticed that some sulphonamides

caused hypoglycaemia in exploratory creatures. These perceptions were expanded, and 1-butyl-3-sulfonylurea (carbutamide) turned into the primary clinically valuable sulfonylurea for the treatment of diabetes. Sulfonylureas cause hypoglycemia by stimulating insulin release from pancreatic ß-cells. They bind to sulfonylurea (SUR) receptors on the ß-cell plasma membrane, causing closure of adenosine triphosphate (ATP) sensitive potassium channels, leading to depolarization of the cell membrane. This in turn unlocks voltage gated channels, permitting entry of calcium ions and subsequent secretion of preformed insulin granules. Acute administration of sulfonylureas to type 2 DM patient's increases insulin release from the pancreas and also may further increase insulin levels by reducing hepatic clearance of the hormone. Initial studies showed that a functional pancreas was necessary for the hypoglycaemic actions of sulfonylureas (Levine, 1984). Sulfonyl ureas enlarge insulin activity in the cells in culture and invigorate the combination of glucose transporters. Sulfonyl ureas additionally have been appeared to stifle hepatic gluconeogenesis (Bluementhal, 1977). Anyway it isn't clear if this is an immediate impact of the medication or an impression of expanded affectability of Insulin. Glibenclamide is presumably one of the most broadly utilized oral hypoglycemic operators in the treatment of diabetes mellitus today. This operator can adequately control a critical extent of patients creating auxiliary inability to original mixes. The receptors of sulphonyl urea are available in cardiovascular muscle cells, smooth muscle cells, liver and fat tissue. There are a few reactions interceded by the utilization of sulphonyl ureas. They are interminable renal disappointment, hepatic and cardio vascular ailments. Patients who are utilizing the sulphonyl urea treatment will in general put on weight from 1-5 kg (Zimmerman, 1997).

6. DRAWBACKS OF PRESENTLY AVAILABLE ANTIDIABETIC THERAPY

1. Up to 2.5% and 17.5% of sulfonylurea (SU) treated patient's incident major and minor hypoglycemia.
2. Additional side effects of sulfonylureas incorporate nausea and vomiting, cholestatic jaundice, agranulocytosis, aplastic and hemolytic anemias, generalized hypersensitivity reactions, and dermatological reactions.
3. Body weight gains of 2.2 to 11.0 lb (1 to 5 kg) are general with sulfonylurea (Bolen et al, 2007).
4. Unfortunately, conventional human insulin is associated with several characteristics that limit its prospective. Original human insulin injected intravenously has a 17-minute half-life and a short duration of action (Tong et al, 2008).
5. Insulin remedy is frequently accompanied by weight increase that may go beyond 10 kg is associated with increasingly intensive insulin treatment.
6. Patients with renal injury should not receive biguanides. Other contraindications include hepatic disease, a past history of *lactic acid* overproduction (of several causes), heart malfunction requiring pharmacological therapy, or chronic hypoxic lung ailment.
7. Severe side effects of biguanides include diarrhoea, abdominal discomfort, nausea, metallic taste, and anorexia.
8. Peripheral edema is observed in up to 26% of thiazolidinedione treated patients. Thiazolidinediones are very prone to cause hepatotoxicity and can cause weight gain and oedema

7. CONCLUSION:

An underlying and often unsuspected abnormality in carbohydrate metabolism in the patient or a family history of diabetes greatly increases the risk for developing drug induced diabetes. A lot of drugs can damage insulin secretion. The foremost group interferes with insulin production or secretion (e.g. Beta Blockers), the second group blocks insulin action (e.g. Steroids), the third group interferes with both insulin secretion and action (e.g. Thiazides), and the final group increases blood glucose using mechanisms independent of insulin's actions (for example Nicotinic corrosive). Weight lifters who take enormous portions of anabolic androgens have the option to create debilitated glucose resilience. So drug used during diabetes management affect the abnormality metabolism process.

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