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Oral Hypoglycaemic Agents: Non-Insulin Medications for Type 2 Diabetes Patients

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Abstract

Among type 2 diabetes (T2D) patients, oral medications are called oral hypoglycaemic agents (OHAs), which are preferred over injections due to convenience and acceptability. These are a group of drugs that have been used successfully worldwide for controlling T2D patients to reduce the high blood sugar. These can be classified as either hypoglycaemic agents, such as sulfonylureas and benzoic acid derivatives or antihyperglycaemic agents, such as Biguanides, α-glucosidase inhibitors, and Thiazolidinediones. Most of these stimulate β-cells of the Islets of Langerhans within the pancreas to produce insulin. These should be taken at about the same time every day according to the advices of physician. The most common side-effects of OHAs are hypoglycaemia and weight gain.

Keywords: oral hypoglycaemic drugs, Metformin, Sulfonylureas

1. Introduction

Type 2 diabetes (T2D) is a group of metabolic disorders and a progressive life-long condition. The overproduction and underutilization of glucose characterizes T2D. If T2D is poorly managed or remains untreated for a long-time, may cause a significant morbidity due to micro- and macro- vascular complications (Mohajan & Mohajan, 2023a). The effects of T2D are long-term damage, dysfunction, and failure of various organs (WHO, 2002). Diet, exercise, and oral medications are the main tools to control over glucose of T2D patients (Shrestha et al., 2017). Oral administration is the most popular way of T2D patients due to its ease of ingestion, pain, avoidance, versatility, and patient compliance (Pravallika et al., 2023).

Glucagon-like peptid (GLP) receptor agonists, such as Liraglutide, Exenatide, and Pramlintide are administered orally, and are called oral hypoglycaemic/antihyperglycaemic agents (OHAs). At present there are a series of OHAs to treat T2D patients. Some of these types of medications are Metformin, Sulphonylureas, Glinides, Thiazolidinediones, Disaccharidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists, etc. Actually, these are used to improve blood sugar control policy (Torre et al., 2011).

2. Literature Review

The literature review section is an introductory portion of research, which highlights the contributions of other scholars in the same field within the existing knowledge (Polit & Hungler, 2013). It deals with a secondary research sources and does not think about future research work (Gibbs, 2008). It helps the new researchers to realize the subject area of research that has been carried out before (Creswell, 2007). Edelmiro Menéndez Torre and his coauthors have discussed three steps OHAs treatment for T2D patients: In the first step, if the hyperglycaemia is not severe (HbA1c: 6.5%-8.5%), Metformin is the first choice. If blood glucose levels are

high (HbA1c>8.5%), the initial treatment must begin with several oral drugs in combination or with insulin. The second step involves adding a second synergistic drug, several options are available for this, but patients must receive personalized treatment in accordance with their characteristics. The third step involves introducing basal insulin as the option of choice rather than triple oral therapy, which is reserved only for cases of resistance to insulin (Torre et al., 2011).

Margaret Bannister and Jenny Berlanga explore the mode of action on currently available oral treatments, factors to consider when individualizing HbA1c targets, the relevance of estimated glomerular filtration rate assessment, and the importance of reviewing the clinical impact of all treatment decisions (Bannister & Berlanga, 2016). Jyoti Tara Manandhar Shrestha and her coauthors aim to determine the pattern of adverse effects resulting from the use of OHAs among T2D patients (Shrestha et al., 2017). Devajit Mohajan and Haradhan Kumar Mohajan have tried to discuss about overweight and obesity, and their related diseases (Mohajan & Mohajan, 2023b,d,f,h,I,j,k,l). They have also highlighted on some direct and indirect anthropometric measurements that measure overweight and obesity (Mohajan & Mohajan, 2023c,e,g). They have briefly consulted on the Diabetics Mellitus (DM) and its related complications (Mohajan & Mohajan, 2023m-u).

Belen Dalama and Jordi Mesa have observed that Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors effectively lower blood glucose and glycated hemoglobin levels without increasing the risk of hypoglycaemia, and also reduce body weight and systolic blood pressure. They describe the mechanism of action, efficacy, and safety of currently marketed drugs, as well as other risk factors besides glucose that can potentially be modulated positively (Dalama & Mesa, 2016). Richard A. Harrigan and his coworkers have briefly discussed the pharmacology of OHAs agents through the examination of their adverse effects, drug-drug interactions, and toxicities with treatment, general supportive care and the management of T2D patients. They have also discussed adjunctive roles of glucagon, diazoxide, and octreotide for refractory hypoglycaemia (Harrigan et al., 2001).

Rajesh Dupaguntla and Hima Bindu Gujjarlamudi have tried to find out the percentage variation of cost among different brands of oral hypoglycaemic drugs available in Indian market. They want to introduce low cost drugs and to select the cost effective oral hypoglycaemic drugs based on the economic status of the patient to reduce the economic burden on the patient and healthcare system (Dupaguntla & Gujjarlamudi, 2017). Lilian Beatriz Aguayo Rojas and Marilia Brito Gomes have reviewed the role of Metformin in the treatment of patients with T2D and describe the additional benefits beyond its glycemic effect. They have also discussed its potential role for a variety of insulin resistant and pre-diabetic states, obesity, metabolic abnormalities associated with gestational diabetes, cancer, and neuroprotection (Rojas & Gomes, 2013).

3. Research Methodology

The research design is a plan of the researchers to develop research area that is reinforced by philosophy, methodology, and method (Tie et al., 2019). Methodology is the guideline to perform a good research, where scientific methods are followed precisely and efficiently (Kothari, 2008). It is the systematic and theoretical analysis of the methods applied to a field of study (Patel & Patel, 2019). Therefore, research methodology is a strategy for planning, arranging, designing and conducting a fruitful research confidently to obtain a successful result (Legesse, 2014). It is the science of studying how research is done scientifically (Patel & Patel, 2019).

We enter our main research area through the discussion of the treatment options with OHAs. Then we have preceded the research activities by the step by step discussion of Biguanides, Sulfonylureas, Thiazolidinediones, Meglitinides, α-Glucosidase inhibitors, Glucagon-like Peptide-1 (GLP-1), DPP-4 inhibitors, and SGLT-2 inhibitors. The paper is organized on the basis of secondary data analysis. We have followed published and unpublished research articles, published books, handbooks, conference papers, websites, etc. to prepare this article (Mohajan & Mohajan, 2023).

4. Objective of the Study

The main target of this study is to control glucose for the prevention of micro- and macro-vascular complications of T2D patients. Other minor objectives of the study are as follows:

- to focus on treatment options of OHAs, and
- to encourage the T2D patients on the treatment with OHAs.

5. Treatment Options with OHAs

All diabetes medicines are grouped into “classes” according to their actions in the body. At present there are eight different classes of non-insulin glucose-lowering drugs, and these are i) Biguanides, ii) Sulfonylureas (SU), iii) Meglitinides, iv) Thiazolidinediones (TZDs), v) α-Glucosidase inhibitors, vi) GLP-1 analogues, vii) DPP-4 inhibitors, and viii) SGLT-2 inhibitors (Boulton et al., 2005). Each of these drugs has with their own mechanism of action and side effects, costs; and their selection depends on the nature of diabetes, age, and situation of the patients, as well as other factors (Harrigan et al., 2001).

Treatments of T2D with the agents that i) increase the amount of insulin secreted by the pancreas, ii) increase the sensitivity of target organs to insulin, iii) decrease the rate at which glucose is absorbed from the gastrointestinal tract, and iv) increase the loss of glucose through urination (Powers, 2011).

5.1 Biguanides

Three Biguanides, such as Metformin, Phenformin, and Buformin have historically been used for the treatment of T2D, but only Metformin remains in wide use today; and it works in liver and intestine by stopping to release too more glucose (Verdonck et al., 1981). The word "Metformin" was first described in the scientific literature in 1922, by Emil Werner and James Bell, as a product in the synthesis of N, N-dimethylguanidine. French physician Jean Sterne (1909-1997) first used Metformin to treat diabetes in 1957 (Fischer, 2010).

Metformin is one of the oldest treatments for diabetes, dating back to the 1960s. It reduces hepatic glucose output and increases uptake of glucose by the periphery, including skeletal muscle (Bannister & Berlanga, 2016). It is the first-line medication and the best choice for patients, and usually use for the treatment of T2D. It is at an increased risk of lactic acidosis, and should be temporarily discontinued before any radiographic procedure (Verdonck et al., 1981; Fimognari et al., 2006). It primarily inhibits hepatic glucose output; and it is not necessarily an insulin sensitizer. Additionally, it increases the sensitivity of muscle cells to insulin, improving peripheral glucose uptake and utilization (Shrestha et al., 2017). It can be combined with insulin to reduce insulin requirements. It is available in both standard- and modified- release forms (Khandwala, 2003).

It should be introduced in low dose, with 250 to 500 mg twice or thrice a day, and should increase gradually up to 1 g thrice a day if required within 1 or 2 weeks. For example, 500 mg once daily for one week, 500 mg twice daily in week two, 500 mg thrice daily in week three, and 1 g twice daily in week four (Harrower, 2000). It lowers glycated hemoglobin (HbA1c) values up to 1-1.5%. It also reduces plasma triglyceride levels and low-density lipoprotein (LDL) cholesterol levels. It should be taken with or immediately after a meal. Some individuals may not tolerate higher doses, in which case, dose reduction is appropriate (NICE, 2015). Metformin is an old and widely accepted first-line agent that is antihyperglycaemic and improves endothelial dysfunction, hemostasis and oxidative stress, insulin resistance, lipid profiles, and fat redistribution (Rojas & Gomes, 2013).

Side Effects of Biguanides: After use of Metformin the patients may face problem of mild loose stools in 10% initially, which reduces gradually, persistent loose stools in 5%, and marked weight loss. Sometimes the patients may face acute/chronic liver failure, cardiac failure, hypotension/sepsis, active vitamin B_{12} deficiency for long-term use (Tahrani et al., 2007). Sometimes, it may cause a metallic taste in the mouth, nausea, vomiting, diarrhea, and abdominal pain in about 5% patients. These side effects often improve after a few days of continued therapy, or with a small dose reduction (Salpeter et al., 2010).

Cautions: Metformin should be discontinued during a severe illness, such as during pneumonia, myocardial infarction, and dehydration. Patients with moderate to severe renal impairment Metformin should be used with caution or avoided when kidney function is declined. In these situations, other glucose lowering therapies may be required (Umpierrez et al., 2014).

5.2 Sulfonylureas

Sulfonylureas are the first widely used oral anti-hyperglycaemic medications. These lowers blood glucose by stimulating insulin secretion from the pancreatic β-cells (Hellman & Taljedal, 1975). These are generally well-tolerated, and are well-established drugs for the treatment of T2D patients. These are typically the next class of drugs used when Metformin is unsuitable or insufficient in achieving control. These lower HbA1c values up to 1–2%, and also are affordable and have long-term safety data (NICE, 2015). These also decrease hepatic insulin clearance that result in increased serum insulin concentrations (Marshall et al., 1970).

Two commonly used sulfonylureas agents are i) first-generation drugs, and ii) second-generation drugs. First-generation agents are Tolbutamide, Acetohexamide, Tolazamide, and Chlorpropamide. Second-generation agents are Glipizide, Gliburide or Glibenclamide, Glimepiride, Gliclazide, Glyclopyramide, and Gliquidone (Harrower, 2000). These are more effective and readily penetrate cell membranes than first-generation drugs, feature a greater selective binding capacity, and have fewer side-effects (Campbell, 1998).

Commonly prescribed SUs are Gliclazide and Glimepiride; and Gliclazide is available in both standard- and modified- release forms. These are beneficial only for T2D patients for stimulating endogenous release of insulin. These can be safely used with Metformin or Glitazones (Shyangdan et al., 2011). All SUs increase insulin secretion and enhance insulin activity. Doses of SUs are 2.5-5 mg of Glyburide once daily, 80-320 mg of Gliclazide twice daily, 1-8 mg of Glimepiride once daily. SU drugs should ideally be taken 30 minutes before a meal (Monami et al., 2007).

Side Effects of Sulfonylureas: These medicines cause weight gain. The primary side-effect is hypoglycaemia, especially in the elderly and those with renal or hepatic impairment, which appears to happen more commonly

with Sulfonylureas than with other treatments (Shyangdan et al., 2011). Chlorpropamide, Glyburide, and the long-acting Glipizide are the most likely to cause prolonged hypoglycaemia (Stahl & Berger, 1999).

5.3 Thiazolidinediones

Thiazolidinediones (TZDs) are known as Glitazones, and these act as agonists on the peroxisome proliferator activated receptor γ (PPARγ), which are presented in several tissues, such as in the skeletal muscle, liver adipose tissue, pancreatic β-cells, vascular endothelium, macrophages, heart, and kidney (Park et al., 1997). PPAR-α is expressed mostly in liver, heart, skeletal muscle, and vascular walls. The PPAR is a type of nuclear regulatory protein involved in transcription of genes regulating glucose and fat metabolism. The PPARs influence insulin-sensitive genes that enhance production of mRNAs of insulin-dependent enzymes. These work in adipocytes and hepatocytes to increase insulin receptors (Watkins & Whitcomb, 1998).

TZDs increase whole-body insulin sensitivity by activating nuclear receptors, and promoting esterification; and storage of circulating free fatty acids in subcutaneous adipose tissue. These enhance the effect of insulin in skeletal muscle, adipose, and hepatic tissues without increasing pancreatic secretion of insulin. TZDs lower glycated hemoglobin (HbA1c) values within 1.5–2.0% (Henry, 1997). TZDs are favorite options to treat T2D patients. These are used as monotherapy or in combination with other oral hypoglycaemic agents, which are generally safe and well-tolerated. These lower blood pressure, no hypoglycaemia, and progressive rise in HDL levels, reduce microalbuminuria and vascular intimal thickening (Khandwala, 2003).

Two TZDs generics are Pioglitazone and Rosiglitazone; both are approved to treat T2D. Rosiglitazone is the second and Pioglitazone is the next TZD available. Rosiglitazone has been shown to have either a neutral effect on triglycerides, whereas Pioglitazone has been demonstrated to decrease triglyceride levels up to 25%. Rosiglitazone is approved in combination with Sulfonylureas and Metformin except in susceptible congestive heart failure (CHF) individuals. Overall, these medications are expensive (Guan et al., 2005).

Side Effects of TZDs: The main side effects of TZDs are fluid retention and weight gain of 2 to 4 kg. Fluid retention shows lower extremity edema, hemodilution-anemia, and in susceptible individuals may cause congestive heart failure (CHF). A low sodium diet can reduce the frequency and severity of the fluid retention. Weight increase is found in both Rosiglitazone and Pioglitazone due to the fluid retention and mobilization of fat from the intra-abdominal or visceral sites to the subcutaneous tissue (Khandwala, 2003). The medication should not be initiated if the patient exhibits clinical evidence of active acute or chronic liver disease of increased serum transaminase levels. Some other disadvantage of TZDs are LDL elevation, worsens osteoporosis, and occasional fluid overload. These may create ulcers of the colon, intestinal obstruction, and kidney disease (Lichtor et al., 2008).

5.4 Meglitinides

Meglitinides have a capacity of rapid absorption and help the pancreas to produce insulin. These can be taken with or shortly before meals to boost the insulin response to each meal. If a meal is skipped, the medication is also skipped. These are often called short-acting non-Sulfonylurea insulin secretagogues with less risk of hypoglycemia, weight gain and chronic hyperinsulinemia compared with Sulfonylureas (Rendell, 2004). These are the substrates of cytochrome P450 (CYP) enzymes and organic anion transporting polypeptide 1B1 (OATP1B1 transporter). These are useful to treat T2D patients who follow a flexible lifestyle (Maideen et al., 2018). These reduce glycated hemoglobin (HbA1c) values up to 0.5-1.0%. Two Meglitinides generics are Repaglinide and Nateglinide. Repaglinide is a benzoic acid derivative and Nateglinide is a di-phenylalanine derivative. These are rarely used because of their short-acting and thus require more frequent dosing (Guardado-Mendoza et al., 2013).

Repaglinide stimulates to release insulin from the pancreatic β-cells by inhibiting potassium efflux via closure of ATP-regulated K+ channels. It rapidly absorbs and eliminates, and allows a relatively fast onset and offset of action (Gromada et al., 1995). Nateglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas β-cells. It closes ATP-dependent potassium channels in the β-cell membrane by binding at characterizable sites that blockade depolarizes the β-cells, and induce insulin secretion (Pravallika et al., 2023). Doses are for Repaglinide 0.5-4 mg twice or thrice daily before meals, and for Nateglinide doses are 60-120 mg twice or thrice daily before meals. Patients with kidney failure or mild hepatic impairment, and patients with irregular meal patterns can use it confidently (Maideen et al., 2018).

Side Effects of Meglitinides: These may cause weight gain and hypoglycaemia (Maideen et al., 2018; Pravallika et al., 2023).

5.5 α-Glucosidase Inhibitors

Alpha-glucosidase inhibitors are not technically hypoglycaemic agents, simply diabetes pills. These do not have a direct effect on insulin secretion or sensitivity. These work on the brush border of the intestine and cause

cirrhosis, inflammatory bowel disease, predisposition to bowel obstruction, and carbohydrate mal-absorption syndromes (Yee & Fong, 1996). These breakdown and absorb carbohydrates, such as dextrins, maltose, sucrose and starch; and no effect on glucose. Three alpha-glucosidase inhibitors generics are Acarbose, Miglitole, and Voglibose (Chiasson et al., 1994).

These slow the digestion of starch in the small intestine. Consequently, glucose from the starch of a meal enters the bloodstream more slowly. These reduce glycated hemoglobin (HbA1c) values up to 0.5–1.0% (Chiasson et al., 1994). These are selective for postprandial hyperglycaemia and no hypoglycaemic symptoms are seen. Doses are for Acarbose 25–50 mg thrice a day, for Miglitol 25–100 mg thrice a day, and for Voglibose 0.2–0.3 mg thrice a day. These can be used as monotherapy and in combination with the Sulfonylureas or insulin for T2D (Yee & Fong, 1996).

Side Effects of α-Glucosidase: These cause the weight loss by lowering the amount of sugar metabolized. These have severe side-effects, such as flatulence, bloating, diarrhea, and abdominal pain (Spiller, 1998). These are only effective in mild hyperglycaemia. Side effects may decrease in 1 to 2 months, and gradual escalation from low to higher doses may weaken the adverse effects. Also these have no severe toxicity (Hanefeld, 1998).

5.6 Glucagon-Like Peptide-1 (GLP-1)

Glucagon-Like Peptide-1 (GLP-1) is a multifaceted incretin hormone with broad pharmacological potential. It enhances glucose-dependent stimulation of insulin secretion, decreases gastric emptying, inhibits food intake, increases natriuretic and diuresis, and modulates of rodent β-cell proliferation. It also has cardio- and neuro-protective effects, decreases inflammation and apoptosis, and has implications for learning and memory, reward behavior, and palatability (Müller et al., 2019). GLP-1 agonist drugs are based therapies that reduce hyperglycaemia in T2D. It exerts its action by binding its receptor at the cell surface. At present the GLP-1 agonist drugs available are Dulaglutide, Exenatide, Liraglutide, Lixisenatide, and Semaglutide. These GLP-1 analogues are resistant to degradation by DPP-4, and thus have a longer half-life than endogenous GLP-1 (Kreymann et al., 1987).

Limitations of GLP-1: The plasma half-life of native GLP-1 is very short, owing to its rapid inactivation by DPP-4, continuous infusion or multiple injections of GLP-1 are required to attain adequate glycaemic control (Müller et al., 2019).

5.7 DPP-4 Inhibitors (Gliptins)

Dipeptidyl peptidase-4 (DPP-4) inhibitors are weight-neutral, well-tolerated, rarely cause hypoglycaemia (FDA, 2015). But, weight gain and/or hypoglycaemia have been observed when DPP-4 is used with Sulfonylureas (Amori et al., 2007). The DPP-4 increases blood concentration of the incretin Glucagon-Like Peptide 1 (GLP-1) by inhibiting its degradation by DPP-4. The DPP-4 inhibitors are suitable for patients with renal impairment with dose adjustments. These lower HbA1c values up to 0.5-0.74% (Bennett et al., 2011; Doucet et al., 2011).

GLP-1 augmented in the presence of hyperglycaemia, and action less at euglycaemia and in normal subjects (Richter et al., 2008). DPP-4 inhibitors are oral agents that inhibit the activity of the enzyme DPP-4, and hence prolong the actions of endogenous GLP-1. These are a suitable treatment option for the elderly and occupational drivers (Rai et al., 2019). Six DPP-4 inhibitors available are Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Septagliptin, and Allogliptin (Green et al., 2015). These work by inhibiting DPP-4, which is an enzyme that destroys the hormone GLP-1 that aids glucose-dependent insulin production (Bannister & Berlanga, 2016).

Side Effects of DPP-4 Inhibitors: DPP-4 inhibitors increase risk for infection and headache. These have the associated increased risk of pancreatitis and should be avoided in patients with high triglycerides. These may cause severe and disabling joint pain among some patients (Scirica et al., 2013).

5.8 SGLT-2 Inhibitors

Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors are necessary who are at risk of hypoglycaemia, overweight, or with cardiovascular disease, and cannot tolerate Sulfonylureas. These are the newest group of oral hypoglycaemic agents that have revolutionized in the treatment of T2D (Garber et al., 2019). These are proteins which encourage glucose reabsorption in the proximal tubule in the kidney. These may provide an attractive, insulin independent target for increasing glucose excretion. These reduce renal glucose reabsorption resulting in increased glucose excretion equivalent to a net loss of 200-300 kcal per day. These may also reverse β-cell dysfunction and insulin resistance in T2D. These lower HbA1c up to 0.6–0.9% by inhibiting the absorption of glucose from the proximal tubule of the kidney, causing glycosuria, and also lower both body weight and blood pressure, and may benefit those who are overweight or obese. On the other hand, these do not cause hypoglycaemia (Thaddanee et al., 2013).

Some SGLT-2 agents are Canagliflozin, Dapagliflozin, Sergliflozin, Remogliflozin, Ipragliflozin, Empagliflozin, Luseogliflozin, Tofogliflozin, and Desoxyrhaponticin. These inhibitors block receptor site, preventing activation

of the glucose channel and glucose reabsorption, so the glucose remains in the renal filtrate and ultimately in the urine (Chao & Henry, 2010).

Side Effects of SGLT-2: These increase the risk of euglycemic diabetic ketoacidosis (DKA), urinary and genital tract infections, candidal vulvovaginitis, and hypoglycaemia (Zinman et al., 2015). Some more adverse effects of these agents are lower limb amputations (LLA), Fournier gangrene, bone fractures, female breast cancer, male bladder cancer, orthostatic hypotension, and acute kidney injury (AKI) (Nadkarni et al., 2017; Szalat et al., 2018).

6. Conclusions

From this study we have observed that Oral hypoglycaemic agents (OHAs) are used to reduce the high blood sugar of the type 2 diabetes (T2D) patients. As a result, these reduce the risk of micro- and macro- vascular diseases of them. There are many side-effects of OHAs, such as hypoglycaemia, weight gain, lactic acidosis, gastrointestinal disturbance, and fluid retention. Therefore, when these are used targets should be set with patients in order to balance benefits with harms, at least in hypoglycaemia and weight gain. A maximum of three oral treatments may be required due to the progressive nature of T2D. OHAs, diet, and exercise are the triad recommendations of the physicians for the treatment of T2D patients. Almost all oral anti-diabetic agents are contraindicated during pregnancy, but then insulin is preferred. During the treatment with OHAs some factors must be considered, such as risk of hypoglycaemia, age of patients, comorbidities, diabetic complications, and costs of OHAs and treatment.

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