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Oral Hypoglycemic Drugs in the Management of Type 2 Diabetes Mellitus: A Review

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Abstract
Diabetes mellitus is a chronic, progressive, heterogeneous group of metabolic disorder mainly characterized by hyperglycemia. T2DM results due to insulin resistance or secretory defects of a beta cell or both and gradually progress to a state characterized by complete loss of pancreatic beta cells secretion. 2hour oral glucose tolerance test or HbA1c testing is performed for the screening for diabetes mellitus. In this review, we attempt to outline the basic pharmacological and non-pharmacological principles for the management of T2DM.
Keywords: diabetes, clinical management, non-pharmacological management, primary care

1. Introduction

Diabetes mellitus is one of the common chronic metabolic diseases which is mainly characterized by hyperglycemia. It is a progressive disease. So, as a disease progresses there is a high chance of developing microvascular and macrovascular complications. Many studies have been conducted to find the effective measure to reduce these complications. Based on the pathology, there are different types of diabetes mellitus. Among them, type 2 diabetes (T2D) is very common accounting for approximately 90% of diabetic cases worldwide. The prevalence rate of T2DM is increasing due to a sedentary lifestyle, increasing obesity and an aging population (Johnson JA et al, 2006). Early and regular use of antidiabetic therapy is necessary to achieve good glycemic control and reduce complication in type 2 diabetic patients (Vinki A et al, 2007)

Diabetes is diagnosed based on the following criteria: (a) FPG >126 mg/dl, (b) OGTT>200 mg/dl, (c) random blood glucose >200 mg/dl with classic signs of hyperglycemia, and (d) HbA1C level >6.5%. Patient with at least one of the above criteria is said to have diabetes (ADA Diabetes Care, 2016). Screening for diabetes plays a vital role in reducing or preventing diabetic complication in future. American Diabetes Association (ADA) has recommended screening to asymptomatic adults who are obese, present with the diagnostic symptom, and have a risk factor for developing diabetes, and to the adults>45 years of age irrespective of body weight (ADA Standard of medical care in diabetes, 2016). Sometimes two different tests with variable results are encountered. In this condition, the previously positive diagnostic test is repeated again for the confirmation of diabetes. For people whose test results come negative for diabetes, repeating test at 3 years interval is recommended (ADA screening for diabetes, 2000).

Prediabetes or impaired fasting glucose (IFG) is a state of an abnormally high blood sugar level with not all diagnostic symptoms of diabetes. It is associated with obesity, dyslipidemia, and hypertension, and may predispose patients to diabetes (ADA Standard of medical care in diabetes, 2016). Lifestyle modification should be emphasized.

2. Management of Type 2 Diabetes

Managing T2DM is a great challenge for the physician. There are many factors that should be taken into consideration before initiating therapy like patient's risk factor, presence or absence of diabetic complication, and previous therapy. So, a thorough patient's history, physical examination, and the blood test are necessary in order to choose an appropriate therapy for the patient (ADA Standard of medical care in diabetes, 2016). Lifestyle intervention, pharmacological therapy, and routine blood test are the main base for the management of diabetes.

2.1. Lifestyle Intervention

Lifestyle modification is an important aspect in the management of prediabetes and DM. It helps to prevent or delay the progression to diabetes by targeting obesity and physical inactivity.

In a randomly conducted trial, the patient with prediabetes was divided in placebo group and lifestyle intervention program group. Lifestyle modification reduces 58% risk of developing diabetes with 5.8kg weight loss compared to 0.1kg weight loss in the placebo group. Further, 37% patient receiving placebo develops diabetes in 4 years compared to 20% in another group (Tuso P, 2014). Diabetic patient should strictly follow the diet as advised by the dietitian. The patient should be counseled to lose at least 5% of their body weight. High-carbohydrate along with high-fiber diet seems to improve glycemic control and reduces plasma cholesterol level.

Dietary fiber delays food digestion and absorption. A diet with high fiber, low cholesterol, and low saturated fat is recommended to all diabetic patients. A systemic review and meta-analysis suggested that organized physical exercise (>150mins per week) combined with dietary advice reduces the HbA1c level and improve glycemic control (Umpierre D et al, 2011). Moderate consumption of alcohol (≤1 drink for women, ≤2 drinks/men), decrease salt intake and tobacco use, and immunizations are also equally important in the treatment of diabetic patients (Pietraszek A et al, 2010). Pharmacological therapy should be initiated in the patients who are not responding to 2-3 months of lifestyle intervention and HbA1c level of >6.5% (Bailey CJ, 2015).

2.2. Pharmacologic Management

Two form of a hypoglycemic agent is available. The injectable form includes insulin, exenatide, liraglutide, and pramlintide. Whereas, an oral hypoglycemic agent includes: biguanides, sulfonylureas, DPP-4 inhibitor, TZD, SGLT2 inhibitors, meglitinide, and an alpha-glucosidase inhibitor. Pathogenesis of T2DM includes: (i) decreased insulin secretion, (ii) increased glucagon secretion, (iii) increased hepatic glucose production, (iv) neurotransmitter dysfunction, (v) increased lipolysis, (vi) increased glucose reabsorption from kidney, (vii) decreased incretin effect, and (viii) decreased glucose uptake in peripheral tissues (Defronzo RA, 2009) Each hypoglycemic agent has their own mechanism of action and targets one or more of the above pathology. If monotherapy fails to achieve good glycemic control and HbA1c level raises to 7.5%, combination therapy with two oral agents, or with insulin, can be initiated. Combination therapy is started in the patient presenting with an initial HbA1c level of more than 9% (James JC et al, 2016).

2.2.1. Biguanide

Biguanide was discovered in the middle ages. It was derived from a herbaceous plant called *Galega officinalis*, was found to have galegine, guanidine, and biguanide. The primary function of metformin is to decrease hepatic glucose production by activating AMP-activated protein kinase (AMPK) in the liver through complex effects on the mitochondrial enzymes. In addition, it also increases insulin sensitivity due to its positive effects on insulin receptor expression and tyrosine kinase activity and decreases glucose absorption from the GI tract by acutely increasing the GLP-1 levels in the plasma (Viollet B et al, 2012). Metformin is highly effective if there is enough insulin production; however, as the disease progress beta cells fail to produce the insulin resulting in type 1 phenotype and metformin loses its efficacy.

Currently, metformin is the drug of the first choice for treating T2DM irrespective of age. It has a half-life of approximately 5hours. It is mainly excreted through the kidney. Metformin is quite a safe drug with low risk of hypoglycemia and weight gain, although might cause gastrointestinal disturbances in nearly 30% of the patient. So it should be started at a low dose. Especially in elderly patients, metformin can cause vitaminB12 and folic acid deficiency (Fogelman K et al, 2016). Lactic acidosis is reported in some patient with renal insufficiency, liver disease, and respiratory failure and in alcoholics, with the use of metformin. A low dose of metformin is prescribed when GFR is significantly diminished (30-45 ml/min/1.73m2) and should be stopped if GFR deteriorates further (Inzucchi SE et al, 2014). Renal function should be assessed before using metformin.

2.2.2. SGLT2 Inhibitors

Sodium-glucose cotransporter 2 (SGLT2) is responsible for reabsorbing almost 90 % of the glucose filtered by the kidneys (Scheen AJ, 2015).Sodium-glucose cotransporter 2 (SGLT2) inhibitors are an insulin-independent hypoglycemic agent that acts by blocking glucose reabsorption in the proximal tubule of the kidney, thus resulting in increased urinary excretion of glucose (Taylor SI et al, 2015; Riser Taylor S et al, 2013) .e.g. canagliflozin, dapagliflozin, and empagliflozin. SGLT2 inhibitors are as effective as metformin, sulfonylureas or sitagliptin in promoting glycemic control, with low risk of hypoglycemia (Scheen AJ, 2015). It promotes weight loss by increasing renal glucose excretion and may help to reduce blood pressure. According to current safety and efficacy data, in case of poor glycemic control with metformin monotherapy, SGLT2 inhibitors can be used as an effective alternative option (Nauck MA, 2014).

SGLT2 inhibitors are generally well-tolerated. Adverse effects like female genital mycotic infections, urinary tract infections leading to urosepsis and pyelonephritis have been frequently reported (Scheen AJ, 2015). It is often required to decrease insulin dose when it is used with SGLT2 inhibitors in order to avoid hypoglycemia. Due to this, given insulin dose may not be sufficient to suppress the lipolysis and ketogenesis, predisposing patients to ketoacidosis (Taylor SI et al, 2015).

2.2.3. Sulfonylureas

Sulfonylureas act on the “sulfonylurea receptors” on the pancreatic beta cell membrane causing depolarization by reducing conductance of ATP sensitive K+ channels. This enhances Ca ++ influx into the cell leading to increased insulin secretion (Proks P et al, 2012). Sulfonylureas are common second-line or add-on options for management of T2DM. The major adverse effect of sulfonylureas is hypoglycemia and other minor side effects like a headache, nausea, dizziness, hypersensitivity reaction and weight gain are also common. Due to its prolonged hypoglycemic effect, it is contraindicated in pregnancy and also it is secreted in milk so should not be given to the nursing mother. Drugs (allopurinol, sulfonamides, aspirin, beta antagonist, chloramphenicol, etc.)

that enhance the sulfonylurea action should be used with caution in order to avoid hypoglycemia. It is contraindicated in the patient with a hepatic and renal disease.

Currently, sulfonylureas are classified as first-generation drugs (chlorpropamide, tolazamide, and tolbutamide) and second-generation drugs (glipizide, glimepiride, and glyburide), although there is no structural or functional basis for this classification. Second-generation sulfonylureas have a short half-life, fast onset of action and have a low risk of hypoglycemia. So, second-generation sulfonylureas are in more use. Among those drugs, glimepiride has the safest profile.

2.2.4. Meglitinide

A Meglitinide analog is non-sulfonylurea insulinotropic agents. Meglitinide analogs are mitiglinide, nateglinide, and repaglinide. It has the same mechanism of action as that of sulfonylurea. It is regarded as short-acting insulin secretagogues as it binds weakly to the receptor. It is preferred over sulfonylureas in patients, who have irregular eating habits and who develops late postprandial hypoglycemia (while using sulfonylurea). Meglitinide induced beta-cells stimulation required a high blood sugar level for insulin secretion, which makes it less effective than sulfonylurea.

2.2.5. Thiazolidinedione

Thiazolidinedione (TZD) is a PPAR agonist, act as insulin sensitizers and reduce hepatic glucose output, reduce inflammatory cytokines, increase adiponectin levels, and maintain beta cell integrity and function. Pioglitazone, rosiglitazone, and troglitazone are currently available TZD. Due to its harmful effect on cardiovascular system, its role in the management of T2DM is in danger. Based on the safety profile, several markets have withdrawn rosiglitazone in compare to pioglitazone, which has shown a beneficial cardiovascular profile (Rizos CV et al, 2016). Mainly, combination therapy with insulin and TZD causes heart failure. TZD has also been associated with bone fracture and bladder cancer in several clinical trials (Kobayashi M et al, 2015).

2.2.6. DPP-4 Inhibitors

Dipeptidyl-peptidase 4 inhibitors do not cross the blood-brain barrier so they do not have a direct effect on satiety center or on altering gastric emptying. It lowers DPP4 activity by 70–90%; therefore, increases and prolongs incretin hormone activity (Capuano A et al, 2013). Currently being used DPP4 inhibitors are sitagliptin, teneligliptin, saxagliptini, vildagliptin, linagliptin, and alogliptin. It can be used as a monotherapy, or add-on therapy with metformin, sulfonylurea, or TZD. According to the meta-analysis, when the desired glycemic level is not obtained with metformin monotherapy, DPP-4 inhibitors can be used as add-on option instead of sulfonylureas, which promotes 0.4-0.6% reduction in HbA1c, low incidence of hypoglycemia and weight loss (Mishriky BM et al, 2015). In the diabetic patient with coronary heart disease, the use of sitagliptin improved the cardiac function. Upper respiratory infection, nasopharyngitis, and headache are the commonly reported adverse effect. Few cases of acute pancreatitis were reported.

2.2.7. Alpha-Glucosidase Inhibitors (AGI)

AGI is competitive inhibitors of alpha-glucosidase enzymes, which is responsible for the digestion and absorption of polysaccharide and sucrose. Hence, reduces the post-prandial blood glucose increment and insulin response. It is useful in the patient with impaired glucose tolerance and also in the management of reactive hypoglycemia and dumping syndrome. It is generally not used as add-on therapy in the management of type2 diabetes mellitus but recently it was reported that combination therapy of AGI with DPP-4 inhibitors or SGLT2 inhibitors enhances the GLP-1 secretion. Due to the fermentation of the unabsorbed carbohydrates, the patient often complained of flatulence and loose stool.

2.2.8. Injectable form of Glucose-Lowering Pharmacologic Agents

2.2.8.1. Incretin Mimetics (GLP-1 receptor agonist)

Incretins are hormones that are released from the gut into the bloodstream in response to nutrient ingestion. Incretins reduces gastric emptying and also inhibit glucagon release from the alpha-cells and improves the glycemic control alongside decreases the body weight and systolic blood pressure in type 2 diabetic patients (Maruthur NM et al, 2016). There are two naturally occurring incretin hormones: (i) glucose-dependent insulinotropic polypeptide (GIP); (ii) glucagon-like peptide (GLP-1). The endocrine pancreas remains responsive to GLP-1 but unresponsive to GIP in type2 diabetic patient. Incretin effect is described as the difference in insulin secretion from an oral glucose load in comparison to glucose administered intravenously. It is responsible for 50%- 70% of the total insulin secreted after oral glucose (Nauck MA et al, 2016). These peptides have a short half-life, as these are rapidly inactivated by DPP-4 within 1½ min. Risk of hypoglycemia is low due to the glucose-dependent mechanism of action. Thus, incretin mimetics have become an important part for treating T2DM. Incretin-based drugs include DPP-4 inhibitors and GLP-1 receptor agonists (Exenatide and Liraglutide).

2.2.8.2. Insulin

Many formulations of insulin are available like rapid-acting insulin (e.g. lispro, aspart), short-acting insulin (e.g. regular or Novolin), intermediate-acting insulin (NPH), long-acting insulin (e.g. glargine, detemir, degludec) and mixed insulin. Rapid and short-acting insulin is used as bolus insulin which only provides mealtime insulin requirements, intermediate and long-acting insulin is used as basal insulin which only provides fasting insulin

requirements and mixed insulin is used as basal-bolus insulin which provides both mealtime and fasting insulin requirement. Thus, the premixed insulin is preferred as they cover both fasting and postprandial glycaemia (Garber AJ et al, 2007). Currently, many hypoglycemic drugs are available in the market, but still, insulin remains an important therapy in the management of type2 diabetes. Type2 diabetes is a progressive disease which sooner or later ends up in type1 phenotype, resulting in the necessity for exogenous insulin therapy (Stumvoll M et al, 2005). If insulin is used appropriately, it is very effective in controlling the blood glucose level in both type1 and type2 diabetes.

2.2.8.3. Pramlintide

It is an amylin analog. It delays gastric emptying and suppresses glucagon secretion, and enhances satiety. Food and Drug Administration (FDA) have approved the use of pramlintide in adults with T1DM. Pramlintide therapy was associated with improved A1C and decreased body weight, with a low rate of severe hypoglycemia, among patients with T2DM, regardless of baseline insulin use(Herrmann K et al, 2014).

3. Management of Diabetes Complications

Standard management of diabetes involves taking care of diabetic complication as well as comorbidities like hypertension, dyslipidemia, endothelial cell dysfunction, nephropathy, retinopathy, hyper-coagulopathy and atherosclerotic cardiovascular disease (ASCVD). Aspirin should be continuously used in a diabetic patient with existing CVD, as it is the most important cause of morbidity and mortality. ACEI or ARB is used as anti-hypertensive drugs for the diabetic patient with hypertension. The recommended goal blood pressure is ≤140/80 mmHg. Blood pressure and glucose level should be control strictly in order to delay the progression of nephropathy and retinopathy in these patients. Statins drugs are used in the patient with hyperlipidemia to maintain LDL level of <70mg/dl (ADA Standard of medical care in diabetes, 2016). The regular follow-up, monitoring, compliance to medications and patient education is very important in the management of diabetes complication.

4. Conclusion

Type 2 diabetes mellitus is a chronic metabolic disease and is one of the leading causes of end-stage kidney disease, atherosclerotic cardiovascular disease, non-traumatic limb amputation, blindness and a major source of morbidity and mortality worldwide. Many factors should be taken into consideration before initiating therapy like patient's risk factor, presence or absence of diabetic complication, previous therapy, economic status, HbA1c level and side effects of drugs like hypoglycemia and weight gain. So, a thorough patient's history, physical examination, and the blood test are necessary in order to choose an appropriate therapy for the patient. To evaluate the effectiveness of the therapy, close and regular follow-up with blood tests, as well as monitoring for diabetic complications are required. All hypoglycemic agents have their own benefits and side effects and some drugs may have important cardiovascular complications, which the physician should always be aware of. Appropriate insulin therapy should be promptly initiated in the patient who is not responding well to combination therapy (lack of control of HbA1c) and decrease level of C-peptide. According to several clinical trials and data, bariatric surgery can be considered in morbid obesity, though it is not conclusive yet. Regular follow up with the dietitian and a balanced hypocaloric diet is a useful approach along with regular physical exercise. Healthcare professionals, dietitians, lifestyle modification to manage body weight, as well as patient education, are essentials for proper management for diabetes.

5. Conflict of interest

The authors declare no conflict of interest.

Reference

Johnson JA, Pohar SL, Majumdar SR (2006) Health care use and costs in the decade after identification of type 1 and type 2 diabetes: a population-based study. Diabetes Care. 2006;29:2403–8.

Vinik A. (2007) Advancing therapy in type 2 diabetes mellitus with early, comprehensive progression from oral agents to insulin therapy. Clin Ther. 2007; 29(Spec No):1236–1253.

Standards of medical care in diabetes-2016: summary of revisions. Diabetes Care (2016) 39(Suppl 1):S4–5.10.2337/dc16-S003

American Diabetes Association. Screening for Type 2 Diabetes. (Vol. 18). Clinical Diabetes (2000) Available from: http://journal.diabetes.org/clinicaldiabetes/v18n22000/pg69.htm

Tuso P. Prediabetes and lifestyle modification: time to prevent a preventable disease. Perm J (2014) 18(3):88–93.10.7812/TPP/14-002

Umpierre D, Ribeiro PA, Kramer CK, Leitão CB, Zucatti AT, Azevedo MJ, et al. (2011) Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. JAMA (2011) 305(17):1790–9

Tabak A, Herder C, Rathmann W, Brunner E, Kivimaki M (2012) Prediabetes: a high risk state for developing diabetes. Lancet (2012) 379(9833):2279–90.10.1016/S0140-6736(12)60283-9

Pietraszek A, Gregersen S, Hermansen K. Alcohol and type 2 diabetes (2010) A review. Nutrition, Metabolism and Cardiovascular Disease (2010) 20(5):366–75.10.1016/j.numecd.2010.05.001

Defronzo RA. Banting Lecture (2009) From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes (2009) 58(4):773–95.10.2337/db09-9028

Bailey CJ (2015) The current drug treatment landscape for diabetes and perspectives for the future. Clinical Pharmacology and Therapeutics (2015) 98(2):170–84.10.1002/cpt.144

James JC, Andrew SR, Charles FS, Jr, Annie N. PA-C (2016) diagnosis and management of diabetes: synopsis of the 2016; American Diabetes Association standards of medical care in diabetes. Ann Intern Med (2016) 164:542–52.10.7326/M15-3016

Viollet B, Guigas B, Garcia N, Leclerc J, Foretz M, Andreelli F. (2012) Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond) (2012) 122(6):253–70.10.1042/CS20110386

Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. (2014) Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA (2014) 312(24):2668–75.10.1001/jama.2014.15298

Fogelman Y, Kitai E, Blumberg G, Golan-Cohen A, Rapoport M, Carmeli E. (2016) Vitamin B12 screening in metformin-treated diabetics in primary care: were elderly patients less likely to be tested?. Aging Clinical Experiment and Research (2016).10.1007/s40520-016-0546-1

Taylor SI, Blau JE, Rother KI. (2015) SGLT2 Inhibitors May Predispose to Ketoacidosis. Journal of Clinical Endocrinology and Metabolism. 2015 Aug;100(8):2849-52. doi: 10.1210/jc.2015-1884. Epub 2015 Jun 18

Riser Taylor S, Harris KB. (2013) The clinical efficacy and safety of sodium glucose cotransporter-2 inhibitors in adults with type 2diabetes mellitus. Pharmacotherapy (2013) 33(9):984–99.10.1002/phar.1303

Nauck MA. (2014) Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. 2014 Sep 11;8:1335-80. doi: 10.2147/DDDT.S50773.

Scheen AJ. (2015) Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs. 2015 Jan;75(1):33-59. doi: 10.1007/s40265-014-0337-y

Proks P, Reimann F, Green N, Gribble F, Ashcroft F. (2002) Sulfonylurea stimulation of insulin secretion. Diabetes (2002) 51(3):5368–76.10.2337/diabetes.51.2007.S368

Rizos CV, Kei A, Elisaf MS. (2016) The current role of thiazolidinediones in diabetes management. 2016 Aug;90(8):1861-81. doi: 10.1007/s00204-016-1737-4.

Capuano A, Sportiello L, Maiorino MI, Rossi F, Giugliano D, Esposito K. (2013) Dipeptidyl peptidase-4 inhibitors in type 2 diabetes therapy – focus on alogliptin. Drug Des Devel Ther (2013) 7:989–1001.10.2147/DDDT.S37647

Nauck MA, Meier JJ. (2016) The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. Lancet Diabetes Endocrinol (2016) 4(6):525–36.10.1016/S2213-8587(15)00482-9

Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, et al. (2016) Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Annals of Internal Medicine (2016) 164(11):740–51.10.7326/M15-2650

Herrmann K, Shan K, Brunell SC, Chen S. (2014) Effects of pramlintide in patients with type 2 diabetes mellitus: an analysis using daily insulin dose tertiles. Endocr Pract. 2014 Oct;20(10):1070-5. doi: 10.4158/EP13477.OR.

Stumvoll M, Goldstein BJ, van Haeften TW. (2005) Type 2 diabetes: principles of pathogenesis and therapy. Lancet. 2005; 365:1333–46.

Kobayashi M, Ueki K. (2015). Thiazolidine, thiazolidinediones. Nihon Rinsho. 2015 Mar;73(3):402-8

Mishriky BM, Cummings DM, Tanenberg RJ. (2015) The efficacy and safety of DPP4 inhibitors compared to sulfonylureas as add-on therapy to metformin in patients with Type 2 diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract. 2015 Aug; 109(2):378-88. doi: 10.1016/j.diabres.2015.05.025

Garber AJ, Ligthelm R, Christiansen JS, Liebl A. (2007) premixed insulin treatment for type 2 diabetes: analogue or human? Diabetes Obes Metab. 2007;9(5):630–639.

American Diabetes Association Diabetes Care 2016 Jan; 39(Supplement 1): S13-S22. https://doi.org/10.2337/dc16-S005