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A Review on Diabetes and Its Management

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The current approach to the treatment of both type 1 and type 2 diabetes is to achieve the best possible glucose control. Past clinical trials have shown that glycemia plays a key role in the prevention of both macro- and microvascular complications. During the past 20 years, a number of new medications to control blood glucose have been introduced, and new approaches to the use of older medications have been developed. Weight and diabetes, especially type 2 diabetes, are closely related. Obesity is a major risk factor for the development of type 2 diabetes, and the current increase in obesity in our society has fueled a major increase in the expression of this disease. Not only does weight, through the mechanism of insulin resistance, aggravate hyperglycemia, it also increases the risk for hypertension, hyperlipidemia, and other conditions that lead to cardiovascular disease.

Keyword: Adiposopathy, Epidemic, Insulin, Leptin, Treatment Target

1. INTRODUCTION: Diabetes mellitus, or simply **diabetes**, is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). [1]

Comparison of anti-diabetic medication [3, 4]

Agent	Mechanism	Advantages	Disadvantages
Sulfonylurea (glyburide, glimepiride, glipizide)	Stimulating insulin release by pancreatic beta cells by inhibiting the K_{ATP} channel	• Fast onset of action • No effect on blood pressure • No effect on low-density lipoprotein • inexpensive • lower risk of gastrointestinal problems than with metformin	• causes an average of 5-10 pounds weight gain • Increased risk of hypoglycemia • Glyburide has increases risk of hypoglycemia slightly more as compared with glimepiride and glipizide • Higher risk of death compared with metformin

		• more convenient dosing not associated with weight gain • low risk of hypoglycemia as compared to alternatives	increased risk of gastrointestinal problems • Contraindicated for people with moderate or severe kidney disease or heart failure because of risk of lactic acidosis
Metformin	Acts on liver to cause decrease in insulin resistance	• Good effect on LDL cholesterol • Decreases triglycerides • no effect on blood pressure inexpensive	• increased risk of Vitamin B12 deficiency • Less convenient dosing Metallic taste .
Alpha-glucosidase inhibitor (acarbose, miglitol)	Reduces glucose absorbance by acting on small intestine to cause decrease in production of enzymes needed to digest carbohydrates	• slightly decreased risk of ypoglycemia as compared to sulfonylurea • not associated with weight gain • decreases triglycerides no effect on cholesterol	• less effective than most other diabetes pills in decreasing glycated hemoglobin • increased risk of GI problems than other diabetes pills except metformin • inconvenient dosing expensive
thiazolidinediones (Actos, Avandia)	Reduce insulin resistance by activating PPAR-γ in fat and muscle	• Lower risk of hypoglycemia • Slight increase in high-density lipoprotein • Actos linked to decreased triglycerides • Convenient dosing	• increased risk of heart failure • causes an average of 5-10 pounds weight gain • associated with higher risk of edema • lassociated with higher risk of anemia • increases low-density lipoprotein • Avandia linked to increased triglycerides and risk of heart attack • Actos linked to increased risk of bladder cancer • slower onset of action • requires monitoring for hepatoxicity • associated with increased risk of limb fractures expensive

Comparison of type 1 and 2 diabetes [2]

Feature	**Type 1 diabetes**	**Type 2 diabetes**
Onset	Sudden	Gradual
Age at onset	Mostly in children	Mostly in adults
Body habit's	Thin or normal	Often obese
Ketoacidosis	Common	Rare
Auto antibodies	Usually present	Absent
Endogenous insulin	Low or absent	Normal, decreased or increased
Concordance in identical twins	50%	90%
Prevalence	~10%	~90%

There are three main types of diabetes mellitus (DM).

- Type 1 DM results from the body's failure to produce insulin, and presently requires the person to inject insulin or wear an insulin pump. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes".

- Type 2 DM results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. This form was previously referred to as non-insulin-dependent diabetes mellitus (NIDDM) or "adult-onset diabetes".
- The third main form, gestational diabetes occurs when pregnant women without a previous diagnosis of diabetes develop a high blood glucose level.

2. Anti-diabetic medication

Anti-diabetic medications treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, liraglutide and pramlintide, all are administered orally and are thus also called **oral hypoglycemic agents** or **oral antihyperglycemic agents**. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors.

a. INSULIN

Insulin lowers blood glucose (blood sugar). There are many different types of insulins. They differ based on onset (when the insulin begins to work), peak (when it is working the hardest), and duration of action (how long it works). [5]

Examples

Quick-acting insulins Short-acting insulin	• Humalog (insulin lispro) • Novolog (insulin aspart) • Humulin R • Novolin R	**Side effects :** Low blood glucose, weight gain, allergic reaction (rare)
Slow-acting insulins	• Humulin N (NPH) • Novolin N (NPH) • Humulin L (lente) • Novolin L (lente)	
Long-acting insulins	• Humulin U (ultralente) • Lantus (insulin glargine)	
Mixtures (2 insulins are pre-mixed)	• Humulin 50/50 • Humulin 70/30 • Humalog Mix 75/25 • Novolin 70/30 • Novolog Mix 70/30	

b. SULFONYLUREAS

These drugs cause the pancreas to make more insulin. (The drugs listed are the more common sulfonylureas prescribed.) [6]

Examples

Generic name	Brand name	Dosing	Half life	Labeled indications	Dose adjustment, monitoring, precautions	Mechanism of Action	Side effects

Glimepiride	Amaryl	1-8 mg od. Max; 8 mg od	5-9 hours	Management type 2 diabetes	In elderly and renal dysfunction	Increase insulin secretion by pancreatic beta cells	Low blood glucose, weight gain, rash, nausea
Glipizide	Glucotrol	5-15 md od or 5-20 mg bid; max dose 20 mg bid 20 mg od XL	2-4 hours	Management type 2 diabetes	In elderly, renal dysfunction and hepatic, start dose at 2.5 mg od and titrate slowly		
Glipizide	Glucotrol XL						
Glyburide	DiaBeta	2.5-20 mg od or bid; max dose: 20 mg od	5-16 hours	Management type 2 diabetes	Not recommended for patients with renal dysfunction (CrCl<50 mL/min)		
Glyburide	Glynase PreTab						
Glyburide	Micronase						

c. **MEGLITINIDE / D-PHENYLALANINE**

These drugs cause the pancreas to make more insulin and act more quickly.

Examples [7, 8]

Generic name	Brand name	Dosing	Half life	Labeled indications	Dose adjustment, monitoring, precautions	Mechanism of Action	Side effects
Repaglinide	Prandin	0.5-4 mg before meals; max. 16 mg	1 hours	Management type 2 diabetes * Not indicated for use in combination with NPH insulin due to potential cardiovascular events	Use with caution in patients with severe renal and hepatic impairment. Start at lowest dose and titrate slowly	Increase insulin secretion by pancreatic beta cells	Low blood glucose (rare)
Nateglinide	Starlix	60-120 mg before meals	1.5 hours	Management type 2 diabetes	Use with caution in patients with severe renal and hepatic impairment. Start at lowest dose and titrate slowly		

d. BIGUANIDE

These drugs reduce the amount of glucose that is made by the liver and helps the body better use insulin.

Examples [9]

Generic name	Brand name	Dosing	Half life	Labeled indications	Dose adjustment, monitoring, precautions	Mechanism of Action	Side effects

Metformin	Glucophage	500-2550 mg divided doses	6.2 hours	Management type 2 diabetes	Avoid in liver disease	Inhibit glucose production by the liver	Nausea, diarrhea, gas, loss of appetite
Metformin	Glucophage XR	2550 mg; 2000 mg for XR	6.2 hours	Management type 2 diabetes	In elderly, dose with caution and titrate slowly		

e. THIAZOLIDINEDIONE (GLITAZONE OR TZD)

These drugs help the body cells better use insulin and reduce the amount of glucose that is made by the liver.

Examples [10, 11]

Generic name	Brand name	Dosing	Half life	Labeled indications	Dose adjustment, monitoring, precautions	Mechanism of Action	Side effects
Pioglitazone	Actos	15-30 mg od; max 45 mg od.	3-7 hours	Management type 2 diabetes	Not recommended in Class III or IV heart failure	Increase glucose uptake by skeletal muscle	• Liver damage (nausea, vomiting, fatigue, dark urine, abdominal pain) • Fluid retention/or swelling • Decrease how well some birth control pills work
Rosiglitazone	Avandia	4-8 mg od or 2-4 mg bid; max. 8 mg od usually or 4 mg od with insulin or sulfonylureas	3-4 hours	Management type 2 diabetes	Not recommended in Class III or IV heart failure		

f. ALPHA-GLUCOSIDASE INHIBITORS

These drugs help keep blood sugar in target range after a meal.

Examples [12, 13]

Generic name	Brand name	Dosing	Half life	Labeled indications	Dose adjustment, monitoring, precautions	Mechanism of Action	Side effects
Acarbose	Precose	25-100 mg	2	Management	Not	Inhibit	Gas, bloating,

		tid; max:100 mg tid	hours	type 2 diabetes	recommended for severe renal impairment (CrCl<25 mL/min)	carbohydrate absorption in the small intestine	diarrhea, stomach pain
Miglitol	Glyset	25-100 mg tid; max:100 mg tid	2 hours	Management type 2 diabetes	Not recommended for severe renal impairment (CrCl<25 mL/min)		

g. COMBINATION DRUGS

Sometimes several drugs are combined and sold as one pill. The action is based on the two drugs that have been combined.

Examples [14, 15]

Generic name	Brand name	Doses	Side effects
Glyburide & Metformin	Glucovance	2.5 mg/500 mg bid 5 mg/500 mg bid	Because you are taking a drug that combines two medications it is possible you will have side effects from both types of drugs. These can include nausea, low blood sugar, weight gain, rash, diarrhea, and excess gas, loss of appetite, liver damage, and fluid retention/swelling.
Glipizide & Metformin	Metaglip	2 mg/4 mg daily 4 mg/4 mg daily	
Rosiglitazone & Metformin	Avandamet	500 mg/4 mg bid 1000 mg/2 mg bid	

Anti-Diabetes Medications with Their Reductions in A1C and Effects on Weight [16, 17, 18]

Drug Class	Reductions in A1C (%)	Weight Effects (lb)
Insulin	> 2.5	+8.8-11.0
Inhaled insulin	1-2	+2.2-4.4
Sulfonylureas	1.6	+3.5-5.7

Repaglinide and nateglinide	0.8-1.5	+1.54-3.9
Metformin	1.5	-10.1-+0.88
Thiazolidinediones	0.8-1.5	+9.2-10.6
a-Glucosidase inhibitors	0.5-0.8	+0.0-0.44
DPP-IV inhibitors	0.5-1.0	+0.0-0.88
GLP-1 mimetic	0.6-0.8	-2.8-6.6
Amylin analogs	0.6	-3.1

3. Natural substances

A number of medicinal plants have been studied for the treatment of diabetes; however there is insufficient evidence to determine their effectiveness. Cinnamon has blood sugar-lowering properties; however whether or not it is useful for treating diabetes is unknown. While chromium supplements have no beneficial effect on healthy people, there might be an improvement in glucose metabolism in individuals with diabetes, although the evidence for this effect remains weak. Vanadyl sulfate, a salt of vanadium, is still in preliminary studies. There is tentative research that thiamine may prevent some diabetic complications however more research is needed. Researchers from Australia's Swinburne University have found extracts from Australian Sandalwood and Indian Kino tree slows down two key enzymes in carbohydrate metabolism. [19]

4. Assessing Risks

a. Hypoglycemia

Sulfonylureas and repaglinide cause similar rates of hypoglycemia. It occurs in about 14 percent of people taking a sulfonylurea and 12 percent of people taking repaglinide. Sulfonylureas are more likely to cause hypoglycemia than metformin or TZDs. People taking sulfonylureas have about a 7-percent higher risk of hypoglycemia. [20]

b. Lactic acidosis

Lactic acidosis is relatively uncommon. In one year, about 1 of 10,000 people who are generally healthy (without significant pulmonary, renal, or hepatic dysfunction) and taking any oral hypoglycemic will develop lactic acidosis. The rate of lactic acidosis is similar for metformin and other oral hypoglycemics. [21]

c. Cardiac Problems

TZDs are 1–2 percent more likely to exacerbate congestive heart failure than the other oral hypoglycemics. These drugs are not recommended for people with symptomatic heart failure. The risk of ischemic cardiovascular events with TZDs has received considerable attention. It is still unknown whether TZDs are more likely than other oral hypoglycemics to increase the risk of myocardial infarction. [22]

d. Gastrointestinal Problems

People who take metformin have more gastrointestinal (GI) problems, including diarrhea, nausea, and gas, than those who take TZDs or sulfonylureas. GI problems are about 10 percent more common for people taking metformin than for people taking other oral hypoglycemics. [23]

e. Edema

TZDs are 5–10 percent more likely to cause peripheral edema than the other oral hypoglycemics. [24]

f. Anemia

TZDs are about 3 percent more likely to cause anemia (hematocrit drop of 1–3 percent) than the other oral hypoglycemics. [25]

5. Management [26, 27]

a. Lifestyle

There are roles for patient education, dietetic support, sensible exercise, with the goal of keeping both short-term and long-term blood glucose levels within acceptable bounds.

b. Medications

Metformin is generally recommended as a first line treatment for type 2 diabetes, as there is good evidence that it decreases mortality.Routine use of aspirin, however, has not been found to improve outcomes in uncomplicated diabetes. Type 1 diabetes is typically treated with combinations of regular and NPH insulin, or synthetic insulin analogs.

c. Support

In countries using a general practitioner system, such as the United Kingdom, care may take place mainly outside hospitals, with hospital-based specialist care used only in case of complications, difficult blood sugar control, or research projects.

6. The Future of New Antidiabetic Therapies

The united States FDA in 200864 and the Committee for Medicinal Products for Human use (CHMP) of the European Medicines Agency in 2010, released draft guidelines on evaluation of new antidiabetic therapies before approval for marketing. Lowering of HbA1c remains the preferred endpoint for demonstrating efficacy of new drugs. However, a new antidiabetic agent should also be studied for effects on macrovascular complications including mortality. To claim cardiovascular benefit, a new drug should be assessed in a large long-term clinical trial with at least 3 years of follow-up. Since individual cardiovascular events may be few in number and may not reach statistical significance, the guidance recommends use of a composite endpoint termed MAjor Cardiovascular Events (MACE), which includes cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, myocardial ischemia and hospitalization for acute coronary syndrome, coronary revascularization or worsening heart failure. Recognizing that demonstration of reduction of macrovascular complications will increase drug development costs and also delay the approval of potentially useful antidiabetic drugs, the draft guidance states that at the very least, the new drug must be shown to be devoid of adverse cardiovascular effects.[28,29]

7. Newer Agents [30]

- TZDs
- DPP-4 inhibitors

8. STILL UNKNOWN

Most studies of oral hypoglycemics last year or less and focus on short-term outcomes. There is insufficient evidence from comparative studies to determine whether oral hypoglycemics differ in their effects on long-term outcomes, such as cardiovascular disease, retinopathy, kidney disease, and neuropathy. Better postmarketing studies and research that includes long-term assessments would help address this critical need. It is not known whether the safety and effectiveness of oral hypoglycemics for adults with type 2 diabetes vary among people of different genders, races, ethnicities, or age groups, or those who have coexisting medical conditions. [31]

9. CONCLUSIONS

Diabetes is a complex and progressive disease, requiring increasingly more complex treatments over time. Multifactorial intervention, in addition to glycemic control, may provide cardiovascular protection, but the complexity of the therapeutic strategy may become a challenge for both the patient and physician. Achieving treatment goals requires continuous effort by both. The patient

must appreciate the short- and long-term benefit of treatment; the physician should be able to recognize the patient's needs and concerns. The result of this process should personalize treatment where goals and medication options are based on individual factors such as age, duration of the disease, presence or absence of diabetes complications, underlying pathophysiology, and risk/bene.t of each medication and their combination. With this goal in mind, we have recently proposed an HbA1c and ABCD algorithm for the treatment of diabetes. The algorithm helps in identifying individualized HbA1c targets as well as personalized therapy based on Age (A), Body weight (B), Complications (C), and Duration of diabetes (D). Treatment personalization may improve adherence to multitherapy; reduction of clinical inertia may provide a more sustained metabolic control. Obviously, this is not an easy task, but new opportunities may be available. The use of metformin, glucagon-like peptide-1 receptor agonists, and dipeptidyl-peptidase inhibitors are all associated with very low risk of hypoglycemia and neutral, if not favorable, effects on body weight, two common concerns for both the patient and the physician. A series of fixed combination of oral antidiabetes agents as well as the use of rational combinations of oral and injectable drug treatments may reduce the number of tablets taken per day and provide a better opportunity for sustained glycemic control. The basis of a successful therapy relies on being aware of the complexity of the pathogenesis of the disease and on the need for careful assessment of risk-to-benefit ratio of each form of treatment. [32, 33]

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