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 medication1, 4

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| 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 |
### Comparison of type 1 and 2 diabetes \[^2\]

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Sudden</td>
<td>Gradual</td>
</tr>
<tr>
<td>Age at onset</td>
<td>Mostly in children</td>
<td>Mostly in adults</td>
</tr>
<tr>
<td>Body habit’s</td>
<td>Thin or normal</td>
<td>Often obese</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Auto antibodies</td>
<td>Usually present</td>
<td>Absent</td>
</tr>
<tr>
<td>Endogenous insulin</td>
<td>Low or absent</td>
<td>Normal, decreased or increased</td>
</tr>
<tr>
<td>Concordance in</td>
<td>50%</td>
<td>90%</td>
</tr>
</tbody>
</table>

**Identical twins**

| 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

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quick-acting insulins</td>
<td>Humalog (insulin lispro)</td>
</tr>
<tr>
<td>Short-acting insulin</td>
<td>Novolog (insulin aspart)</td>
</tr>
<tr>
<td>Slow-acting insulin</td>
<td>Humulin N (NPH)</td>
</tr>
<tr>
<td>Long-acting insulins</td>
<td>Humulin U (ultralente)</td>
</tr>
<tr>
<td>Mixtures (2 insulins are pre-mixed)</td>
<td>Humulin 50/50</td>
</tr>
</tbody>
</table>

**Side effects:** Low blood glucose, weight gain, allergic reaction (rare)

### b. SULFONYLUREAS

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

#### Examples

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Dosing</th>
<th>Half life</th>
<th>Labeled indications</th>
<th>Dose adjustment, monitoring, precautions</th>
<th>Mechanism of Action</th>
<th>Side effects</th>
</tr>
</thead>
</table>

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c. MEGLITINIDE / D-PHENYLALANINE

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

**Examples** [7, 8]

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Dosing</th>
<th>Half life</th>
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<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repaglinide</td>
<td>Prandin</td>
<td>0.5-4 mg before meals; max. 16 mg</td>
<td>1 hour</td>
<td>Management type 2 diabetes * Not indicated for use in combination with NPH insulin due to potential cardiovascular events</td>
<td>Use with caution in patients with severe renal and hepatic impairment. Start at lowest dose and titrate slowly</td>
<td>Increase insulin secretion by pancreatic beta cells</td>
<td>Low blood glucose (rare)</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>Starlix</td>
<td>60-120 mg before meals</td>
<td>1.5 hours</td>
<td>Management type 2 diabetes</td>
<td>Use with caution in patients with severe renal and hepatic impairment. Start at lowest dose and titrate slowly</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

d. BIGUANIDE

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

**Examples** [9]
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]

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

f. ALPHA-GLUCOSIDASE INHIBITORS
These drugs help keep blood sugar in target range after a meal.

Examples [12, 13]

<table>
<thead>
<tr>
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<th>Brand name</th>
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<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>Precose</td>
<td>25-100 mg</td>
<td>2</td>
<td>Management</td>
<td>Not</td>
<td>Inhibit</td>
<td>Gas, bloating,</td>
</tr>
</tbody>
</table>
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]

<table>
<thead>
<tr>
<th>Generic name &amp; Brand name</th>
<th>Doses</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide &amp; Metformin &amp; Glucovance</td>
<td>2.5 mg/500 mg bid 5 mg/500 mg bid</td>
<td>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.</td>
</tr>
<tr>
<td>Glipizide &amp; Metformin &amp; Metaglip</td>
<td>2 mg/4 mg daily 4 mg/4 mg daily</td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone &amp; Metformin &amp; Avandamet</td>
<td>500 mg/4 mg bid 1000 mg/2 mg bid</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Reductions in A1C (%)</th>
<th>Weight Effects (lb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>&gt; 2.5</td>
<td>+8.8-11.0</td>
</tr>
<tr>
<td>Inhaled insulin</td>
<td>1-2</td>
<td>+2.2-4.4</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.6</td>
<td>+3.5-5.7</td>
</tr>
</tbody>
</table>
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 2008 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]

➢ 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/benefit of each medication and their combination. With this goal in mind, we have recently proposed an HbA1c and ABCD algorithm helps in identifying individualized algorithm for the treatment of diabetes. The recently proposed an HbA1c and ABCD combination. With this goal in mind, we have risk/benefit of each medication and their complications, underlying pathophysiology, and disease, presence or absence of diabetes individual factors such as age, duration of the disease and on the need for careful assessment of risk-to-benefit ratio of each form of treatment.

10. REFERENCE


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