Overview of hyperglycemia management

Hiba Abbasi, MD,Endocrinologist

Department of Internal Medicine

School of Medicine

University of Jordan

TREATMENT GOALS

1- **Diabetes Education :** instruction on nutrition, physical activity, optimizing metabolic control, and preventing complications.

Very important step

2- Evaluation for micro- and macrovascular complication

3- **Attempts to achieve near normoglycemia** by medications

4- Minimization of cardiovascular and other long-term risk factors

5- Avoidance of drugs that can exacerbate abnormalities of insulin or lipid metabolism.

Diabetes Education

Intensive lifestyle modification

Behavioral modification/therapy > nutrition and physical activity

In patients with established type 2 diabetes, intensive behavioral modification interventions focusing on weight reduction (1) and increasing activity levels are successful in reducing weight, improving glycemic management (2) and, at the same time, reducing the need for glucose-lowering and other medications (3).

→ or at least weight maintanence

1- Medical nutrition therapy

Aiming for weight reduction or at least weight maintenance.

2- Weight reduction

- By diet control, pharmacological or surgical therapy.

- Improved glycemic state is induced by weight loss through partial correction of the two major metabolic abnormalities in type 2 diabetes: insulin resistance and impaired insulin secretion.

- Weight loss and weight loss maintenance supports all effective type 2 diabetes therapy and reduces the risk of weight gain associated with sulfonylureas and insulin.

What's the benefit of weight reduction in glucose control?
It will improve the insulin resistance and improve the insulin secretion

We care about decreasing the number of medications the patient takes for the disease because of:
Compliance + to avoid side effects of the medications

3- Exercise

- Regular exercise is beneficial for diabetics independent of weight loss.

- It leads to improved glycemic management due to : increased responsiveness to insulin and so delay the progression of impaired glucose tolerance to overt diabetes.

Pre-diabetic

- These beneficial effects are directly due to exercise.

- Unfortunately, in one study, only 50% of patients with type 2 diabetes were able to maintain a regular exercise regimen.

PHARMACOLOGIC THERAPY

when to start ???

All patients get started with lifestyle modifications
We don't stop at all

Depends on the level of hyperglycemia

- A reasonable goal of therapy might be an A1C of ≤7% (7 – 7.5%) for most patients.

- Target A1C goals in patients with type 2 DM should be tailored to the individual, balancing the potential for improvement in microvascular complications with the risk of hypoglycemia,

It's a progressive disease, doesn't get better or stays at its place

So there is NO ((ONE SIZE FITS ALL))

- Glycemic targets are generally set somewhat higher for older adult patients and those with comorbidities or a limited life expectancy who may have little likelihood of benefit from intensive therapy.

① older adult → 70s

② comorbidities

③ limited life expectancy

* The target would be up to 8%

- For most patients with A1C at or above target level (>7.5 to 8%), pharmacologic therapy should be initiated at the time of diagnosis (along with lifestyle modification).

- A 3-6 month trial of lifestyle modification prior to initiation of pharmacologic therapy is reasonable for :

1- patients with A1C at or above the target (7.5 – 8%) who have clear and modifiable contributors to hyperglycemia and who are motivated to change them.

2- highly motivated patients with A1C near target (<7.5%).

Has the potential to go on a diet and commit to exercising

Choice of initial therapy??

1st line of treatment: metformin unless contraincated or intolerant

Considerations:

1. Patient presentation: presence or absence of symptoms of hyperglycemia
2. Comorbidities
3. Baseline A1C level
4. Individualized treatment goals and preferences
5. The glucose-lowering efficacy of individual drugs, and their adverse effect profile, tolerability, and cost. → Drug profile

Patient presentation:

Awareness and screening increased for type 2 DM

Asymptomatic, not catabolic:

Means there's no weight loss

- The majority of patients with newly diagnosed type 2 diabetes are asymptomatic, without symptoms of catabolism (without polyuria, polydipsia, or unintentional weight loss).

- Hyperglycemia may be noted on routine lab test or detected by screening.

- **Metformin**: In the absence of specific contraindications, it can be used as initial therapy for those patients.

not very important.

Dosing: We begin with 500 mg once daily with the evening meal and, if tolerated, add a second 500 mg dose with breakfast. The dose can be increased slowly (one tablet every one to two weeks) as necessary to reach a total dose of 2000 mg per day.

Advantages of Metformin :

1- It is the preferred initial therapy because of **glycemic efficacy (1-2%)**

2- Absence of weight gain

3- Absence of hypoglycemia (very rare side effect)

4- General tolerability, and favorable cost.

5- It appears to decrease cardiovascular events and does not have adverse cardiovascular effects.

Adverse effects :

1- Gastrointestinal:

- are the most common side effects including a metallic taste in the mouth, mild anorexia, nausea, abdominal discomfort, and soft bowel movements or diarrhea.

- usually mild, transient, and reversible after dose reduction or discontinuation of the drug. They are minimized by taking the medication with food.

2- Vitamin B12 deficiency

- Due to reduced intestinal absorption of vitamin B12 by metformin.

- In some patients, vitamin B12 deficiency may present as peripheral neuropathy.

3- lactic acidosis : very low incidence but high mortality rate!!

Symptomatic (catabolic) or severe hyperglycemia: Usually type 1

The frequency of symptomatic or severe diabetes has been decreasing in parallel with improved efforts to diagnose diabetes earlier through screening.

-**Ketonuria and/or weight loss present**

We're talking here about type 2, type 1 they're given insulin immediately after diagnosis

- Insulin, rather than oral hypoglycemic agents, is often indicated for initial treatment of symptomatic (polyuria or weight loss) or severe hyperglycemia (fasting plasma glucose >250 mg/dl ,RBG >300 mg/dl or A1C >10%)
- Insulin should also be initiated whenever there is a possibility of undiagnosed type 1 diabetes, which should be suspected among those who are lean or present with marked catabolic symptoms, especially in the presence of a personal or family history of other autoimmune disease and/or the absence of a family history of type 2 diabetes.

- **Ketonuria and weight loss are absent**

We're talking here about type 2 too

- For patients presenting with severe hyperglycemia but without ketonuria or spontaneous weight loss (i.e type 1 diabetes is not likely) insulin or GLP-1 receptor agonists may be used (with or without metformin, depending on contraindications or intolerance).

Glucagon like peptide

- For patients who refuse injections, initial therapy with high-dose sulfonylurea is an alternative option.

* - Metformin monotherapy is not helpful in improving symptoms in this setting ,however, it can be started at the same time as the sulfonylurea, slowly titrating the dose upward.

Comorbidities:

Established cardiovascular or kidney disease

- Patients with cardiorenal comorbidities should be treated with glucose-lowering medications that have evidence of cardiorenal benefit such as GLP-1 receptor agonists and SGLT2 inhibitors.

Sodium-glucose cotransporter-2

- The cardiorenal benefits of GLP-1 receptor agonists and SGLT2 inhibitors have not been demonstrated in drug-naïve patients without established CVD (or at low cardiovascular risk) or without severely increased albuminuria.

Without established cardiovascular or kidney disease

For patients without established CVD or kidney disease who cannot take metformin and :

A1C >9-10% we suggest insulin or a GLP-1 receptor agonist for initial therapy.

Insulin may cause weight gain and hypoglycemia.

If weight loss is a priority, a GLP-1 receptor agonist is a reasonable alternative to insulin.

GLP-1 agonists are FDA approved for being anti obesity medications as well as for diabetes

For patients without established CVD or kidney disease who cannot take metformin and :

A1C ≤ 9% : options includes insulin, GLP-1 receptor agonists, sulfonylureas, SGLT2 inhibitors, DPP-4 inhibitors, repaglinide, or pioglitazone.

Dipeptidyl peptidase

Insulin-secretagogue
Lowers carbohydrates absorption

Insulin-sensitizing
The metformin is also an insulin-sensitizing

GLP-1 agonists + DPP-4 inhibitors > incretin-based therapy

Glucose stimulated insulin secretion

Low risk of hypoglycemia

Incretins are a group of metabolic hormones that stimulate a decrease in blood glucose levels. Incretins are released after eating and augment the secretion of insulin released from pancreatic beta cells of the islets of Langerhans by a blood glucose-dependent mechanism.

Biguanides ← Metformin (AMBOSS) >>Mechanism of action: enhances the effect of insulin
Reduction in insulin resistance via modification of glucose metabolic pathways
Inhibits mitochondrial glycerophosphate dehydrogenase (mGPD) → ↓ hepatic gluconeogenesis and intestinal glucose absorption [7]
Increases peripheral insulin sensitivity → ↑ peripheral glucose uptake and glycolysis
Lowers postprandial and fasting blood glucose levels
Reduces LDL, increases HDL

Considerations in drug selection:

i. If weight loss is a priority, GLP-1 receptor agonists or SGLT2 inhibitors may be a helpful choice. DPP-4 inhibitors, which are weight neutral, also may be reasonable options.

ii. If cost is a concern, a short- or intermediate-acting sulfonylurea, remains a reasonable alternative. The choice of sulfonylurea balances glucose-lowering efficacy, universal availability, and low cost with risk of hypoglycemia and weight gain.

iii. Pioglitazone is another relatively low-cost oral agent, may also be considered in patients with specific contraindications to metformin and sulfonylureas. BUT….. The Side effects and risk of weight gain, heart failure, fractures, and the potential increased risk of bladder cancer may sometimes approach or exceed its benefits.

iv. If avoidance of hypoglycemia is a priority (ie, because of potentially dangerous work or an elderly patient with inability to self-manage himself at all times) ,GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors are options as they are associated with a low hypoglycemia risk.

Insulin therapy:

Although historically insulin has been used for type 2 diabetes only when inadequate glycemic management persists despite oral agents and lifestyle intervention, there are increasing data to support using insulin earlier and more aggressively in type 2 diabetes.

Benefit ??!!

By inducing near normoglycemia with intensive insulin therapy, both endogenous insulin secretion and insulin sensitivity improve; this results in better glycemic management, which can then be maintained with diet, exercise, and oral hypoglycemics for many months thereafter with less future risk of microvascular complications.

↓ Retinopathy, nephropathy and micro vascular complications

Cardiovascular outcomes

- Virtually all trials evaluating the safety and efficacy of all anti diabetes drugs have recruited patients who were already had preexisting CVD or were at very high risk for CVD. So the long-term benefits and risks of using one agent over another in the **absence** of diagnosed CVD are unknown.

- Cardiovascular benefit has been demonstrated for many of these medications, but benefit has not been investigated in drug-naïve patients without established CVD or at low cardiovascular risk.

Microvascular outcomes

- In trials designed to evaluate renal outcomes in patients with DKD and severely increased albuminuria , SGLT2 inhibitors reduced the risk of kidney disease progression and death from renal disease.

- In trials of patients with type 2 diabetes with and without chronic kidney disease, GLP-1 receptor agonists slowed the rate of decline in eGFR and prevented worsening of albuminuria.

MONITORING

- We obtain A1C at least twice yearly in patients meeting glycemic goals and more frequently (quarterly) in patients whose therapy has changed or who are not meeting goals.

- Self-monitoring of blood glucose (SMBG) is not necessary for most patients with type 2 diabetes who are on a stable regimen of diet or oral agents and who are not experiencing hypoglycemia.

- SMBG may be useful for some type 2 diabetes patients who use the results to modify eating patterns, exercise, or insulin doses on a regular basis.

Controlled every 3 months, un-controlled every 1 month

PERSISTENT HYPERGLYCEMIA

- For patients who are not meeting glycemic targets despite diet, exercise, and metformin, combination therapy is necessary to achieve optimal results.

- The balance among efficacy in lowering A1C, side effects, and costs must be carefully weighed in considering which drugs or combinations to choose.

- Avoiding insulin, the most potent of all hypoglycemic medications, at the expense of poorer glucose management and greater side effects and cost, is not likely to benefit the patient in the long term.

Thank you