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CASE 4

Uncontrolled diabetes in a high-risk patient: A case report

A 47-year-old female patient presented with a history of uncontrolled diabetes. The patient's primary complaint was excessive thirst, frequent urination, and fatigue. She reported experiencing frequent high blood sugar levels despite being on metformin 1,000 mg and glimepiride 2 mg daily. Her main concern was the risk of hypoglycemia associated with the current medication regimen.

Medical history

- Ten-year history of diabetes
- Five-year history of hypertension managed with lisinopril 20 mg
- No known allergies to medications

Personal history

- Retired teacher
- Sedentary lifestyle
- Diet includes high carbohydrate intake, with a preference for fried and sugary foods
- Non-smoker but consumes alcohol occasionally

Family history

- Significant for type 2 diabetes mellitus (T2DM) in both parents and an older sibling.
- There is also a history of cardiovascular disease in her family.

Diagnostic workup

Physical examination

Height	Weight	BMI
5'2"	85 kg	34.3 kg/m²

Body temperature	Heart rate	Blood pressure	Respiration rate	CV system
Normal	**78** bpm	**130/85** mmHg	**17** breaths/min	**Normal**

Laboratory investigations

PARAMETERS	FINDINGS
HbA1c	9.5%
Fasting blood glucose (FBG)	210 mg/dL
Postprandial blood glucose (PPG)	290 mg/dL
Lipid profile	Total cholesterol: 210 mg/dL
	HDL cholesterol: 40 mg/dL
	LDL cholesterol: 100 mg/dL
	Triglycerides: 200 mg/dL
Creatinine	1.0 mg/dL
Urine microalbumin-to-creatinine ratio	30 mg/g
Kidney function test	Within normal limits
Liver function tests	Within normal limits
Complete blood count	Within normal range
Microalbuminuria	Not detected

Diagnosis

Uncontrolled type 2 diabetes mellitus, with an HbA1c level well above the target range.

MANAGEMENT

Non-pharmacological

- **Dietary modifications:**
  The patient was referred to a registered dietitian for individualized dietary counseling. A diabetic-friendly, low carbohydrate, and balanced meal plan was provided, with emphasis on portion control and glycemic index.
- **Lifestyle modification:**
  The patient was advised to increase physical activity gradually, aiming for at least 150 minutes of moderate-intensity exercise per week. She was also counseled on weight reduction goals and the importance of stress management and adequate sleep.

Pharmacological

To minimize the risk of hypoglycemia, the patient's medication regimen was adjusted as follows:

- Glimepiride dose was reduced to 1 mg and metformin was continued at 1,000 mg once daily.
- Sitagliptin 100 mg daily was added to the treatment regimen as an adjunct therapy.
- She was advised to continue with her existing antihypertensive medicine.

FOLLOW-UP

FOLLOW-UP MONTH 03

Follow-up at Month 3

- The patient reported improved glycemic control. Her HbA1c had decreased to 8.8%, and she experienced no episodes of hypoglycemia (Table 1).
- Her weight decreased by 5 kg, and she was adhering to dietary and lifestyle recommendations.
- She was advised to continue the combination of glimepiride 1 mg and metformin 1,000 mg twice daily along with sitagliptin 100 mg once daily.

FOLLOW-UP MONTH 06

Follow-up at Month 6

- The patient's HbA1c further improved to 7.8% (Table 1).
- Her weight had decreased by an additional 3 kg.
- The patient was advised to maintain a healthy lifestyle, with regular exercise and a balanced diet.

FOLLOW-UP MONTH 09

Follow-up at Month 9

- The patient's HbA1c was further reduced to 7% (Table 1).
- Her weight loss had plateaued, but she was instructed to continue with her lifestyle changes and medication regimen.
- She was asked to continue with same treatment regimen to avoid long-term complications.

Table 1: Clinical and biochemical parameters at presentation and follow-up visits

Parameter	At presentation	At Month 3	At Month 6	At Month 9
Body weight (kg)	85	80	77	76.5
FBG (mg/dL)	210	185	150	130
PPG (mg/dL)	290	253	210	160
HbA1c (%)	9.5	8.8	7.8	7.0

FBG: Fasting blood glucose; PPG: Postprandial blood glucose.

Discussion

Recent guidelines for T2DM management emphasize on a patient-centered approach, favoring triple oral treatments with complementary mechanisms of action to minimize side effects. Metformin, along with two other orally administered antidiabetic medications has been most suggested as triple treatment therapy.

The combination of metformin, a dipeptidyl peptidase-4 inhibitor (DPP-4i), and a sulfonylurea (SU) effectively targets key aspects of T2DM pathogenesis, i.e., increased hepatic glucose synthesis and decreased insulin secretion. Metformin reduces hepatic glucose synthesis, while DPP-4i and SU increase insulin levels through different mechanisms. DPP-4i boost insulin levels in a glucose-dependent manner by enhancing incretin hormones such as glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP). SUs on the other hand, increase insulin levels independently of glucose levels by acting on SU receptors. Due to its weight neutrality and low risk of hypoglycemia, DPP-4i are well-suited for use in combination with other medications.[1]

In this case, the patient reported symptoms of uncontrolled diabetes such as excessive thirst, frequent urination, fatigue, and frequent high blood sugar levels despite taking metformin 1000 mg and glimepiride 2 mg daily. She had a 10-year history of diabetes and 5-year history of well-controlled hypertension. The patient's main concern regarding the current medication regimen was uncontrolled diabetes and the risk of hypoglycemia.

WHAT DOES GUIDELINES SAY?

- The American Diabetes Association (ADA)/ The European Association for the Study of Diabetes (EASD) and the International Diabetes Federation (IDF) guidelines recommend the use of DPP-4i as part of triple oral therapy regimen with metformin and an SU or a thiazolidinedione (TZDs).[1]

- The Research Society for the Study of Diabetes in India (RSSDI) 2022 recommends the following:[2]
  - Initiate a third oral agent (alpha glucosidase inhibitors [AGI] DPP4i, SGLT2i, or TZDs or oral GLP-1 agonist) if glucose targets are not achieved with two agents.
  - Dipeptidyl peptidase-4 inhibitor are weight neutral and can be used as the second- or third-line of treatment for of diabetes.
  - To manage postprandial hyperglycemia, use of AGIs, DPP4i, SGLT2i or GLP-1 analogs (preferably short-acting) is recommended as the first add-on to metformin therapy.

DID YOU KNOW?[3]

In patients with a history of hypoglycemia or at a high risk of hypoglycemia, DPP-4i, SGLT2i, GLP-1 agonists, AGIs or pioglitazone should be considered as the first choice of drug in combination with metformin. While initiating DPP-4i with SUs, the dose of SUs should be reduced with close monitoring of blood glucose.

WHAT DOES EVIDENCE SUGGEST?

A 24-week, randomized, double-blind study evaluated the effects of sitagliptin 100 mg once daily in combination with metformin and glimepiride in 441 patients with T2DM. The use of triple combination resulted in a significantly greater mean reduction in HbA1c than placebo at 24 weeks (least squares [LS] mean change from baseline: –0.59% vs. 0.30%; between-group difference [95% confidence interval] –0.89% [–1.10% to –0.68%]; p <0.001).[3]

A randomized, open-label study evaluated the effect of sitagliptin 100 mg once daily vs. pioglitazone 30 mg as add-on therapy to metformin (≥1500 mg) and an SU (≥half maximal dose) for 24 weeks in 119 patients with inadequately controlled T2DM. Both groups reduced HbA1c from baseline (LS mean [SE]: Pioglitazone –0.94 [0.12%], p <0.001); Sitagliptin –0.71% [0.12%], p <0.001); between-group difference –0.23% [0.16%]; p = 0.17). However, pioglitazone significantly increased body weight from baseline (1.34 [0.32] kg, p <0.001), whereas sitagliptin had a weight-neutral effect (–0.26 [0.32] kg, p = 0.43; between-group difference 1.60 [0.46] kg, p <0.001).[4]

To address the issue, the patient's treatment was modified to a triple-drug regimen along with regular exercise and a balanced diet. Sitagliptin 100 mg daily was added as an adjunct to metformin and glimepiride combination. Glimepiride dose was reduced, while metformin at 1,000 mg daily was continued.

After 3 months, the patient reported weight loss and improved glycemic control. Her HbA1c decreased from 9.5% to 8.8%, with no episodes of hypoglycemia. She was advised to continue the triple combination of metformin, glimepiride, and sitagliptin.

At 6- and 9-month follow-up, HbA1c levels decreased to 7.8% and 7.0%, respectively. Her weight dropped from 85 kg at presentation to 76.5 kg at 9 months. The patient was advised to continue the triple drug therapy of metformin, glimepiride, and sitagliptin, in addition to lifestyle modifications to prevent long-term complications

Expert Views

- Several clinical guidelines recommend an individualized approach to the management of T2DM.
- Metformin is considered the first-line therapy unless in case of contraindications or patient intolerance.
- If monotherapy and dual therapy fails to maintain optimal blood glucose levels, a third agent should be added to the treatment.
- Reports suggest that addition of a third drug to metformin + sulfonylureas therapy was statistically and clinically superior to dual therapy at reducing HbA1c level.
- In patients with a history of hypoglycemia or at high risk of hypoglycemia, DPP-4i may be considered as the first choice of drug in combination with metformin. Additionally, the dose of sulfonylureas should be educed while initiating DPP-4i.
- Glimepiride has good cardiovascular safety.

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