Insulin therapy

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A 62- year- old retired schoolteacher attended the diabetes clinic on a routine follow- up visit.

He had a background history of hypertension and Type 2 DM for 20 years.

He was currently taking zipmet50.1000 (twice daily), diabezide 60 (twice daily), and valsartan, amlodipine (80.5 mg once a day).

On examination, his BMI was 38 kg/ m2. His blood pressure was 152 /92 mm of Hg.

Investigations:

HbA1c 8:9

The next step ???????

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therapeutic inertia, reassess Use principles in Figure 9.3, including reinforcement of behavioral interventions (weight management and modify and physical activity) and provision of DSMES, to meet individualized treatment goals treatment regularly (3-6 months) If injectable therapy is needed to reduce A1C¹ Consider GLP-1 RA or dual GIP and GLP-1 RA in most individuals prior to insulin² If already on GLP-1 RA or dual GIP/GLP-1 RA, or if INITIATION: Initiate appropriate starting dose for agent selected (varies within class) these are not appropriate, or if insulin is preferred TITRATION: Titrate to maintenance dose (varies within class) If A1C is above goal Considerations for adding basal insulin3

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Consider insulin as the first injectable if
evidence of ::::::::::
ongoing catabolism is present,
Symptoms of hyperglycemia
A1C > 10\% or
Blood glucose ≥300 mg/dL) or
when a diagnosis of type 1 diabetes is a
possibility.
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case2

A 62- year- old woman with Type 2 DM for over 20 years was reviewed In the diabetes clinic on a routine follow- up visit.

She was on metformin, gliclazid and sitagliptin tablets for Type 2 DM. She was taking

lisinopril and amlodipine tablets for blood pressure (BP) control. She had weight loss during 6 months and recent polyuria, polydipsia;

On examination, she had a BMI of 23.5 kg/ m2. Her BP was 142/ 84 mmHg. She had clinical evidence of peripheral neuropathy.

Investigations:

Urinary albumin creatinine ratio 35 mg/ mmol

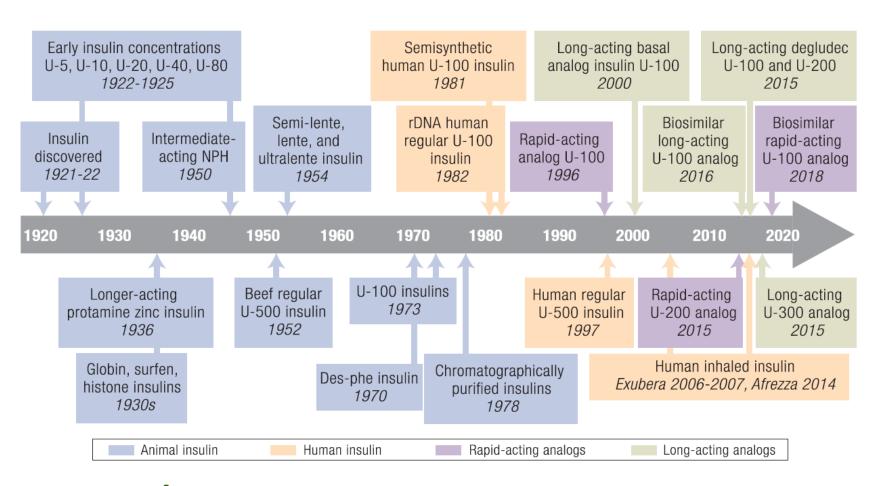
eGFR creatinine 47 ml/ min/ 1.73m2

HbA1c :10.5

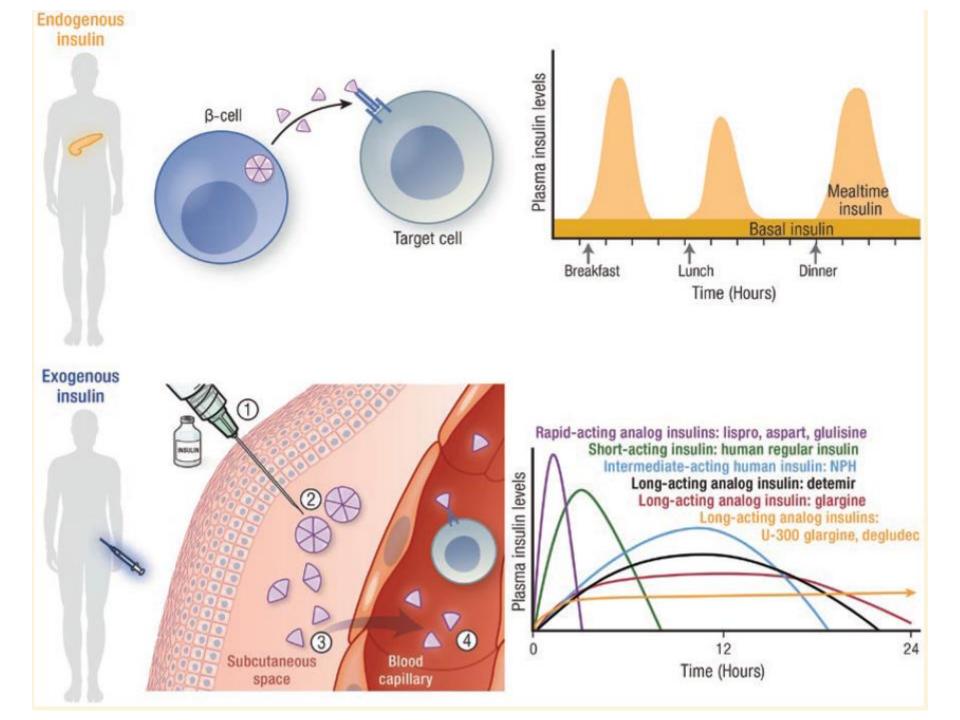
Which one of the following is the most appropriate next step in her further management?

- A. Start SGLT2Inhibitor
- B. Refer to renal clinic
- C. Stop metformin
- D. Start insulin

Timeline of insulin development with approximate historical dates



lcodec , once-weekly basal insulin???????



Insulin

Properties of Insulin Preparations^a

	Time of Acti	Time of Action		
Preparation	Onset, h	Peak, h	Effective Duration, h	
Short-acting ^b				
Aspart	<0.25	0.5-1.5	2–4	
Glulisine	<0.25	0.5-1.5	2–4	
Lispro ^f	<0.25	0.5-1.5	2-4	
Regular ^g	0.5-1.0	2-3	3-6	
Inhaled human insulin	0.5-1.0	2-3	3	
Long-acting ^g				
Degludec	1-9	c	42 ^d	
Detemir	1-4	_c	12-24 ^d	
Glargine ^f	2–4	_с	20-24	
NPH	2-4	4-10	10-16	
Examples of insulin combinations ^e				
75/25–75% protamine lispro, 25% lispro	<0.25	Dual ^f	10-16	
70/30–70% protamine aspart, 30% aspart	<0.25	Dual ^f	15-18	
50/50–50% protamine lispro, 50% lispro	<0.25	Dual ^f	10-16	
70/30–70% NPH, 30% regular	0.5-1	Dual ^f	10-16	
Combination of long-acting insulin and GLP-1 receptor agonist	See text			

NPH, Regular



Glargine 100unit/cc, 30ounit/cc





Levemir(Detemir)



Degludec



Novorapid (aspart)



Apidra (gliulisine)



lispro



NovoMix^{70/30}



Humalog Mix50



Humalog Mix25



RYZODEG

insulin degludec/insulin aspart



lcodec, once-weekly basal insulin



insulin icodec has not been approved by the FDA.

SOLIQUA

basal insulin +GLP-1RA



Soliqua 100 units/mL + 50 microgram/mL solution for injection in a prefilled pen, Soliqua 100 units/mL + 33 microgram/mL solution for injection in a prefilled pen

insulin regimens for the treatment of diabetes

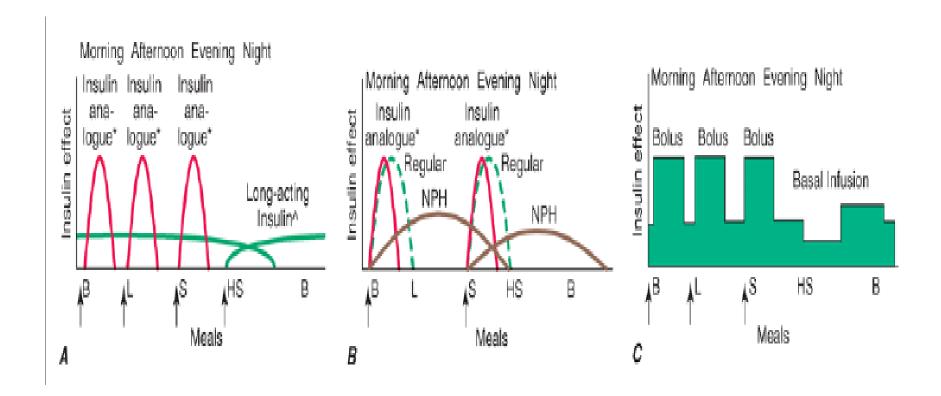
Basal – bolus (multiple-component insulin regimen):

provided by long-acting (NPH insulin, insulin glargine, or insulin detemir) insulin formulations; with short-acting insulin in an attempt to mimic physiologic insulin release with meals.

conventional :mixing of NPH and short-acting insulin formulations is common practice

CSII: continuous subcutaneous insulin infusion

In all regimens, long-acting insulins (NPH, glargine, or detemir) supply basal insulin, whereas regular, insulin aspart, glulisine, or lispro insulin provides prandial insulin. Short-acting insulin analogues should be injected just before or just after a meal; regular insulin is given 30–45 min prior to a meal



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Initiation and titration of basal analog or bedtime NPH insulin4

INITIATION: Start 10 units per day OR 0.1-0.2 units/kg per day

TITRATION:

- Set FPG goal (see Section 6, "Glycemic Goals and Hypoglycemia")
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG goal without hypoglycemia
- . For hypoglycemia: determine cause; if no clear reason, lower dose by 10-20%

Assess adequacy of insulin dose at every visit

Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., elevated bedtimeto-morning and/or postprandial-to-preprandial differential, hypoglycemia [aware or unaware], high glucose variability)

- If A1C is above goal and the individual is not already on a GLP-1RA or dual GIP and GLP-1RA, consider these
 classes in combination and with insulin (may use fixed-ratio product, if available and appropriate)
- If A1C remains above goal:

Initiation and titration of prandial insulin5,6

Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

INITIATION:

- 4 units per day or 10% of basal insulin dose
- If A1C <8% (<64 mmol/mol), consider lowering the basal dose by 4 units per day or 10% of basal dose

TITRATION:

- Increase dose by 1-2 units insulin dose or 10-15% twice weekly
- For hypoglycemia: determine cause; if no clear reason, lower corresponding dose by 10-20%

If on bedtime NPH, consider converting to twice-daily NPH plan

Conversion based on individual needs and current glycemic management. The following is one possible approach:

: INITIATION:

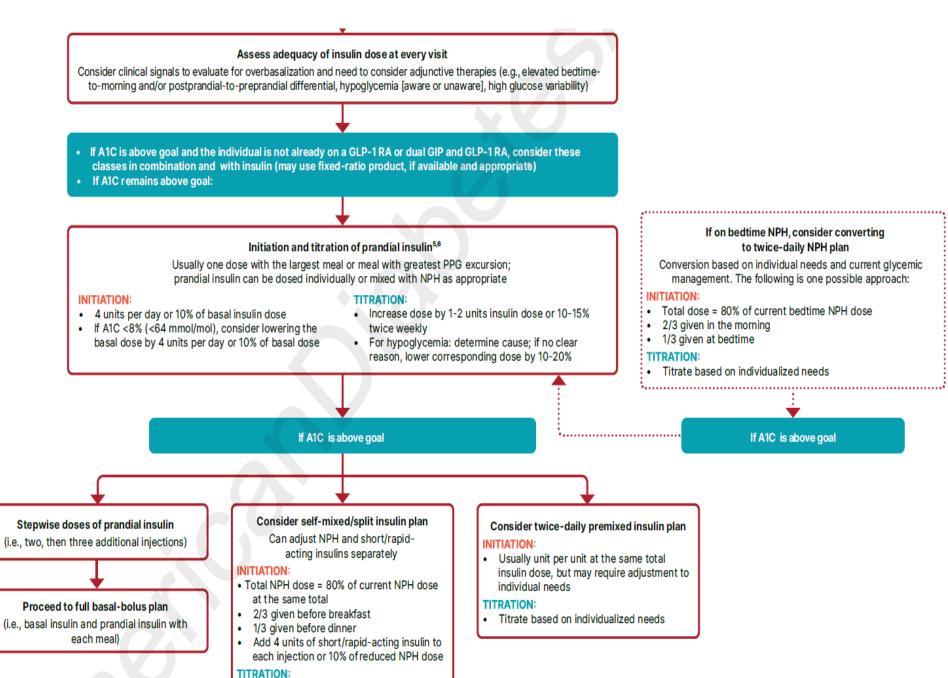
- Total dose = 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION:

Titrate based on individualized needs

If A1C is above goal

If A1C is above goal



Titrate each component of the plan based

on individualized needs

In practice

- In general, individuals with type 1 DM require 0.2 0.3 units/kg per day of insulin divided into multiple doses, with approximately 50% of daily insulin given as basal insulin and 50% as prandial insulin.
- To determine the meal component of the preprandial insulin dose, the patient uses an insulin-to-carbohydrate ratio (a common ratio for type 1 DM is 1 unit/10–15 g of carbohydrate, but this must be determined for each individual).
- 450 or 500/total daily dose insulin=carb count ratio)
- To this insulin dose is added the supplemental or correcting insulin based on the preprandial blood glucose (one formula uses 1 unit of insulin for every 1.6–3.3 mmol/L [30–60 mg/dL] over the preprandial glucose target; this correction factor can be estimated from 1500/[total daily insulin dose]).

In Type 2 DM insulin is usually initiated in a single dose of long-acting insulin (0.2–0.3 U/kg per day), given in the evening or just before bedtime (NPH, glargine, detemir, or degludec).

- Because fasting hyperglycemia and increased hepatic glucose production are prominent features of type 2 DM, bedtime insulin is more effective in clinical trials than a single dose of morning insulin.
- Glargine given at bedtime has less nocturnal hypoglycemia than NPH insulin.
- Some physicians prefer a relatively low, fixed starting dose of long-acting insulin (5–15 units) or a weight-based dose (0.1 units/kg).
- The insulin dose may then be adjusted in 10–20% increments as dictated by SMBG results.
- Both morning and bedtime long-acting insulin may be used in combination with oral glucose-lowering agents.
- Initially, basal insulin may be sufficient, but often prandial insulin coverage with multiple insulin injections is needed as diabetes progresses.

Suboptimal control on oral medications Low risk for CAD

Background

- 60 year old male
- T2DM since 6 years
- No known micro or macrovascular complications of diabetes
- No other known co-morbid conditions

Current Medication

- Metformin 1000 mg twice daily
- Gliclazide 80 mg BID
- Aspirin 80 mg daily
- Multivitamin daily

Life style

- Has met with nutritionist & is following reasonable meal plan
- Walks 4 days per week for 30 minutes each time
- Testing Glucose once or twice daily
- Not keen to take insulin-thinks has severe disease if has to take insulin

Physical Examination

• Weight: 79.5 kg

• Height: 1.82 m

• BMI: 24 kg/m²

• BP: 125/80

 Examination of all systems normal

 No evidence of micro or macrovascular complications

Home glucose monitoring data (mg/dl)

Pre-breakfast	2 hours after breakfast	2 hours after lunch	2 hours after dinner
168	210		
174		175	
158			178
172	196		
182			

HbA_{1c} 8.6%

Laboratory data

Lipids:

– Total cholesterol : 189 mg/dl

– HDL : 55 mg/dl

- TG: 145 mg/dl

– LDL : 95 mg/dl

Creatinine: 0.8 mg/dl

LFTs: normal

What can be done in this case?

- Modification of SU dosage
- Add another OAD
- Add basal insulin
- Add basal insulin glp-1ra
- Add GLP-1RA
- Others options

Action

- Continued Metformin with the same dose
- Reduced SU gradually
- Started on Insulin basal 10 units at bedtime
- Dose titrated every 3 days by 3 units to achieve fasting glucose of (90-120) mg/dl
- Walking daily
- Watching meal plan more carefully

Follow-up ...

1 week

FPG: 142mg/dl

- PPG: 171 mg/dl

No hypoglycemia event

1 month

FPG: 128 mg/dl

- PPG: 162 mg/dl

No hypoglycemia event

Follow-up ...

3 months

- SU D/C, 30 units of Insulin Basal at bedtime
- HbA1c: 7.6%
- FPG: 115 mg/dl, PPG: 155 mg/dL
- No hypoglycemia event
- Follow up 3 months later

Follow-up ...

6 months

Weight: 80 kg

Pre-breakfast	2 hours after breakfast		
105	155		
96		168	
101			176
90	149		

HbA_{1c} 6.8%

Next scenario....

6 months

Weight: 80 kg

Pre-breakfast	2 hours after breakfast		
105	155		
96		190	
101			186
90	149		

HbA_{1c} 7.5%

	Special populations			Administration		Pump use				
	Paediatric	Pregnancy	Hepatic impairment	Renal impairment	Elderly	Pts prone to severe hypoglycaemia	Time	In-use temperature	Reservoir storage	Pre-filled cartridge available
NovoRapid ^{®1,2}	√ ≥1 year	✓	✓	✓	✓	✓	Immediately before – when necessary soon after meal	<30°C (cold in-use) [†]	6 days	✓
Insulin glulisine ^{3,4}	≥6 years	Only exposure data	×		No separate PK/PD studies	No RCT data available	Shortly before – when necessary soon after meal	<25°C	48 hours	×

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Initiation and titration of basal analog or bedtime NPH insulin4

INITIATION: Start 10 units per day OR 0.1-0.2 units/kg per day

TITRATION:

- Set FPG goal (see Section 6, "Glycemic Goals and Hypoglycemia")
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG goal without hypoglycemia
- . For hypoglycemia: determine cause; if no clear reason, lower dose by 10-20%

Assess adequacy of insulin dose at every visit

Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., elevated bedtimeto-morning and/or postprandial-to-preprandial differential, hypoglycemia [aware or unaware], high glucose variability)

- If A1C is above goal and the individual is not already on a GLP-1RA or dual GIP and GLP-1RA, consider these classes in combination and with insulin (may use fixed-ratio product, if available and appropriate)
- If A1C remains above goal:

Initiation and titration of prandial insulin5,6

Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

INITIATION:

- · 4 units per day or 10% of basal insulin dose
- If A1C <8% (<64 mmol/mol), consider lowering the basal dose by 4 units per day or 10% of basal dose

TITRATION:

- Increase dose by 1-2 units insulin dose or 10-15% twice weekly
- For hypoglycemia: determine cause; if no clear reason, lower corresponding dose by 10-20%

If on bedtime NPH, consider converting to twice-daily NPH plan

Conversion based on individual needs and current glycemic management. The following is one possible approach:

: INITIATION:

- Total dose = 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION:

Titrate based on individualized needs

If A1C is above goal

If A1C is above goal

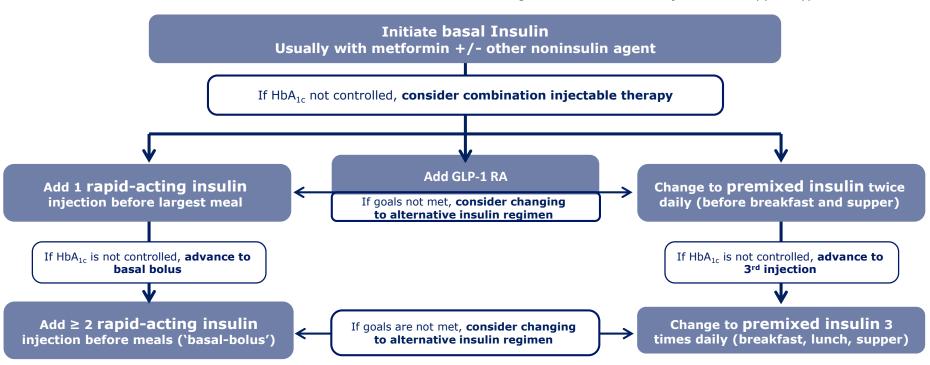
Section 8. Pharmacological approaches to Glycemic Treatment (contd.)

Table 8.1-Drug-specific and pation	ent factors to consider when select	ing antihyperglycemic treatment	in adults with type 2 diabetes

	Fifficano	U a abasania	Weightshauer		CV -#	Donal officia
	Efficacy	Hypoglycemia	Weight change	CV effects		Renal effects
				ASCVD	CHF	CKD progression
Metformin	High	No	Neutral	Potential benefit	Neutral	Neutral
SGLT-2is	Intermediate	No	Loss	Benefit: Canagliflozin Empaglifozin †	Benefit: Canagliflozin Empaglifozin	Benefit: Canagliflozin Empaglifozin
GLP-1 RAs	High	No	Loss	Neutral: Lixitenatide, exenatide extended release Benefit: Liraglutide†	Neutral	Benefit: Liraglutide
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: Saxagliptin, alogliptin	Neutral
Thiazolidinediaones	High	No	Gain	Potential Benefit: Pioglitazone	Increased risk	Neutral
Sulphonylureas (2 nd generation)	High	Yes	Gain	Neutral	Neutral	Neutral
Insulins	Highest	Yes	Gain	Neutral	Neutral	Neutral

Section 8. Pharmacological approaches to Glycemic Treatment (contd.)

Figure 8.2—Combination injectable therapy for type 2 diabetes



GLP-1 RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes; TID, thrice daily Adapted from American Diabetes Association Diabetes Care 2017;40(Suppl.1):564–574.

Suboptimal control in type 2 diabetes with coronary artery disease & weight loss

Background

- 66 year old female
- T2DM since 10 years
- Co-morbid conditions
 - ✓ HTN
 - √ Hyperlipidemia
 - ✓ CAD(stent 2month ago)
- Family history of T2DM, HTN & CAD

Current Medication

- Empagliflosine/Metformin 5/1 000mg BID
- Gliclazide 60mg BID
- Atorvastatin 40 mg QD
- Lisinopril 40 mg QD
- HCTZ 12.5 mg QD
- Amlodipine 5 mg QD
- Aspirin 80 mg QD

Life style

- Consistent carbohydrate intake
- Walks 4 times per week for 30 minutes each time
- Testing Glucose once or twice daily

Physical Examination

Weight: 101 kg
 Height: 1.65 m
 BMI: 37 kg/m²

BP: 120/70 Pulse: 66Acanthosis nigricans

• Non proliferative retinopathy

• No known neuropathy or nephropathy

Laboratory Data

- HbA1c: 6.5% soon after 2 agents started (3 years ago)
- HbA1c: 7% a year previously
- HbA1c: 11.8%
- FPG: 195 mg/dl
- PPG: 230mg/dl
- Lipids
 - ✓ Chol 175 mg/dl
 - ✓ TG 142 mg/dl
 - ✓ HDL 44 mg/dl
 - ✓ LDL 103 mg/dl
- LFTs normal
- Cr : 0.9 mg/dl

What can be done in this case?

- Modification of SU dosage
- Add another OAD
- Add basal insulin
- Add GLP-1RA or GLP-1Ra/GIP
- Other options

Action

- Aim to achieve HbA1c around 7%
- Avoid hypoglycaemia
- Reduced SU gradually
- Started on Insulin Basal 10 units at bedtime
- Dose titrated cautiously to achieve FPG around 120 mg/dl
- Walking daily
- Watching meal plan more carefully

Follow-up ...

1 week

- F: 150 mg/dl

- PP: 175 mg/dl

No hypoglycemia event

1 month

- F: 131 mg/dl

PP: 163 mg/dl

No hypoglycaemia event

Follow-up ...

3 months

- FPG average 118 mg/dl
- HbA1c: 7.9%
- No hypoglycaemia event
- SU D/C, 42 units of Insulin Basal at bedtime
- Weight: 115 kg
- Next step??

What can be done in this case?

- Add another OAD
- Add rapid insulin
- Add GLP-1RA or GLP-1Ra/GIP
- Other options

Adjust medications to help with lower hypoglycaemia events

Background

- 50 year old male
- T2DM since 11 years
- No known micro or macrovascular complications of diabetes

Current Medication

- Metformin 2000 mg daily
- NPH 18 U morning
- NPH 14 U pre-dinner

Physical Examination

Weight: 65 kg
BMI: 23 kg/m²
Cr: 1.29 mg/dl
BP: 130/80

- No evidence of any micro or macrovascular complications
- Complain of nocturnal hypoglycaemia
- Hospitalization due to severe hypoglycaemia

Home glucose monitoring data (mg/dl)

FBS	2 h after breakfast	2 h after lunch	2 h after dinner	03:00 am
110	170	140	160	60
90	165	180	140	

HbA_{1c} 7.5%

What can be done in this case?

- Add another OAD
- Decrease dose of evening NPH
- Change in injection time of evening NPH
- Switch from NPH to once daily of insulin degludec
- Other options

Action

Continue metformin

- Switch from NPH to once daily insulin Basal & titrate
 - Twice daily NPH ----> (~ 80% of NPH) total daily dose

Start dose of insulin basal: 25 U morning

Titration algorithm: -3, 0, 3

Follow-up..

1 week

- F: 111mg/dl
- 2 h PPG ~ 160
- Without hypoglycemia event

1 month

- F: 98 mg/dl
- 2 h PPG ~ 148
- Happy that no hypoglycemia event since changing the therapy
- More satisfaction with once daily injection instead of twice daily

Follow-up..

3 months later

- Insulin Basal 32 U at morning
- Metformin 2000 mg daily
- No hypoglycemia event
- No weight gain

HbA1c: 7.3%

FPG: 95 mg/dl

Adjust medications to help without weight gain

Background

- 67 year old male
- T2DM since 12 years
- Co-morbid conditions
 - ✓ HTN
 - ✓ Hyperlipidemia
 - √ hypothyroidism
- No known micro or macrovascular complications of diabetes

Current Medication

- Metformin 1 g twice daily
- NPH 15 U morning
- NPH 10 U pre-dinner
- Atorvastatin 40 mg daily
- Lisinopril 40 mg daily
- Levothyroxine 150 mcg daily

Physical Examination

Weight: 111kg
 Height: 1.78 m
 BMI: 35.5 kg/m²

• BP:130/80

• No evidence of any micro or macrovascular complications

Home glucose monitoring data (mg/dl)

Pre-breakfast	2 hours after lunch	2 hours after dinner	Bedtime
(80-150)	(130-160)	(150-170)	(110-200)

HbA_{1c} 8.9%

Issues

- Suboptimal glucose control
- Obesity
 - difficulty losing weight
- not really following a specific meal plan or exercising regularly
- Motivated to make some lifestyle changes
- Plan
 - Weight management programme
 - Review and change medications

Action

- Multidisciplinary weight management programme
 - ✓ Percent of calorie from carbohydrate in the main meals: (40/30/30)%

(most of them complex carb)

- ✓ Exercise prescription
- ✓ Change medication
 - 1)start insulin Basal and liraglutide /or sems glutide/ or tirzepatide (Basal insulin 10 u+ 0.6 mg/d
 - 2) Or Change NPH to Insulin soliqua (decrease dose/ titrate according to FPG target)

Start dose: 20 U

Action

 1)start insulin Basal and liraglutide /or sems glutide/ or tirzepatide (Basal insulin 10 u+ 0.6 mg/d

Follow-up..

1 week

- FPG: 135mg/dl
- Nausea
- Reduced appetite
- — ↑ liraglutide dose to 1.2 mg
- Titrate insulin Basal according to FPG target

1 month

- FPG: 122 mg/dl
- Nausea still persisting, but better
- Happy that no hypoglycaemia event since changing the therapy
- Titrate insulin Basal according to FPG target

Follow-up..

3 months later

- Insulin Basal 30U at bedtime
- Metformin 1 g twice daily
- LIRAGLUTIDE 1.2 MG daily

Weight 97 kg (Lost 15kg)

BP: 120/70

HbA1c: 7.3%

FPG: 110 mg/dl

Background

- 56 year old male
- T2DM since 10 years
- Co-morbid conditions
 - ✓ HTN
 - √ Hyperlipidemia
- No known micro or macrovascular complications of diabetes

Current Medication

- Empa-metformin 5/1000mg twice daily
- NPH 14U morning
- NPH 12 U pre-dinner
- Atorvastatin 40 mg daily
- telmisartan 40 mg daily

Physical Examination

Weight: 100kg
 Height: 1.78 m
 BMI: 31.5 kg/m²

• BP:130/80

• No evidence of any micro or macrovascular complications

Home glucose monitoring data (mg/dl)

Pre-breakfast	2 hours after lunch	2 hours after dinner	Bedtime
(80-150)	(130-160)	(150-170)	(110-200)

HbA_{1c} 8.9%

Action

 Or Change NPH to Insulin soliqua (decrease dose/ titrate according to FPG target)

Start dose: 20 U

Follow-up..

1 week

- FPG: 135mg/dl
- Nausea
- Titrate soliqua according to FPG target

1 month

- FPG: 122 mg/dl
- Happy that no hypoglycaemia event since changing the therapy
- Titrate soliqua according to FPG target

Follow-up..

3 months later

- Insulin soliqua 38U at bedtime
- Empa/Metformin 5/000mg twice daily

Weight 99kg

BP: 120/70

HbA1c: 7.3%

FPG: 110 mg/dl

Q&A



work Don

