Case study:
Adolescent newly diagnosed with type 2 diabetes

Authored by James LaSalle and Stephan Matthaei on behalf of the Global Partnership for Effective Diabetes Management.

The Global Partnership for Effective Diabetes Management is supported by an unrestricted educational grant from Bristol-Myers Squibb, AstraZeneca LP.
• This case study outlines the treatment of an adolescent who is newly diagnosed with type 2 diabetes
• The case reflects a full range of treatment and management tools available in the European/US context*

*The management of any patient is subject to social, economic, gender, age, co-morbidity and ethnic variables, and is dependent on the range of treatment options available in specific regions or countries.
Adolescent newly diagnosed with type 2 diabetes

- Lucy, aged 16 years, lives at home with her parents and younger sister
- Recently she has been experiencing bouts of extreme thirst, an increased need to urinate and unexplained weight loss – Lucy usually struggles to lose weight
- She’s also been feeling increasingly tired and has noticed she craves sugary food types throughout the day
- Normally Lucy is very sociable and this sudden tiredness is affecting her quality of life
- Her mother had gestational diabetes while pregnant with Lucy, and was herself diagnosed with type 2 diabetes 7 years ago
- Owing to her symptoms, Lucy’s mother makes her an appointment with their family doctor

**Current status**
- 16 years old
- Weight: 86 kg (189.6 lbs)
- Height: 169 cm (5 ft 6 in)
- BMI: 30.1 kg/m²

BMI, body mass index
First consultation with GP

- Lucy explains her symptoms and family history to the doctor
- The doctor measures Lucy’s blood pressure and performs some blood tests

### Clinical chemistry
- **FPG:** 12.8 mmol/l
- **HbA\(_{1c}\):** 10.2%
- **Ketone body:** Negative
- **Anti-GAD antibody:** Negative
- **C-peptide:** 1.2 nmol/l
- **ACR:** 0.88 mg/mmol
- **eGFR:** 118 ml/min

### Blood pressure*
- Systolic/diastolic: 118/78 mmHg

*Confirmed on subsequent visits

Testing for dyslipidaemia in adolescents should be performed soon after diagnosis and after blood glucose control has been achieved

### History/symptoms
- Mother had gestational diabetes; diagnosed with type 2 diabetes 7 years ago
- Polyuria
- Thirst/sugar craving
- Tiredness/weight loss

ACR, albumin:creatinine ratio; anti-GAD, glutamic acid decarboxylase; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA\(_{1c}\), glycosylated haemoglobin.
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<th>Normal range</th>
</tr>
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<tbody>
<tr>
<td>FPG: 12.8 mmol/l</td>
<td>3.9–5.5 mmol/l</td>
</tr>
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<td>HbA₁c: 10.2%</td>
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</tr>
<tr>
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<td>Systolic/diastolic: 118/78 mmHg</td>
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*Confirmed on subsequent visits
First consultation with the GP

- Lucy explains her symptoms and family history to the doctor
- The doctor measures Lucy’s blood pressure and performs some blood tests

**Clinical chemistry**
- FPG: 231 mg/dl
- HbA$_{1c}$: 88 mmol/mol
- Ketone body: Negative
- Anti-GAD antibody: Negative
- C-peptide: 3.6 ng/ml
- ACR: 7.8 mg/g
- eGFR: 118 ml/min

**Blood pressure***
- Systolic/diastolic: 118/78 mmHg

Testing for dyslipidaemia in adolescents should be performed soon after diagnosis and after blood glucose control has been achieved.

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<td>231 mg/dl</td>
<td>70–100 mg/dl</td>
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<td>HbA₁₀₀</td>
<td>88 mmol/mol</td>
<td>20–42 mmol/mol</td>
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<td>Ketone body</td>
<td>Negative</td>
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</tr>
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Diagnosis of type 2 diabetes: what is Lucy’s glycaemic target

• The doctor explains to Lucy that her test results show she has type 2 diabetes*
  – Measurement of antibodies to GAD allows exclusion/confirmation of type 1 diabetes
• Controlling BG is a priority for Lucy; onset of type 2 diabetes at an early age points to a glycaemic legacy if the disease is uncontrolled for long periods
• The doctor discusses with Lucy what her glycaemic target should be as her current BG levels are far too high

**Question**
What is the most appropriate HbA$_{1c}$** target for Lucy?

<table>
<thead>
<tr>
<th>Target</th>
<th>Equivalent Value (mmol/mol)</th>
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<tbody>
<tr>
<td>&lt;6.0%</td>
<td>42</td>
</tr>
<tr>
<td>6.0–6.5%</td>
<td>48–53</td>
</tr>
<tr>
<td>6.5–7.0%</td>
<td>58–64</td>
</tr>
<tr>
<td>7.0–7.5%</td>
<td>53–58</td>
</tr>
<tr>
<td>7.5–8.0%</td>
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*Clinical classification of diabetes can be difficult in overweight or obese young people. **Equivalent values: 6.0% = 42 mmol/mol, 6.5% = 48 mmol/mol, 7.0% = 53 mmol/mol, 7.5% = 58 mmol/mol and 8.0% = 64 mmol/mol.

BG, blood glucose; GAD, glutamic acid decarboxylase; HbA$_{1c}$, glycosylated haemoglobin.

Glycaemic target: long-term safety is a priority in children and adolescents

- Glycaemic targets should always be individualized based on a number of factors
- Long-term safety is a priority for children and adolescents diagnosed with type 2 diabetes
- An HbA$_{1c}$ target as near to normal as possible (<7.0%), while minimizing risk of hypoglycaemia, is appropriate
- Other factors favouring more stringent glycaemic targets include a strong support system, lack of co-morbidities/complications and recent diagnosis

What is the most appropriate HbA$_{1c}$* target for Lucy?

- <6.0%
- 6.0–6.5%
- 6.5–7.0%
- 7.0–7.5%
- 7.5–8.0%

*Equivalent values: 6.5% = 48 mmol/mol and 7.0% = 53 mmol/mol. HbA$_{1c}$, glycosylated haemoglobin.

Glycaemic control

• The doctor and Lucy discuss her options for glycaemic control
• The doctor also arranges for Lucy and her family to be referred to a specialist diabetes nurse who will provide dietary and lifestyle advice, as well as teaching Lucy about self-monitoring of BG (SMBG)
  – The nurse and Lucy agree on an initial weight loss target of $\geq 5$ kg (11 lbs) within 3 months

**Question**
Which of the following is an appropriate choice of therapy for Lucy?

- Lifestyle alone
- Lifestyle + metformin
- Lifestyle + insulin
- Lifestyle, metformin + GLP-1 agonist
- Lifestyle, metformin + sulphonylurea

BG, blood glucose; GLP-1, glucagon-like peptide; SMBG, self-monitoring of blood glucose.
Option selected: Lifestyle alone

- Achieving good glycaemic control safely and without delay is a priority for newly diagnosed individuals with type 2 diabetes\(^1\)
- As Lucy is young, preventing/delaying the onset of diabetes complications through optimal glycaemic control is particularly important
  - In adolescents, the onset of type 2 diabetes points to a glycaemic legacy if the disease is uncontrolled for long periods of time\(^2\)
- Lifestyle interventions do not appear as effective as in adults but still form an integral part of any type 2 diabetes treatment regimen\(^2\)
  - They should only be considered in isolation for highly motivated individuals who are already close to glycaemic target (<7.5%; 58 mmol/mol)
- Lucy has marked hyperglycaemia and even a strict regimen of diet and exercise is unlikely to restore glycaemic control

Achieving good glycaemic control safely and without delay is a priority for newly diagnosed individuals with type 2 diabetes\(^1\).

As Lucy is young, preventing/delaying the onset of diabetes complications through optimal glycaemic control is particularly important.

- In adolescents, the onset of type 2 diabetes points to a glycaemic legacy if the disease is uncontrolled for long periods of time\(^2\).

Choice of pharmacotherapy should aim to preserve β-cell function and improve insulin sensitivity; at present, metformin is the only oral antihyperglycaemic agent approved for use in children and adolescents\(^1,3\).

However, Lucy is severely hyperglycaemic and single-agent therapy alongside lifestyle interventions is unlikely to lower her HbA\(_{1c}\) to target levels.

- Metformin would be expected to lower HbA\(_{1c}\) by 1.0–2.0\%,\(^1\) leaving Lucy with uncontrolled hyperglycaemia.

\(\text{Metformin}^{1,4} \)

\[
\begin{array}{ll}
\text{↓HbA}_{1c}\text{ efficacy:} & \text{High} \\
\text{Hypoglycaemia risk:} & \text{Low} \\
\text{Weight effect:} & \text{Neutral/loss} \\
\text{Major side effects:} & \text{GI Lactic acidosis} \\
\text{Cost:} & \text{Low}
\end{array}
\]


\(\text{HbA}_{1c}\), glycosylated haemoglobin.
Treatment should aim to preserve β-cell function and improve insulin sensitivity.

Currently, metformin is the only oral agent approved for use in children and adolescents. Lucy is severely hyperglycaemic, however, and metformin alongside lifestyle interventions is unlikely to lower her HbA₁c to target levels.

Insulin can be considered alongside lifestyle interventions from the outset for the treatment of children and adolescents with type 2 diabetes.

For adolescents presenting with HbA₁c ≥8.5% (69 mmol/mol) or severe manifestations of insulin deficiency, insulin is the most effective way to achieve rapid metabolic control.

However, Lucy is nervous about the prospect of having to inject herself every day and is worried about weight gain. The doctor explains:

- The benefits of using insulin to lower risk of diabetes-related complications
- That once glycaemic control is achieved, it might be possible to switch to oral therapy (e.g. metformin) and lifestyle interventions

Following this discussion, the doctor and Lucy decide upon a basal-bolus insulin regimen.

HbA₁c, glycosylated haemoglobin.

• Lucy is severely hyperglycaemic: it is likely that combination therapy or insulin alongside lifestyle changes will be needed to lower HbA₁c to target.
• Agents that address insulin resistance (metformin) or preserve β-cell function (GLP-1 receptor agonists) may be preferred for adolescents¹.
• Exenatide has been shown to be well-tolerated and to improve postprandial glucose concentration in a pharmacokinetics and safety study in adolescents².
  — However, GLP-1 receptor agonists are not currently approved for use in this patient group¹,³.
• For adolescents presenting with HbA₁c ≥8.5% (69 mmol/mol) or severe manifestations of insulin deficiency, insulin is the most effective way to achieve rapid metabolic control³.
• Together, Lucy and the doctor decide to begin on lifestyle changes + basal-bolus insulin, and review the decision once glycaemic control is achieved.

**Metformin¹,⁴**
- ↓HbA₁c efficacy: High
- Hypoglycaemia risk: Low
- Weight effect: Neutral/loss
- Major side effects: GI, Lactic acidosis
- Cost: Low

**GLP-1 agonist¹,⁴**
- ↓HbA₁c efficacy: High
- Hypoglycaemia risk: Low
- Weight effect: Neutral/loss
- Major side effects: GI
- Cost: Moderate

GLP-1, glucagon-like peptide; HbA₁c, glycosylated haemoglobin.

This combination would be a reasonable option for adults presenting with severe hyperglycaemia\(^1\)

However, sulphonylureas are not approved for use in adolescents in many countries, and are not generally recommended in this patient population\(^1\)

### Metformin\(^{1,2}\)
- ↓HbA\(_{1c}\) efficacy: High
- Hypoglycaemia risk: Low
- Weight effect: Neutral/loss
- Major side effects: GI Lactic acidosis
- Cost: Low

### Sulphonylurea\(^{1,2}\)
- ↓HbA\(_{1c}\) efficacy: High
- Hypoglycaemia risk: Moderate
- Weight effect: Gain
- Major side effects: Hypoglycaemia
- Cost: Low

HbA\(_{1c}\), glycosylated haemoglobin.

Metformin in adolescents: monotherapy can be inadequate for BG control

• In the TODAY (Treatment Options for type 2 Diabetes and Adolescents and Youth) study, 50% of children and adolescents failed to maintain durable glycaemic control with metformin monotherapy\(^1\)
• Combination therapy (or insulin) was often necessary to achieve BG control within a few years of diagnosis\(^1\)

![Graph showing failure rates of metformin alone, metformin–rosiglitazone, and metformin–lifestyle.](image)

Failure rates:
- Metformin alone, 51.7%
- Metformin–rosiglitazone, 38.6%
- Metformin–lifestyle, 46.6%

Pairwise tests:
- Metformin–lifestyle versus metformin–rosiglitazone, p=0.15
- Metformin alone versus metformin–rosiglitazone, p=0.006
- Metformin alone versus metformin–lifestyle, p=0.17

**Figure Legend:**
- Months since randomization
- Proportion free of glycaemic failure
- No. at risk

BG, blood glucose.

Distribution of basal-bolus insulin

- Insulin regimens should mimic physiological insulin as closely as possible while achieving optimal glycaemic control
- The doctor and Lucy agreed to use a basal-bolus insulin regimen

**Question**
How should the total daily insulin requirements be divided between night-time intermediate-acting basal insulin and pre-prandial ‘regular’ or rapid-acting insulin?

<table>
<thead>
<tr>
<th>Basal insulin</th>
<th>Pre-prandial insulin</th>
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<tbody>
<tr>
<td>10–30%</td>
<td>70–90%</td>
</tr>
<tr>
<td>30–50%</td>
<td>50–70%</td>
</tr>
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Distribution of basal-bolus insulin

How should the total daily insulin requirements be divided between night-time intermediate-acting basal insulin and pre-prandial ‘regular’ or rapid-acting insulin?

- Pre-prandial insulin should be divided into 3–4 pre-meal boluses
- When regular insulin is being used, the basal:pre-prandial split is typically 30%-70% of the total daily insulin requirements
- For rapid acting pre-meal boluses, the basal:pre-prandial split is typically 50%-50%
- This is because regular insulin also provides some basal effect
- The doctor and Lucy decide to use rapid-acting insulin for pre-meal boluses, as it may reduce postprandial hyperglycaemia and nocturnal hypoglycaemia.
- Rapid-acting insulin can also be taken immediately after food, increasing flexibility
Self-monitoring of blood glucose

• The doctor explains that insulin carries a risk of hypoglycaemia
• SMBG is an integral part of optimizing Lucy’s insulin regimen: early optimization of BG levels will allow rapid transition to oral therapy
• Lucy is advised to aim for the following BG levels:¹
  – Pre-meal 5–7.2 mmol/l (90–130 mg/dl)
  – Peak postprandial 10 mmol/l (<180 mg/dl)
• The doctor refers Lucy to a specialist diabetes nurse to learn about SMBG
  – The nurse will instruct her on how to adjust insulin in response to daily glucose measurements, and how to recognize and respond to hypoglycaemia

BG, blood glucose; SMBG, self-monitoring of blood glucose.

Lifestyle education

- Insulin is most effective when used in conjunction with an appropriate diet and exercise regimen designed to increase insulin sensitivity
  - For Lucy, this must be specifically tailored to facilitate appropriate weight loss
- In addition to advice about SMBG and the importance of adhering to diet and exercise interventions, the diabetes nurse discusses involvement of Lucy’s family in the management of her diabetes

**Question**
How should Lucy’s family be involved in her diabetes education?

- It is important that Lucy is able to self-manage her condition; family involvement in the education process should not be encouraged
- Lucy’s mother already has type 2 diabetes and understands the condition – her family need not be educated further
- Lucy’s immediate family should all be educated on diabetes management and prevention

SMBG, self-monitoring of blood glucose.
Lifestyle education

How should Lucy’s family be involved in her diabetes education?

Lucy’s immediate family should all be educated on diabetes management and prevention

• Involving the entire family ensures that the principles of treatment and the importance of lifestyle interventions are clearly understood, allowing appropriate levels of support and encouragement
  – Education of family and friends on the importance of lifestyle choices is essential
• Although Lucy’s mother has diabetes, therapy is always individualized; it is important that Lucy’s family understands her individual needs
• In a family with more than one child, parental and sibling education may help to prevent further development of type 2 diabetes

6-month follow-up

- Lucy has returned for her second follow-up appointment – since diagnosis several insulin adjustments have been made to control BG levels.
- Lucy explains that she is feeling well but finds it embarrassing having to inject every day at school and when out with friends.
- In addition, she has not managed to lose weight despite good adherence to diet and exercise, and she expresses a strong desire to switch to oral therapy.
- The doctor sees that Lucy’s SMBG diary has been meticulously completed and she has not experienced any problems with postprandial hyperglycaemia in the past 3 months.

**Question**

What is an appropriate next course of action for Lucy?

- The insulin is working well; Lucy should remain on insulin therapy.
- Gradually introduce metformin while down-titrating the insulin dose.
- Immediately stop insulin and begin metformin therapy.

FPG: 6.7 mmol/l (120 mg/dl)
HbA1c: 6.3% (45 mmol/mol)
BP: 127/76 mmHg
BMI: 31.0 kg/m²

BG, blood glucose; BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; HbA₁₀₀, glycosylated haemoglobin; SMBG, self-monitoring of blood glucose.
Gradually introduce metformin while down-titrating the insulin dose

- Both the risk–benefit ratio and the wishes of each individual should be considered when designing treatment regimens
- Lucy is metabolically stable and is maintaining BG levels below her glycaemic target – she has demonstrated a clear ability to manage her condition$^1$
  - Transitioning from insulin to metformin is therefore a possibility and something that Lucy wishes to pursue
- The insulin dosage should be tapered gradually (to avoid hypoglycaemia) while steadily introducing metformin (which can cause GI discomfort)

- Transition from insulin to metformin can be safely achieved by decreasing the insulin dose by 10–20% each time the metformin dose is increased:$^1$
  - Begin with 250 mg metformin once daily, for 3–4 days
  - Increase to 250 mg twice daily, if tolerated
  - Continue to titrate the dose in this manner over 3–4 weeks until the maximum dose of 1000 mg twice daily is reached
- Meticulous SMBG is integral throughout this process: if BG reaches the impaired range at any time, the taper should be slowed

BG, blood glucose; GI, gastrointestinal; SMBG, self-monitoring of blood glucose.
Long-term follow-up

- 3 years have elapsed since Lucy was first diagnosed with type 2 diabetes
- She manages her condition well using high-dose metformin plus a strict regimen of healthy (and appropriate) eating and a regular exercise routine
- As a consequence she is much happier and has lost 10 kg (22 lbs)
- The doctor continues to stress the importance of sticking to lifestyle interventions to prevent disease progression and the need for more intensive combination/insulin therapy in the future

<table>
<thead>
<tr>
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<th>Values</th>
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</tr>
<tr>
<td>HbA₁₀₀</td>
<td>6.1% (43 mmol/mol)</td>
</tr>
<tr>
<td>BP</td>
<td>122/74 mmHg</td>
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<tr>
<td>BMI</td>
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BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; HbA₁₀₀, glycosylated haemoglobin.
10 Steps to get more people with type 2 diabetes to goal:

• Aim for an appropriate individualized glycaemic target, e.g. HbA$_{1c}$ 6.5–7% (48–53 mmol/mol) (or fasting/preprandial plasma glucose 110–130 mg/dL [6.0–7.2 mmol/L] where assessment of HbA$_{1c}$ is not possible) when safe and appropriate.
• Monitor HbA$_{1c}$ every 3 months in addition to appropriate glucose self-monitoring.
• Appropriately manage all cardiovascular risk factors.
• Refer all newly diagnosed patients to a unit specializing in diabetes care where possible.
• Address the underlying pathophysiology of diabetes, including the treatment of β-cell dysfunction and insulin resistance.
• Treat to achieve appropriate target HbA$_{1c}$ within 6 months of diagnosis.
• After 3 months, if patients are not at the desired target HbA$_{1c}$, consider combination therapy.
• Consider initiating combination therapy or insulin for patients with HbA$_{1c}$ ≥9% (≥75 mmol/mol).
• Use combinations of antihyperglycaemic agents with complementary mechanisms of action.
• Implement a multidisciplinary team approach that encourages patient self-management, education and self-care, with shared responsibilities to achieve goals.

HbA$_{1c}$, glycosylated haemoglobin.

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