

## Diabetic monotherapy failure

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A 65-year-old overweight gentleman with a 15-year history of type 2 diabetes (T2DM) attended a government out-patient clinic for a routine follow-up visit. The patient was taking metformin 750 mg twice a day. He had been diagnosed with hypertension 10 years ago and was currently being treated with lisinopril 10 mg daily. He has no symptoms on questioning. His home blood glucose monitoring shows that his fasting glucose ranges from 7–9 mmol/L, while his post-prandial values are usually below 10 mmol/L.

On investigation, the patient's body mass index was found to be 24 kg/m<sup>2</sup>, and his blood pressure readings were within the normal range. Laboratory findings reported a fasting plasma glucose level of 12.2 mmol/L and HbA1c of 8.6%. His serum total cholesterol level was 4.9 mmol/L, LDL-C was measured at 2.6 mmol/L, triglycerides at 2.2 mmol/L and his HDL-C was 1.1 mmol/L. His serum creatinine levels, at 84 µmol/L, were within the normal range. Diabetic complication screening last year was unremarkable apart from findings similar to above.

These findings are indicative of monotherapy failure in an overweight, hypertensive patient with T2DM, a common scenario in a primary care setting.

The gentleman had recently retired, but would occasionally work as a security guard. This required him to work night shifts, during which his normal meal time schedule was disrupted. For this reason the patient requested a treatment regimen that did not require him to adhere to strict meal times.

The process of selecting an appropriate anti-diabetic treatment must be individualized for each patient. The primary consideration when choosing an anti-diabetic drug is its glucose lowering efficacy together with the safety/tolerability profile. In addition, based on the individual patient profile, factors such as the impact of therapy on body weight, hypertension or dyslipidaemia and the anticipated long-term impact of the treatment on glycaemic control should also be considered.

For patients inadequately controlled on metformin monotherapy, leading international guidelines from the American Diabetes Association and the Canadian Diabetes Association recommend additional therapy with insulin, sulphonylureas or thiazolidinediones (TZDs) [1,2]. Newer agents such as glinides and glucagon-like peptide-1 agonists are limited by inadequate data long-term benefits and risks as well as their role in combination with other diabetes medications. Therefore in common scenarios similar to the one above, such newer agents should be considered only at a later stage when the usual therapy fails to improve control. Alpha-glucosidase inhibitors can also be considered, although its glucose lowering effect is less and can lead to flatulence in around 70% of patients, which in turn may reduce drug compliance.

Insulin therapy is an effective and inexpensive treatment option. Nevertheless, many barriers have been identified which delays insulin initiation [3], including:

- Patient resistance and fear
- Needles and injections equating with pain
- Complications
- Weight gain
- Inconvenience
- Physician resistance
- More time consuming
- Inadequate support or resources
- Lack of updated information

Physicians should actively identify the presence of these barriers if a patient is considered to be in need of insulin therapy. In the above scenario, the patient's shift duty may impose difficulties in terms of injection timing. If, however, insulin is considered in addition to metformin usage, a long-acting or basal, rather than a short-acting pre-meal insulin, is typically regarded as a reasonable first choice. The former is effective in improving nocturnal and fasting glucose, while the latter will decrease post-prandial glycaemic surge. Some physicians may consider insulin monotherapy alone, which although may be related to an increased incidence of weight gain, is still associated with a reduction in microvascular complications [4].

Sulphonylureas enhance insulin secretion from the beta cells of the pancreas and thereby lower blood glucose levels by 20%. They are particularly effective in patients whose weight is normal or increased. The major caveat of sulphonylurea therapy is an increased risk of hypoglycaemia, which is more likely to occur in the following scenarios:

- Excessive dose
- Use of old long-acting drugs
- After exercise or a missed meal
- Undernourished patients
- Patients with alcohol abuse
- Patients with impaired renal or cardiac function or gastrointestinal disease
- Concomitant therapy with salicylates, sulfonamides, fibrates or warfarin

Taking the above into consideration, our security guard patient may experience frequent hypoglycaemias as a result of his shift work, subsequent irregular meal times and/or drug intake. Another alternative option would therefore be glitazones, which improve glycaemic control by increasing insulin sensitivity at the level of the liver and muscle fats. The glycaemic durability of rosiglitazone has been proven

to be superior to metformin and sulphonylureas by long-term randomized controlled trials up to 6 years. Caution should be exercised prior to glitazone initiation, as they are associated with fluid retention, heart failure and loss of bone mineral density. Further studies are underway to clarify the relationship between glitazone usage and cardiovascular disease.

In this scenario, glitazone plus metformin may prove to be of use. In particular, fixed combination pills comprising these two medications are available, which will definitely help to improve patient drug compliance. Financial cost is always an issue with glitazone usage, and therefore some guidelines often recommend other alternatives.

Although diabetes is considered to be a cardiovascular disease equivalent, there is still inconclusive evidence regarding the need for aspirin in diabetic patients [5]. Trials are still underway to elucidate the role of aspirin.

After considering all the options, the patient decided to try the fixed combination pill containing a glitazone and metformin. Besides pharmacotherapy, the patient was advised to make lifestyle changes. Dietary recommendations and a regular exercise regime were advised to help the patient attain a healthy body weight. These interventions have been demonstrated to improve glycaemic control in patients with established T2DM.

The patient was also enrolled in a patient empowerment programme, which aims to empower patients with chronic ailments such as T2DM, by educating them about their disease and how its management can be improved. Patients

are thus motivated to change their lifestyle and remain compliant to their treatment schedule, leading to an overall improvement in the management of their disease.

At the next follow-up visit, the patient's glycaemic profile was within normal limits and his HbA1C was <7%. The patient was satisfied with the outcome of therapy and did not report any side effects.

This patient will need continual monitoring for the side effects of glitazone therapy, such as fluid retention and any resultant heart problems. He will also need to undergo annual screening for diabetes complications. Over time, as his disease progresses, the patient may require further adjustment of the current treatment.

## References

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4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–53.
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## QUESTIONS

Please indicate whether the following statements are true or false

1. The primary consideration when choosing an anti-diabetic drug is the impact of therapy on body weight, hypertension or dyslipidaemia.
2. Insulin therapy is an effective and inexpensive treatment option, and barriers to its initiation are often not encountered.
3. The major caveat of sulphonylurea therapy is an increased risk of diabetes complications (as seen in the diabetes complications screen) and weight gain.
4. Combination therapy provides greater convenience and improves patient compliance.

## ANSWER FORM

1

3

2

4

Name: \_\_\_\_\_

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