Diabetes has developed while the patient was taking a statin: a concerned patient

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Although there is a risk of developing diabetes while taking statins, the net benefit for patients at high cardiovascular risk still strongly favours statin therapy.

In the June 2012 issue of *Cardiology Today* I described the case of a 68-year-old man, a heart attack survivor, who stopped his statin therapy after reading about its potential side effects in a newspaper article.[1] His simple take on the story was that ongoing statin therapy might lead to him developing dementia or diabetes.

I was able to reassure the patient through his GP that the risk of cognitive impairment was low and any problem was essentially reversible upon drug cessation. With regard to his risk of developing statin-induced diabetes, the absolute increase in risk is small, about 0.5 percentage points over two to four years of treatment.[2]

On the grounds that this man was at high risk of a recurrent cardiovascular (CV) event and the benefit of statin therapy was well proven,[2] he agreed to resume his statin therapy and to receive regular monitoring of his plasma glucose levels. However, this matter does not have a simple conclusion, as typified in another patient referred to this consultant about three weeks after the patient in the above previous scenario.

Case scenario

Mr JF is a 63-year-old man with no prior cardiac history. He was diagnosed with a 'cholesterol problem' eight to 10 years ago; he recalled his cholesterol value was about 8 mmol/L. He began a fat-restricted diet, but was eventually started on atorvastatin, reaching a dosage of 20 mg/day. This treatment became associated with generalised myalgia and was terminated about three years ago. At that point he was not well controlled, with the following test results:

- *cholesterol 6.6 mmol/L*
- *triglycerides 1.7 mmol/L (desirable <1.5 mmol/L)*
- *HDL-cholesterol 1.5 mmol/L (desirable >1.0 mmol/L)*
- *LDL-cholesterol 4.3 mmol/L (desirable <2.5 mmol/L*
- *fasting plasma glucose 5.7 mmol/L (desirable <5.5 mmol/L).*

About 18 months ago Mr JF was started on rosuvastatin 10 mg/day, increasing to 20 mg/day because of poor cholesterol control. Two months before his referral to this consultant, his test results were as follows:

- *cholesterol 5.7 mmol/L*
- *LDL-cholesterol 3.2 mmol/L*
- *fasting plasma glucose 8.3 mmol/L.*

On this basis, his GP diagnosed him with type 2 diabetes but noted acceptable glycosylated haemoglobin (HbA_{1c}) levels of 6.6% (acceptable level <7.0%). Intake of rosuvastatin by this patient had been well below the prescribed amount and the GP convinced Mr JF to use the medication on a daily basis. A few weeks later, Mr JF read a newspaper article reporting a link between statin use and diabetes. Although

Key points

- **The risk of developing diabetes is associated with increasing age, excess body weight and genetic factors.**
- **Statin therapy may increase the risk of developing diabetes, either through exacerbation of background factors or through less well-defined mechanisms; however, the absolute risk of this event is low.**
- **Patients taking statins require monitoring of their plasma glucose levels.**
- **The case for statin therapy remains strong, but is dependent on a favourable balance of benefit to risk. Such therapy should be restricted to those at increased cardiovascular risk.**

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he did not stop his statin therapy, Mr JF was somewhat alarmed that his doctor's advice might have induced his diabetes and this generated the current referral.

Mr JF is a clerk who gets little exercise. He is a nonsmoker and nondrinker, with a supposedly stable body weight and no disclosed family history of diabetes or premature CV disease. The only medication he is taking at this time is rosuvastatin 20 mg/day. On examination, he weighs 85 kg and a waist circumference of 105 cm and a body mass index (BMI) of 28.4 kg/m^2. His blood pressure is 128/84 mmHg. He has a prominent corneal arcus but no xanthomatous lesions. His other CV and abdominal signs are unremarkable, but abdominal obesity is present. Dipstick urinalysis is within normal limits.

A panel of fasting blood tests is ordered, with the following results:

- *cholesterol 4.1 mmol/L*
- *triglycerides 1.3 mmol/L*
- *HDL-cholesterol 1.4 mmol/L*
- *LDL-cholesterol 2.1 mmol/L*
- *fasting plasma glucose 7.3 mmol/L*
- *HbA_{1c} 6.7%*
- *electrolytes, liver and muscle enzymes, and thyroid function test were all within normal limits.*

Consultant comments

It appears that Mr JF has gradually developed type 2 diabetes, although his current glycaemic control is acceptable. He has not undergone a formal glucose tolerance test, but two fasting plasma glucose readings of more than 7.0 mmol/L can be taken as evidence of diabetes.

He probably developed diabetes for the usual reasons, including increasing age, being overweight and possibly having a genetic predisposition. On the other hand, it is possible that his years of statin therapy have also contributed to the onset of diabetes. The mechanism of this effect is not known with any certainty, nor do we know if the effect is reversible upon statin cessation.[2]

His LDL-cholesterol level has come under good control in the face of good compliance with medication intake. However, this alone does not justify continuation of the treatment.

Whatever the cause of Mr JF's diabetes, careful consideration is needed of whether the benefits of ongoing statin therapy outweigh the risks, if any, attached to his new diabetes status.[2] Also, this decision must be made without being certain that the statin caused his diabetes or whether statin-induced diabetes has the same bad outlook as in diabetes due to other causes.

Case scenario continued

The above issues were carefully explained to Mr JF, who then recalled that his mother, who died at age 82 years with dementia, might have had diabetes in her later years. He was given standard advice about diabetes management, including a program of weight reduction and increased physical activity.

Mr JF queried whether there was a genuine need for ongoing statin therapy. This question was addressed by calculating his absolute risk of CV disease in the next five years using the conventional risk factors, recognising that a risk of more than 15% is a strong indication for statin therapy. Assuming an untreated cholesterol level of 8.0 mmol/L and the presence of diabetes, his risk was very high at 17%. In the absence of diabetes, this risk would have been 11% and may have been as low as 6% if he had maintained the lipid profile previously noted with statin therapy. Despite this strong indication for continuation of statin therapy, Mr JF requested that it be suspended for a period of eight weeks to see what might be achieved through lifestyle modification. This was mutually agreed.

Consultant comments

There is a move to evaluate CV disease risk through noninvasive coronary imaging, either a calcium score or CT-coronary angiogram. This is not yet an established guideline in Mr JF's clinical situation. There is controversy as to whether mild diabetes of short duration in this setting has the same adverse prognostic significance as long-standing diabetes. To counter-balance these matters, it is standard policy that most patients with diabetes should receive statin therapy and this leads to proven CV benefit.

Ultimately it is the patient's choice what advice to accept. In this situation of conflicting information and uncertainty, it seemed reasonable to suspend statin therapy in the short term.

Case scenario continued

Eight weeks later Mr JF was noted to have lost 5 kg, he felt well and a panel of fasting blood tests was ordered with the following findings:

- *cholesterol 7.7 mmol/L*
- *triglycerides 1.7 mmol/L*
- *HDL-cholesterol 1.3 mmol/L*
- *LDL-cholesterol 5.6 mmol/L*
- *fasting plasma glucose 5.3 mmol/L*
- *HbA_{1c} 6.5%*
- *electrolytes and liver and muscle enzymes were within normal limits.*

Statin therapy was again recommended to Mr JF, given the previous risk calculations. Due to his past history of myalgia with atorvastatin and his emotional concerns about rosuvastatin, he was prescribed simvastatin 20 mg/day and asked to return for further clinical review and blood tests eight weeks later. No further follow-up information is currently available but he will need close supervision for adverse events, both clinical and biochemical.

Implications

If Mr JF had originally shown a considerably lower LDL-cholesterol level, he might never have needed statin therapy, relying instead on diet and lifestyle advice. Given the subsequent development of diabetes, irrespective of the precise causation, he was given the necessary diabetes management. Sustained weight reduction has improved his glycaemic control but has made little impact on his LDL-cholesterol levels, which is not an uncommon situation.

The net benefit for patients at high CV risk strongly favours statin therapy. However, glucose levels need to be monitored in such patients.[2] **CT**

References

1. Simons LA. Never let the facts spoil a good story: a challenging case history. Cardiology Today 2012; 2(2): 16-17.
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