# Preventing all the complications of hyperglycaemia: not a straightforward task

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Individualised multifactorial treatment strategies are required to optimise outcomes

Epidemiological studies have found positive relationships between measures of glycaemia and adverse fetal and maternal pregnancy outcomes,[1] macrovascular disease[2,3] and the microvascular complications of diabetes.[2,3] The relationship between glycaemia and microvascular disease is more complicated, as there is an inflection point below which the risk is very low, but beyond which it rises sharply. The inflection point of the relationship between glycaemia values and the prevalence of retinopathy has been used to determine both the glucose tolerance test values and the glycated haemoglobin ($HbA_{1c}$) level used to diagnose diabetes (see Figure 1 in reference 3).

Epidemiological studies have also found that the prevalence of hyperglycaemia associated with pregnancy,[4,5] macrovascular disease[6] and microvascular complications[7,8] is modified — usually increased — by other known risk factors. For pregnancy, the independent adverse effects of obesity and maternal weight gain are well documented,[4,5] so that the conclusion reached by Abell and colleagues[9] in this issue of the *MJA* is not surprising: "Poor glycaemic control is not wholly responsible for adverse outcomes, reinforcing the importance of other risk factors, such as obesity and weight gain."

Although the association between hyperglycaemia and the adverse effects of diabetes is clear, an association does not establish cause and effect. However, randomised controlled clinical trials have shown the benefits of better glycaemic control in pregnancy for reducing the incidence of fetal adiposity and macrosomia, of maternal pre-eclampsia, and of microvascular complications in both type 1 and type 2 diabetes. An unexpected finding from long term follow-up studies was that improved glycaemic control early in the course of diabetes had a very long lasting benefit with regard to microvascular and macrovascular complications in both type 1 and type 2 diabetes, even though improved control had been lost at the end of the intervention period.[10-12] This long lasting effect has been labelled the "legacy effect", or "metabolic memory".

With regard to macrovascular disease, the situation is more complex, particularly in type 2 diabetes. Long term follow-up of the United Kingdom Prospective Diabetes Study[7] and of the Diabetes Control and Complications Trial for type 1 diabetes[11] found that better early glycaemic control in newly diagnosed patients reduced the long term risk of cardiac infarction or of dying from any cause. On the other hand, more intensive treatment of pre-existing type 2 diabetes in high risk patients in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was not associated with any reduction in macrovascular disease incidence or mortality in either the long or short term.[12] However, a small single-centre study in a different health system showed that a multifactorial intervention in a population at risk of cardiovascular disease, including better glycaemic control (but less than that achieved in the ACCORD trial), resulted in a significant decrease in mortality.[12]

To add to the complexity, the initial effect of better glycaemic control is to increase the risk of retinopathy. Although this risk declines with time,[11] the initial deterioration can threaten vision and may require therapy.

From the above, it can be seen that the benefits of better glycaemic control are not simple, nor are the effects always positive or immediate in onset. Classical cardiovascular risk factors influence the risk of both macrovascular and microvascular complications in patients with diabetes.[6,7] Multifactorial interventions that treat the classical macrovascular risk factors of hypertension, hypercholesterolaemia and smoking have been shown to reduce the incidence of both microvascular and macrovascular complications.[13]

Do these factors influence our treatment of diabetes? What degree of glycaemic control should be targeted? The Australian Diabetes Society recommends that targets for glycaemic control be individualised.[14] Factors that will influence the target include the risks to the patient associated with the degree of hyperglycaemia and the potential benefits of tighter glycaemic control, as well as the risks associated with tighter control. In particular, patients with reduced life expectancy (particularly older patients) and those with a high risk of cardiovascular disease probably require less tight glycaemic control. Treatment should, of course, be holistic, including attention to any other relevant risk factors.

The legacy effect[6,7,10] should strongly influence the therapeutic targets, particularly in younger, recently diagnosed patients, who can often achieve excellent glycaemic control with little risk of hypoglycaemia. It is crucial that the treatment targets and rationale should be discussed with the patient.

**Competing interests:** No relevant disclosures.

**Provenance:** Commissioned; not externally peer reviewed. ■

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