Best practice

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Case study 1

How would you treat a prediabetic patient?

This report is a summary of a webinar presentation by Dr Lombard, 22 September 2020.

Introduction

Diabetes is a global healthcare problem. Type 2 diabetes mellitus (T2DM) may well be one of the next pandemics that we experience after the current COVID-19 pandemic. The related cardiovascular and microvascular complications will present significant challenges. The current global population of 460 million diabetics will be more than 700 million by 2045.[1]

In Africa, where healthcare resources are extremely scarce, undiagnosed diabetes can exist for many years without treatment and patients frequently present for the first time with severe complications. A recent survey showed that 20% of adults in South Africa are either diabetic or prediabetic, with more than 50% being undiagnosed, and that 75% of diabetic deaths occur before the age of 60 years.[2]

Diabetes is the most common cause of preventable blindness and cataracts. Stroke is another common complication of diabetes, as are myocardial infarctions; more than half of people with diabetes will die from cardiovascular complications. Globally, diabetes is the commonest cause of kidney failure in patients on dialysis. Also, diabetes is a common cause of lower-leg non-traumatic amputation. Many of these complications are preventable, especially with earlier management and tighter glucose control.

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T2DM is a progressive disease

The effective treatment of diabetes is made difficult by the progressive nature of the disease (Figure 1).[3] As soon as current glucose targets are met, progressive loss of beta cells eventually results in sub-optimal glucose control.

Insulin resistance is one of the key factors that needs to be managed in type 2 diabetes.

Insulin resistance is addressed first by lifestyle changes, especially weight loss. Metformin is an important contributor to reducing insulin resistance, as is pioglitazone. Most other oral agents work on improving insulin release and reducing or improving beta cell function, which only provides temporary improvement.

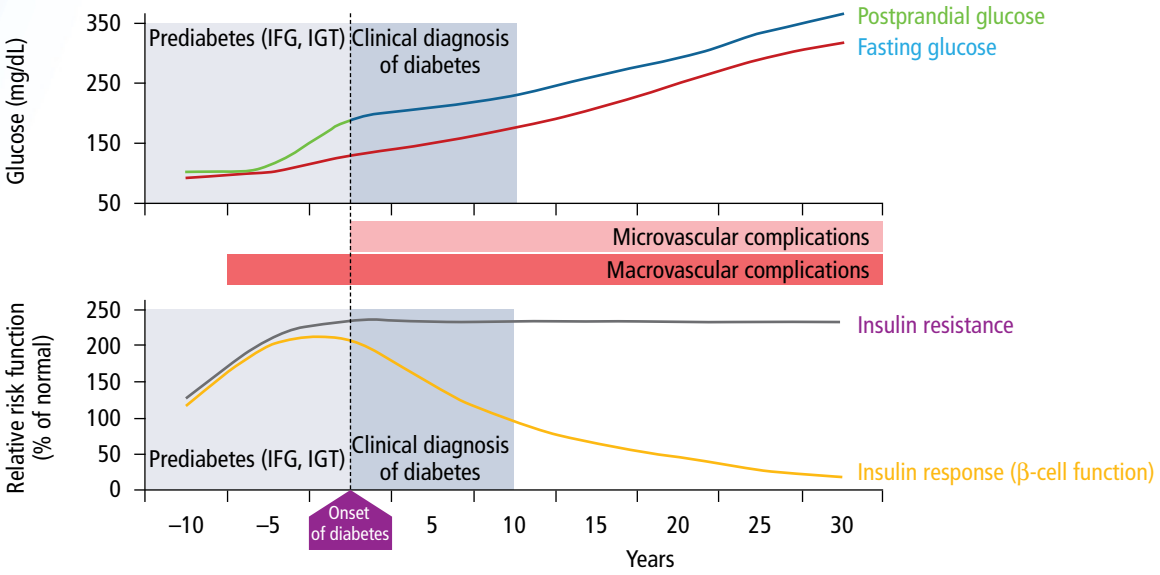


Figure 1. T2DM is a progressive disease[3]

Coronary events and mortality in the prediabetic patient

The EPIC-Norfolk study of an entire town over many decades has shown that even when HbA_{1c} is in the prediabetic range, there are increases in all-cause mortality (80%), cardiovascular disease (80%) and coronary heart disease (113%). It is only when the HbA_{1c} is < 5.0% that this increased risk is not evident (Figure 2).[4] The study pre-specified an HbA_{1c} < 5% as an equivalent relative risk of 1, comparing other HbA_{1c} levels against this baseline. It is quite impressive how greatly cardiovascular risk increases long before the parameters of being diagnosed as diabetic are reached.

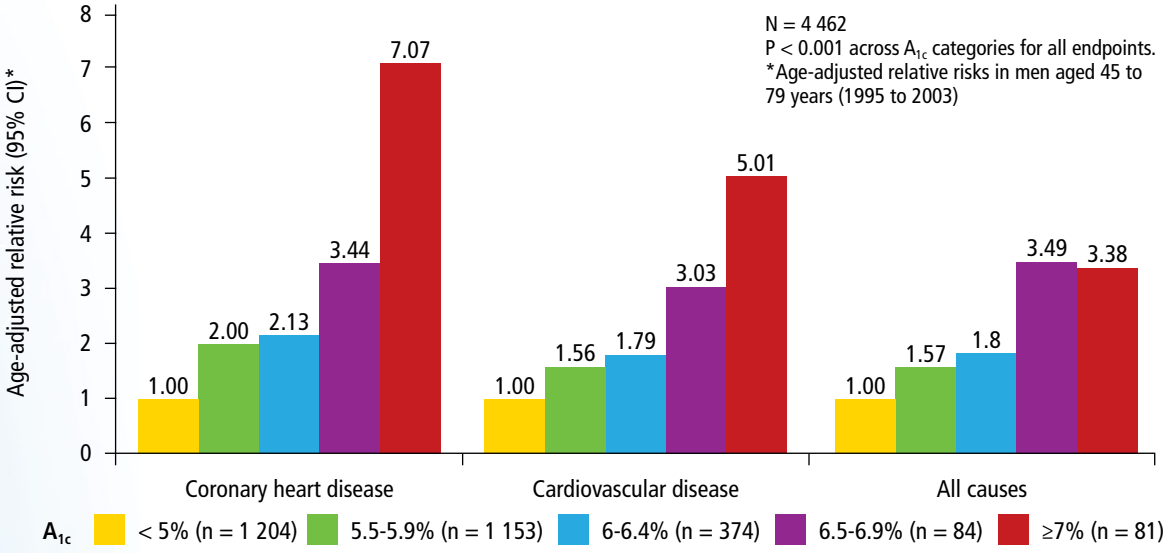


Figure 2. EPIC-Norfolk study - HbA_{1c}, coronary events and mortality[4]

Impact of glycaemic control on cardiovascular risk

In the extended United Kingdom Prospective Diabetes Study (UKPDS), there was a clear increase in macrovascular disease as HbA_{1c} increased, and this occurred in both the non-diabetic patient and the well-controlled diabetic patient. It is important to remember that the initial UKPDS was of newly diagnosed diabetics; in those patients who were well controlled, the microvascular complication risk was still markedly increased, even with HbA_{1c} levels as low as 5.5%.

What are the diagnostic criteria for prediabetes?

When screening patients for diabetes during routine check-ups, fasting glucose tests, sometimes oral glucose tolerance tests (OGTTs) and frequently HbA_{1c} tests are undertaken. We often find abnormalities during this screening and need to be confident in knowing what to do with these results. The American Diabetic Association (ADA) has published good guidelines on prediabetes care.

Table 1 describes how various guidelines define the criteria for prediabetes.[5] The World Health Organization has not yet committed to a diagnostic HbA_{1c} level for prediabetes. In South Africa, we are also less committed to using HbA_{1c} for this purpose, but I think we can use the ADA guidelines. The National Institute for Health and Care Excellence guidelines use somewhat higher HbA_{1c} levels for the diagnosis of prediabetes. The use of a two-hour OGTT shows more consistent interpretation (7.8-11.0 mmol/l across all guidelines). The problem with following the ADA guidance is that you will include many patients if you use the criterion of HbA_{1c} ≥ 5.7%.

It is important to remember that the initial UKPDS was of newly diagnosed diabetics; in those patients who were well controlled, the microvascular complication risk was still markedly increased, even with HbA_{1c} levels as low as 5.5%

Table 1. Prediabetes diagnostic criteria according to health authorities

Diagnostic criterion	WHO	ADA	NICE
HbA_{1c}	Not recommended for diagnosis	39-47 mmol/mol (5.7-6.4%)	42-47 mmol/mol (6.0-6.4%)
2-hour OGTT	7.8-11.0 mmol/l	7.8-11.0 mmol/l	7.8-11.0 mmol/l
Fasting plasma glucose	6.1-6.9 mmol/l	5.6-6.9 mmol/l	6.1-6.9 mmol/l

ADA: American Diabetes Association; NICE: National Institute for Health and Care Excellence; OGTT: oral glucose tolerance test; WHO: World Health Organization

Case 1 – Mrs BA, routine check-up

- 48-years-old
- Overweight, BMI: 34 kg/m^2, waist circumference: 90 cm
- No significant findings except central obesity
- Biochemistry: Normal U&E, FBC and TSH
- HDL: 0.9 mmo/l, LDL: 3.4 mmol/l
- HbA_{1c}: 6.2%, fasting glucose: 5.8 mmol/l

Dr Lombard's clinical approach

The patient appears to be in reasonable health overall, although with an HbA_{1c} of 6.2%, she would fall into the prediabetic category, with a markedly increased risk of developing T2DM in the near future due to her current fasting glucose level of 5.8 mmol/l. The clinical question is: what would you do in this case?

General practitioners see this type of patient on a nearly daily basis and are faced with the dilemma of making a decision. One could say that all prediabetic patients should go on an intensive lifestyle modification programme, and that may well be very true. However, if not guided by a biokineticist and a good dietitian, very few positive lifestyle changes occur as it is difficult to motivate people to 'do lifestyle' well. So, the question comes to mind: do you have medication that could be added?

What is the evidence of benefit from lifestyle and metformin treatment in the prediabetic patient?

The Diabetes Prevention Program (DPP)[6] was a multicentre study of 3 200 people who were non-diabetic, with fasting plasma glucose in the range of what we would define as prediabetic. They also had OGTT values in the prediabetic range, were older than 25 years of age and were overweight (BMI > 25 kg/m^2). These participants were randomised to either placebo, metformin (850 mg bd) or an intensive lifestyle programme. The lifestyle modification programme was truly intensive with the exercise component being supervised by a biokineticist; in addition, some of the diabetic meals were delivered (Figure 3).[6] These patients were followed up for three years.

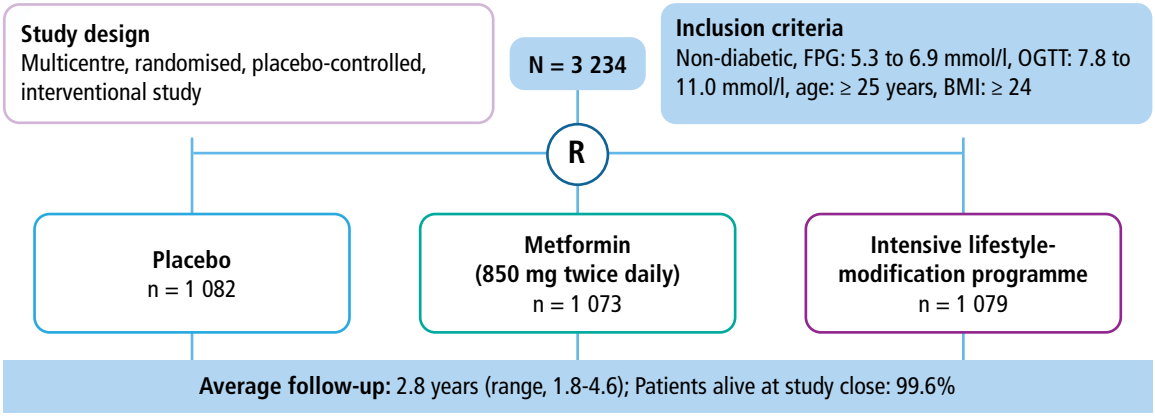


Figure 3. DPP study design[6]

There are certain genetic aspects that play a role, but a critical factor is how long the patient has had diabetes. With lifestyle intervention, you can delay the development to diabetes and potentially reduce complications

Significant reductions in progression to T2DM

In the DPP study, there was a significant reduction in the development of T2DM in those patients who received metformin and lifestyle interventions - 31% and 58%, respectively (Figure 4).[6] Improvement was still observed in an extension study, the Diabetes Prevention Program Outcomes Study (DPPOS), during a further seven years of remote follow-up. The benefit was impressive. Diabetes is life-threatening and poor glucose control may reduce a patient's number of retirement years. There are certain genetic aspects that may play a role, but critical factors include duration of diabetes and the level of glucose control achieved. With lifestyle intervention, you can delay the development to T2DM and potentially reduce complications.

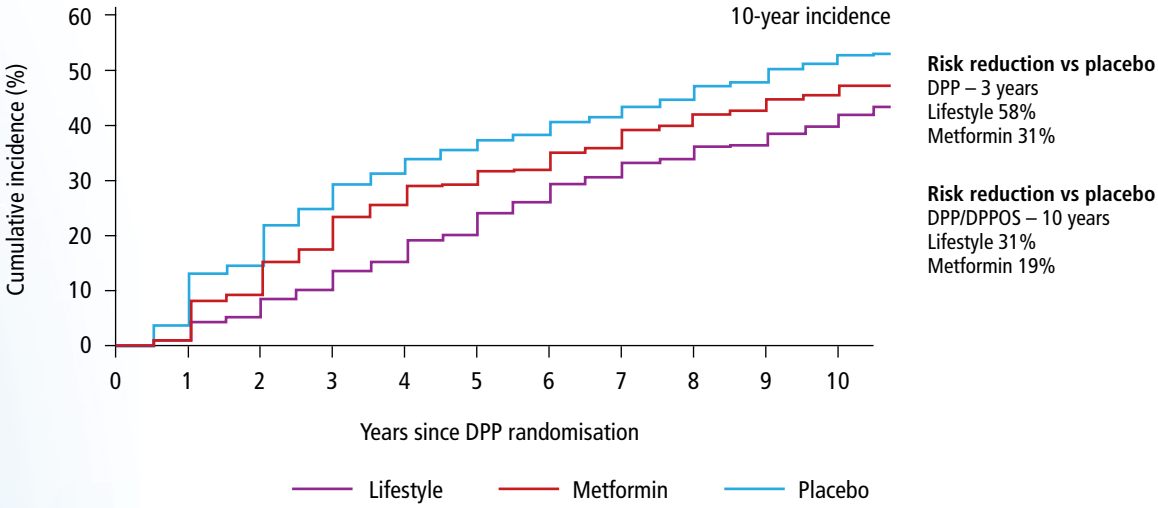
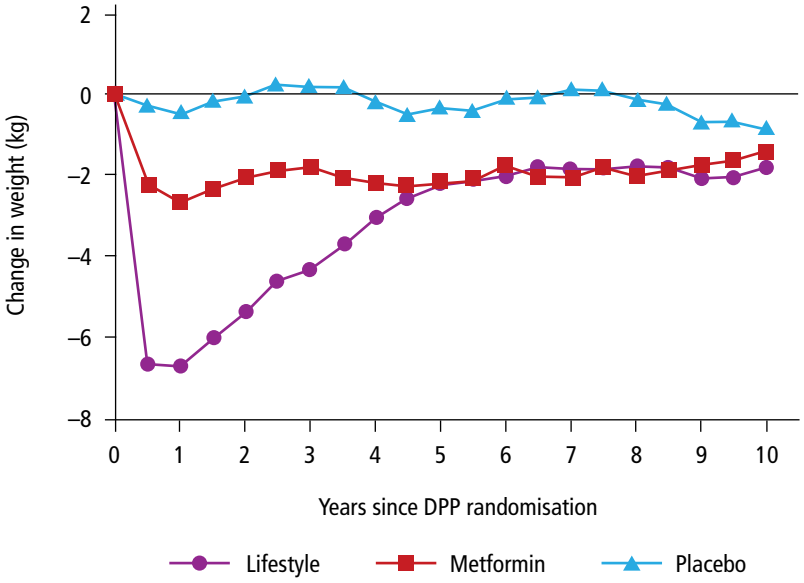


Figure 4. DPP and DPPOS: 10-year incidence of T2DM with placebo, intensive lifestyle intervention or metformin[6]

Significant weight loss

The intensive lifestyle intervention group lost an average of 5.6 kg, while the metformin-treated group lost 2.1 kg, which they actually maintained over time (Figure 5).[6] However, for those participants in the lifestyle intervention arm, when they discontinued the lifestyle modification, after about four years they had regained most of the weight to the same level as those who were treated with metformin. This is what clinicians see in daily practice; people lose weight, but they regain it quite quickly.



Placebo
Average weight loss over 4 years = 0.1 kg

Metformin
Average weight loss over 4 years = 2.1 kg (maintained in DPPOS)

Lifestyle
Average weight loss over 4 years = 5.6 kg (not maintained in DPPOS)

Figure 5. Lifestyle interventions: Insights from DPP and DPPOS[6]

If HbA_{1c} > 6.0%, these prediabetic patients should go on metformin

Prediabetes treatment in this case study

Intensive lifestyle therapy should be introduced and emphasised, preferably with the guidance of a biokineticist and a dietitian to assist with reducing carbohydrate and kilojoule intake. The patient must lose weight; a weight loss > 5 kg is needed to make a difference, but > 10 kg is preferred. The ADA suggests that the patient should lose > 7% of their baseline weight. Regular cardiovascular exercise for at least 150 minutes a week, divided into at least four exercise time slots, is recommended.

Who should get metformin? The ADA recommends metformin use in those patients with a very strong family history of T2DM, obesity (BMI ≥ 35 kg/m^2), those < 60 years old, and those with impaired fasting glucose and impaired glucose tolerance. If fasting glucose and glucose tolerance are both impaired, the risk of developing diabetes is much higher. If HbA_{1c} is > 6.0%, these prediabetic patients should be put onto metformin; similarly, the prediabetic patient with dyslipidaemia and hypertension should also be treated with metformin (Table 2).

Table 2. Prediabetes treatment

- Lifestyle change
- Reduce carbohydrates and kilojoules: weight loss > 5 kg, > 7% of baseline weight
- Regular cardiovascular exercise: 150 min/week
- Metformin for high-risk patients:
  - Strong family history
  - Obesity: BMI > 35 kg/m^2
  - <60 years old
  - IFG and IGT
  - HbA_{1c} > 6%
  - Dyslipidaemia, hypertension
  - Previous gestational diabetes
- Screen yearly for diabetes.

Key learnings

- Metformin is the benchmark affordable antidiabetic product
- Metformin is recommended by all diabetes guidelines
- Metformin is stopped in the case of contraindications or dose adjusted to manage side effects.

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I received an honorarium for this talk and I serve on several advisory boards, including in the past for Merck.

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