Diabetes in remission

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Bernard: 'I have lost 30 kg (66 lbs) and I look and feel so much better… Today I am cured of diabetes.'[1] 'Millions of people suffering from Type 2 diabetes could be cured of the disease if they just lost weight, a new study suggests.'[2]

If we are ill we want to be cured. We want our illness to vanish completely and never return. Is this possible with diabetes? Patients and the media seem to think so. I am not so sure.

What is diabetes?

See Box 1. Diabetes is diagnosed on laboratory confirmation of hyperglycaemia. Glucose is a continuum. It is challenging to decide which diagnostic test for glycaemia to use. Normoglycaemia alone does not define freedom from diabetes – otherwise anyone who achieves this on medication could say they were 'cured'. Normoglycaemia off all glucose-lowering medication for some time could be said no longer to fulfil the diagnostic criteria. But hyperglycaemia is only one component of diabetes. There are more distressing and damaging problems.

The microvascular complications of diabetes – retinopathy, neuropathy and nephropathy – are thought to be virtually specific to diabetes. People with diabetes are at risk of damage to every major body system. A person with diabetes with prolonged normoglycaemia off all hypoglycaemic medication may still have the damage inflicted by past hyperglycaemia. New microvascular disease, for example retinopathy, can appear months or years later.

WHO 2006: 'Diabetes is a condition primarily defined by the level of hyperglycaemia giving rise to risk of microvascular damage (retinopathy, nephropathy and neuropathy).'[18]

WHO 2011: 'The term diabetes mellitus describes a metabolic disorder with heterogenous aetiologies which is characterized by chronic hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The long-term relatively specific effects of diabetes include development of retinopathy, nephropathy and neuropathy. People with diabetes are also at increased risk of cardiac, peripheral arterial and cerebrovascular disease.'[19]

American Diabetes Association 2017: 'Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control.'[20]

Box 1. Definitions of diabetes

- Partial remission
  - Hyperglycaemia below diagnostic thresholds for diabetes
  - At least 1 year's duration
  - No active pharmacologic therapy or ongoing procedures
- Complete remission
  - Normal glycaemic measures
  - At least 1 year's duration
  - No active pharmacologic therapy or ongoing procedures
- Prolonged remission
  - Complete remission of at least 5 years' duration

Box 2. Diabetes in remission: 2009 American consensus statement[3]

Definition of remission in diabetes

There is no recent definition. A US consensus group suggested the definition in Box 2. They state: 'The distinction between successful treatment and cure is blurred in the case of diabetes.'[3]

The old Read code for 'diabetes resolved' was replaced by 'diabetes in remission' to ensure that patients remain on the GP's list of patients with diabetes so continue to be monitored and managed for diabetic tissue damage.

Type 1 diabetes

Honeymoon phase

'I'm in the honeymoon phase and not using any insulin at the moment. I know it won't last, but I'm enjoying being injection free for a while.'[4]

This brief remission due to temporarily improved insulin release may last weeks or months, rarely longer. Warn patients it may happen but that it won't last. Measurable C-peptide may persist for years but people with type 1 diabetes still need insulin treatment to control hyperglycaemia.

Transplant

Among 84 UK islet-cell transplant recipients with known insulin dose at one year, 14% achieved insulin independence at some point during that year. There were 2219 whole pancreas transplants in the UK over the past 10 years. When transplanted with a kidney, the five-year pancreas graft survival was 47–83% and patient survival 81–90%. Transplant patients require immunosuppressive medication.[5]

Type 2 diabetes

Spontaneous remission

An American study followed 122 781 adults with diabetes who had not had bariatric surgery. In patients off ongoing hypoglycaemic medication, remission was defined as: '1) partial: at least 1 year of subdiabetic hyperglycemia (HbA_{1c} level 5.7–6.4% [39–46mmol/mol]); 2) complete: at least 1 year of normoglycemia (HbA_{1c} level <5.7% [<39mmol/mol]); and 3) prolonged: complete remission for at least 5 years.' Seven-year cumulative incidence of any remission was 1.6% (1.53–1.68%). Incidence of partial, complete, or prolonged remission was 2.8/1000 person years (2.6–2.9), 0.24 (0.20–0.28), and 0.04 (0.01–0.06), respectively. Remission was defined by absence of hyperglycaemia but at baseline 16.5% of patients had retinopathy and 19.4% neuropathy. Complications were not described subsequently.[6]

Weight loss

Diet and lifestyle interventions

A 600kcal diet in 11 patients with type 2 diabetes normalised beta-cell function and liver insulin sensitivity within one week. By eight weeks their first-phase insulin response was the same as that of non-diabetic controls.[7]

In the Look AHEAD study, 3.5% (95% CI 2.7–4.3%) of patients who received intensive lifestyle weight-loss intervention had continuous, sustained remission for at least four years.[8]

Bariatric surgery

Multiple studies have shown diabetes remission (long-term normoglycaemia off hypoglycaemics) following various bariatric procedures so it is now supported by NICE for specific patients with type 2 diabetes.[9]

The UK Bariatric Surgery Register recorded 4121 people with type 2 diabetes who received primary bariatric procedures in 2011–13. Clinical reports (without glycaemic details) at three years showed diabetes remission in 80%. 'Reported remission was strongly related to weight loss at every time point.'[10]

Retinal screening results in 318 bariatric surgical patients with type 2 diabetes were reviewed. At their first post-operative retinal check 16% showed progression in retinopathy grade, 11% regression and 73% no change.[11] A meta-analysis of people with type 2 diabetes after bariatric surgery found that 7.5±7.4% of patients without pre-operative retinopathy developed this afterwards; among those with pre-operative retinopathy 23.5±18.7% progressed, and 19.2±12.9% improved.[12] (See Box 3.)

A small study showed that eight of 12 bariatric surgical patients with documented diabetic neuropathy lost neuropathic symptoms post-operatively.[13]

Among 52 bariatric surgical patients with type 2 diabetes, 37.6% had micro- or macroalbuminuria pre-operatively. After five years, the albuminuria resolved in 58.3%. However, 25% of those without pre-operative albuminuria developed this by five years. Patients whose diabetes had 'improved or remitted' had less albuminuria than those who were still hyperglycaemic.[14]

Increased activity in slimmer people may worsen pre-existing diabetic foot disease.[15]

Steroid-induced diabetes

Steroid therapy is common and may induce hyperglycaemia in people without known diabetes. This may be because the patient had undiagnosed diabetes or impaired glucose tolerance. However, many patients will become normoglycaemic again after steroids are stopped. Guidance on managing this situation is available.[16]

Ketosis-prone diabetes (Flatbush diabetes)

This uncommon variant of type 2 diabetes is usually seen in overweight people of African ancestry with a strong family history of diabetes. They may develop ketoacidosis and need insulin but subsequently the glucose falls. It may be possible to stop glucose-lowering treatment. The normoglycaemia may persist for months or longer, although the glucose can rise again, sometimes worryingly fast.[17]

'Some people with diabetes have fallen through the net in recent years due to issues with the way patients are coded on GP practice IT systems.

'Current evidence shows that all people with diabetes should be screened for diabetic retinopathy for life once there has been a definite diagnosis of diabetes, excluding gestational diabetes. New GP Read codes were introduced in 2014 to take this guidance into account.

'Before 2014, many GPs used the code "Diabetes resolved" for patients whose blood sugar levels normalised following treatment, such as pancreatic transplant, or intensive weight reduction. These patients were then removed from the register of people requiring annual retinal screening – even though their risk of developing diabetic retinopathy may have increased following a rapid improvement in diabetes control.

'Such patients should now be classified as "Diabetes in remission". This ensures they are still invited for screening.'[21]

Box 3. Keep people with diabetes in remission on the retinal screening list

Summary

Use the term 'diabetes in remission'; do not tell patients their diabetes is cured or resolved. But what is diabetes in remission?

Significant weight loss can produce prolonged normoglycaemia off glucose-lowering medication in people with type 2 diabetes. Pancreatic or islet-cell transplant may achieve this in type 1 diabetes. Such patients no longer fulfil diagnostic criteria for diabetes so could be described as having diabetes in remission if one ignores diabetic tissue damage. Over time, hyperglycaemia returns in many patients.

But can we ignore diabetic tissue damage? While prolonged normoglycaemia may reduce the risk of new complications and can improve existing ones, this is not always so. New microvascular disease may appear. Existing complications may worsen.

For optimal understanding of 'diabetes in remission' we need more long-term studies with full pre- and post-intervention assessment of both glycaemia and diabetes complications. However, increasing evidence is emerging. Buse *et al.*[3] stated: 'As new therapies of curative intent emerge for type 1 and type 2 diabetes and… evidence regarding prognosis builds, these issues will surely require further deliberation.' I suggest an international expert group does just that!

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POEMs

ESSENTIAL EVIDENCE PLUS

HbA1c underestimates past glycaemia in African Americans with sickle cell trait

Clinical question

Does the haemoglobin A1c level underestimate past glycaemia in African Americans with sickle cell trait?

Reference

Lacy ME, *et al.* Association of sickle cell trait with hemoglobin A1c in African Americans. *JAMA* 2017;317(5):507–15.

Synopsis

The life span of red blood cells is shorter in adults with sickle cell trait (SCT), which may result in less available time for haemoglobin glycation and lower measured HbA1c levels in relation to glucose values. These investigators retrospectively evaluated data obtained from self-identified African Americans who participated in one of two community-based cohorts, originally established to evaluate the long-term (≥25 years) risk of developing coronary heart disease. SCT status was defined as the presence of one abnormal allele for haemoglobin S. A total of 4620 participants provided 9062 concurrent measures of HbA1c and fasting glucose and 2001 concurrent measures of HbA1c and 2-hour glucose. Of these, 367 participants were identified with SCT. According to all available data, the mean HbA1c was significantly lower in adults with SCT than in those without SCT (5.7% vs 6.0%), despite similar mean fasting glucose and 2-hour glucose values. After adjusting for potential confounders – including age, sex, BMI, ferritin levels, GFR, and use of diabetes medication – HbA1c levels remained significantly lower in adults with SCT than in those without SCT (mean difference -0.32%; 95% CI -0.38 to -0.26).

POEMs

ESSENTIAL EVIDENCE PLUS

Screening for pre-diabetes: neither HbA1c nor fasting glucose results are very accurate

Clinical question

Are screening tests for pre-diabetes accurate?

Reference

Barry E, *et al.* Efficacy and effectiveness of screen and treat policies in prevention of type 2 diabetes: systematic review and meta-analysis of screening tests and interventions. *BMJ* 2017;356:i6538.

Synopsis

The authors conducting this systematic review and meta-analysis searched several databases for all research papers that evaluated the diagnostic accuracy of laboratory-based (not clinic-based) HbA1c or fasting blood glucose tests to identify impaired glucose tolerance, using an oral glucose tolerance test as the reference standard for diagnosis. Heterogeneity among the studies was high, probably due to the differences in populations and settings. Across all studies the prevalence of impaired glucose tolerance was 27% but varied by study, which will make predictive values bounce around. For HbA1c tests, the sensitivity was 0.49 (95% CI 0.4–0.58) and the specificity was 0.79 (0.73–0.84). For fasting blood glucose tests, the sensitivity was 0.25 (0.19–0.32) and the specificity was 0.94 (0.92–0.96). In other words, neither is very good at predicting oral glucose tolerance test results.