Routine OGTT screening for CFRD – no thanks

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DECLARATIONS

Competing interests
None declared

Funding
None

Ethical approval
Not applicable

Guarantor
MW

Contributorship
MW is the sole contributor

Acknowledgements
None

With improvements in therapy and the organization of care, people with CF alive today can expect to survive, on average, well into their fourth decade.[1] Indeed, it is anticipated that most of those born since the millennium may survive into their sixth decade,[2] and already the majority of CF people in the Western world have reached adulthood. However, this improvement in survival has brought with it an increasing incidence of complications, either from the condition itself or as an unforeseen consequence of treatment. Such complications now include osteoporosis,[3] gall stones,[4] secondary biliary cirrhosis with subsequent portal hypertension and varices,[5] kidney stones,[6] and acute and chronic renal failure as a consequence of repeated nephrotoxic drug therapy (mainly aminoglycosides).[7,8] In addition, women may wish to bear children, which complicate their management, and since nearly all men are infertile sperm harvesting and *in vitro* fertilization[9] may be necessary. A good example of one such temporally-related complication is that of glucose intolerance,[10] which in its extreme form may fulfil the diagnostic criteria used in non-CF patients for diabetes mellitus. Such people may then be labelled as suffering from CF-related diabetes (CFRD).[11] This is unusual before the age of 10 years,[12] but increases with age such that at least 25% of the CF population will suffer from significant glucose intolerance by the age of 25 years.[13]

The annual review

As part of good clinical governance, the UK CF Trust has produced a number of so-called 'consensus' guidelines,[14] aimed at various aspects of clinical care including recommendations for annual assessment. Thus, it is possible that at an annual review, each CF person may require a comprehensive medical history, full physical examination, biochemical testing (including reserve renal function), a medication review by the CF pharmacist, a dietetic assessment, a psychological profile, a nursing and welfare assessment, bone health (including densitometry) and a physiotherapy schedule. They will also require chest radiography, and in those with liver disease, relevant organ imaging and surveillance endoscopy. Additionally, in 2004 the UK CF Trust recommended that all CF people above the age of 12 years should be screened annually for CFRD, using an oral glucose tolerance test (OGTT).[15]

However, such annual review assessments are uncomfortable (if they involve fasting), possibly painful (if they require endoscopy or venepuncture) and inevitably time consuming: if the full range of assessments is made, it can stretch the consultation period to more than one day. It is therefore the responsibility of the supervising clinician to ensure that only the assessments relevant to each patient are performed, not only to avoid a waste of resource, but more importantly to limit the impact on the CF person's life. The investigations involved in such assessments are best described as screening tests.

'Screening' versus 'diagnostic' tests

It is important to understand the difference between 'screening' and 'diagnostic' tests. Screening is carried out in a population which bears no obvious signs of the condition being tested,[16] whereas tests which are diagnostic are those targeted to a condition which is already suspected.[17] Unlike Types I and II diabetes, the presenting features of CFRD include recurrent chest infections, weight

loss and unexplained clinical deterioration.[18] Glucose tolerance investigations carried out under these circumstances are, by definition, diagnostic rather than screening tests.

In order for a screening test to be of any value, it must have a high sensitivity (only miss a low number of cases of the condition)[19] and a high specificity (only include a low number of cases who do not have the condition).[19] Furthermore, it needs to be relevant to the condition in question, be efficient to carry out, and if possible be the 'gold standard' for that particular condition. If the screening test fails any of these parameters, it may mislead the clinician. This is particularly important in CF, where many well young adults (i.e. the population in which screening can be carried out) have busy lives: it is incumbent on healthcare staff to ensure that their demands on the CF person's time are made wisely: screening tests that have such an impact should be closely scrutinized.

This paper will assess the utility of screening tests for glucose intolerance, including CFRD, in adults with cystic fibrosis.

Possible CFRD 'screening' tests

There are a number of tests that can be used to assess glucose handling.

Random blood sugar

This is only of value if it demonstrates high blood glucose, which is unlikely except in very severe persistent glucose intolerance. Single measurements of RBG cannot reflect the true underlying glycaemic pattern.

Fasting blood glucose (FBG)

This will only be elevated if the glucose intolerance is very severe: many individuals who may be unable to handle a glucose load may still exhibit a normal fasting value,[20] and a raised FBG may detect only 16% of CFRD cases.[12] It is therefore of little use in looking at the spectrum of glucose intolerance in CF, although interestingly it is recommended as a screening test by the US CFF.[21]

HbA1c

HbA1c is not recommended as a diagnostic tool or as a screening test for diabetes in the non-CF population,[22] and in CF it may be particularly misleading due to altered red blood cell mass and its shortened life span,[23] since glycosylation of haemoglobin occurs in a non-linear fashion throughout the lifespan of red blood cells.[22]

Preprandial blood glucose

This is analogous to the fasting sample, and is only of value if the glucose intolerance is severe.[24]

Oral glucose tolerance test

This artificially tests pancreatic endocrine function by giving a glucose challenge against a fasting background: it is time consuming and relatively uncomfortable for the patient. It is the gold standard diagnostic test in Type I and Type II diabetes, where the pathogenesis of the condition results in permanent glucose intolerance.[11] However, glucose intolerance in CF is often very variable, and the OGTT when used as a single point test will often give misleading results.

Postprandial glucose monitoring (SGM)

This is effectively a heavily modified OGTT, measuring serum glucose two hours after a meal: it more accurately reflects the true day-to-day glucose challenge experienced by CF people.[24] It is easy to carry out and can be performed serially.

The OGTT and CF glucose intolerance

Since glucose intolerance in CF is variable, in order for the OGTT to be an appropriate screening test for CFRD (as recommended by some workers),[15] it needs to be validated by demonstrating acceptable repeatability and reproducibility. Such validation will require multiple OGTTs in the same CF people over a period of time: there are only three published studies which have done this. Lanng performed OGTTs in 191 CF people of all ages over 5 years, and showed that although a proportion of them had apparently worsening glucose intolerance over time, of 108 people whose tests initially showed glucose intolerance, 63 reverted to a normal profile and 15 to frank CFRD.[12] However, it is not clear if any of these latter cases

underwent further OGTTs. Sterescu performed serial OGTTs in 317 adult CF people over 10 years and showed that in many cases glucose handling varied wildly. Over half of the 38 with an initial CFRD profile lost this over time: seven subsequently returned to a normal glucose tolerance, including one that had had fasting hyperglycaemia.[25] In a similar study in 38 CF adults, Battezzati showed that of six with an initial CFRD profile, only two remained so at one year and three had returned to a normal profile.[26] These studies demonstrate that the OGTT has a poor specificity in the diagnosis of CFRD.

Does the OGTT have good sensitivity? Clinical experience dictates that many patients who have a normal OGTT may develop glucose intolerance within a short space of time. In one study, Dobson showed that five of 15 CF adults undergoing continuous subcutaneous glucose monitoring over a 72-hour period had glucose peaks within the diabetic range despite having a normal OGTT,[24] and in a further study demonstrated that four CF people with clinical deterioration and normal OGTTs had episodes of significant hyperglycaemia (fulfilling the criteria for CFRD) with SGM: they all improved when treated with insulin therapy.[27] Thus, the OGTT has a poor sensitivity in the diagnosis of CFRD.

A test with poor specificity and sensitivity cannot be described as a 'gold standard'. Furthermore, the OGTT is inefficient since it requires an overnight fast followed by serial blood samples over several hours. Thus, if the standard screening test rules are applied to the OGTT in CFRD, it is clear that it fails all of these other than relevance, calling into question its value in the screening of this CF condition.

The difference between CFRD and other types of DM

Although the pathogenesis of diabetes mellitus is complex, the following simplified explanation will help the understanding of why CFRD does not behave like other forms of diabetes and requires a different approach.

In Type I diabetes, there is an autoimmune destruction of pancreatic beta cells, which leads to a rapid, profound and permanent loss of the ability to produce insulin (insulinopena).[11]

In Type II diabetes, there is increasing resistance to the effects of insulin in the liver, adipose tissue, and muscle cells which outstrips the pancreas's ability to produce insulin such that hyperglycaemia occurs.[11] Such resistance is usually accompanied by obesity, and weight loss may ameliorate the glucose intolerance. Insulinopenia is a late feature.

However, in CFRD, progressive pancreatic fibrosis lessens the ability of the pancreatic beta cells to produce insulin, probably by reducing their number but also by altering their ability to function. Thus, over time, the potential of the pancreas to perform its endocrine function diminishes: this relative insulinopenia may be accompanied by insulin resistance in the liver.[15] However, the effects of these changes in glucose handling are very variable, and can be affected by stress, infection and the altered bowel function (including transit time)[28] that occurs in all CF individuals with exocrine pancreatic disease. Since this glucose intolerance is a dynamic process, it is apparent that single point tests (including the OGTT) will not give an accurate picture of overall glucose handling in CF. Serial testing is necessary, and this must apply for screening as well as diagnosis and subsequent monitoring. Serial OGTT measurements are impractical and only possible in a research environment.

Serial postprandial glucose measurements

One way of reliably measuring a CF person's ability to handle a glucose load in the real world is to perform serum postprandial glucose estimations which will allow the clinician to build up a glucose handling profile for that individual.[24]

What is recommended?

Despite the obvious deficiencies of the OGTT as a screening tool for CFRD, some authorities still recommend its use.

In 2004 the UK CF Trust produced guidelines for the management of CFRD which state that all CF people over the age of 12 years should undergo annual screening using OGTT:[15] however, confusingly, the guidelines then acknowledge that 'in a

person with CF, a diabetic OGTT does not mean that the individual necessarily has diabetes', and suggest that these individuals then go on to have serial glucose monitoring (which could of course, have been undertaken in the first place). Furthermore, the CF population has been shown to be at risk of abnormal glucose handling from the age of 10. Also, the guidelines make no mention of the fact that a single OGTT may miss significant glucose intolerance, thereby potentially delaying the opportunity for treatment in those CF people who have clinical deterioration.

The US CFF has recognized the fallibility of the OGTT in CFRD, and does not recommend its use in the annual assessment for CF people.[21]

How is CFRD diagnosed in the UK?

A survey by Mohan of 37 recognized UK CF centres (caring for over 80% of CF people) showed that 20% did not use the OGTT in screening, but 49% did rely upon a single OGTT to make the diagnosis.[29] Given the variability of glucose handling in the CF population, this implies that a number of adults with CF in the UK will be receiving insulin inappropriately and a number of others will remain undiagnosed.

My colleague Dr Peckham is a strong advocate for single point OGTT screening for CFRD: despite this, it is of interest to note that, according to the current *Leeds Method of Management for CF Care*,[30] which he co-authored, such testing is not carried out in up to one-third of the adult CF people under his care.

What should we do with a positive screen for CFRD?

Although a number of studies have shown that the treatment with insulin of significant glucose intolerance in CF can result in an improvement in clinical condition, all these were carried out in individuals who were deteriorating, i.e. the treatment was given as a result of diagnostic testing. Thus, these individuals did not therefore fulfil the criteria for 'screening' in that they were not in a well, stable, asymptomatic state when the diagnosis was made. There are no studies in the CF literature indicating the effect of insulin treatment on well, stable CF people, the only group in which screening for CFRD could be carried out.

The diagnosis of CFRD and the subsequent institution of insulin therapy constitute a major step increase in the treatment burden for the CF person, who may already be taking multiple therapies to combat their existing CF complications. Since there is no convincing evidence that giving such treatment to well, stable individuals with glucose intolerance is beneficial, its initiation must be viewed with caution.

The Liverpool way

We have adopted a different and more rational approach to the diagnosis and subsequent treatment of CFRD in the adult CF people we care for. Since glucose intolerance is very common in the adult CF population, we actively look for this complication at any time when the CF person is unwell, unstable or deteriorating: this is not a screening but a diagnostic process. We believe that limiting this to an annual review will delay the opportunity to offer appropriate treatment at an appropriate time. Given the poor specificity and sensitivity of the OGTT in CF, and the fact that it is time consuming and uncomfortable for the patient, we do not routinely perform it as either a screening or diagnostic test in our clinic. Instead, we advocate the use of serial postprandial glucose monitoring (SGM). Those CF people admitted to hospital have a fasting sample and SGM two hours after every meal for the first three days of their admission: if they show glucose intolerance which settles, they will then undertake a further period of SGM after discharge, supervised by the Specialist CF Nurses. Any severe glucose intolerance is treated with insulin. Those people managed in the community who have clinical features that could suggest glucose intolerance (i.e. frequent chest infections, are unstable or deteriorating) undertake home fasting and SGM for three days with further monitoring or treatment as appropriate. We also regularly review the need for insulin in those people who are taking this therapy.

Using this protocol, of the 250 adult CF people cared for by the Liverpool Adult Clinic, 29% have severe glucose intolerance and take insulin regularly, 4% use insulin intermittently, and at any one time a further 20% of the clinic population will be undertaking home SGM.

Conclusion

Although glucose intolerance is common in the adult CF community, the degree of glucose handling is very variable over time such that single time-point tests will mislead the clinician. As such, basing a diagnosis of CFRD on the result of an annual screening procedure is inappropriate. In particular, the OGTT has poor specificity and sensitivity and cannot be recommended as a tool to plan long-term treatment. Management should rely upon a flexible and ongoing approach to monitoring glucose handling in any one individual and serial postprandial glucose measurement is the best way of achieving this.

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