Closing the loop, squaring the circle: Studies on insulin delivery, glucose monitoring and the artificial pancreas
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Citation for published version (APA):

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Chapter 3

The added value of oral glucose tolerance testing in pre-diabetes

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ABSTRACT

With the increased acceptance of glycated hemoglobin measurement as the test of choice for the diagnosis and detection of diabetes, doubts which surround the use of the oral glucose tolerance test (OGTT) in detecting disturbances in glucose levels have become even more apparent. Metabolically, there are still arguments to use the OGTT. Epidemiological studies though, have not always supported the efficacy of the OGTT when used for screening in obese patients. In our opinion, current evidence suggests an additive value of the OGTT, its main advantage being the ability to detect stages of pre-diabetes more accurately than HbA1c and the ability to investigate postprandial glucose levels in a physiological way.
INTRODUCTION

Although the obesity epidemic is growing to enormous proportions, there is still much debate on the preferred way of screening for deregulated glucose levels i.e. pre-diabetes (impaired glucose tolerance (IGT), impaired fasting glucose (IFG)) and type 2 diabetes mellitus (DM2), in the obese population (1). Why a disorder of such magnitude still raises questions when it comes to screening, is quite puzzling. The answer to this question is multifactorial and concerns issues like definitions of cut-off values, uncertainty of what test to use, purpose of screening (research vs. clinical use) and cost-effectiveness (1). The lack of systematic screening is one of the reasons why a substantial amount of patients with type 2 diabetes remains undiagnosed (2;3).

The oral glucose tolerance test (OGTT), fasting glucose and measurement of glycated hemoglobin A1c (HbA1c) are methods which can be used to detect pre-diabetes and DM2 (2;3). The metabolic characteristics of the OGTT provide compelling reasons to use the test. However, in clinical practice, the OGTT has not become a widely used tool for screening in obesity. With the recent attention for the use of HbA1c measurements as the preferred diagnostic test for diabetes, questions arise about the future of OGTT as a screening tool (4). Here we discuss the different physiological backgrounds of these diagnostic tests and problems which arise in their interpretation. Finally, we contemplate on the added diagnostic value of the OGTT at a time in which screening of diabetes is becoming increasingly synonymous with HbA1c testing.

Pathophysiology of basal and postprandial glycaemia

The fasting plasma glucose concentration predominantly depends upon endogenous glucose production (EGP) and basal glucose uptake, with plasma insulin levels which are typically low (5). Impaired insulin secretion and insulin resistance, resulting in increased EGP, mainly explain disturbances in glucose levels in obese subjects and disturbances in insulin stimulated glucose uptake. These disturbances do not occur in all patients simultaneously and to the same extent, especially in the prediabetic stage.
Basal EGP is the major determinant of plasma glucose concentration in the post-absorptive state (PAS) and is an indirect derivative of insulin sensitivity since plasma insulin levels are typically low in the PAS. However, it has been shown that the homeostasis model assessment of insulin resistance (HOMA-IR), which takes basal glucose and basal insulin levels into account, correlates highly with insulin sensitivity measured during a hyperinsulinemic euglycaemic clamp (6).

While fasting plasma glucose (FPG) is mainly determined by EGP, the plasma glucose after an oral glucose load or meal is predominantly the result of an integrated metabolic response. This response is dependent on incretin action, insulin secretion (beta-cell function), hepatic insulin sensitivity (inhibition of endogenous glucose production) and stimulation of peripheral glucose uptake.

**Pathophysiologically based testing of glycaemia**

The OGTT seems to be very helpful to diagnose IGT and DM2 in a clinical setting in obese subjects (7). This test provides direct information regarding postprandial glucose levels. The plasma glucose after two hours (2hr-PG) is the result of the concerted actions of the integrated metabolic response. The importance of the 2hr-PG is supported by the fact that during the development of IGT or DM2, disturbed handling of an oral glucose load, and thus increased 2hr-PG, generally precedes the increase in FPG (8). This implies that patients at risk of developing IGT/DM2 should be tested after a carbohydrate load to be diagnosed earlier. Additionally, the 2hr-PG has also been identified as an independent risk factor for developing IGT/DM (9). However, a normal FPG in a single patient does not preclude this patient from having IGT or DM2: using FPG as a screening tool for the presence of IGT or DM2 may be inferior to using the OGTT and its 2hr-PG.

In contrast to the OGTT, the measurement of glycated hemoglobin type A1c (HbA1c) does not provide any specific information about postprandial glucose levels. The glycation of hemoglobin is a gradual process in which hemoglobin is glycated in a non-enzymatic pathway by exposure to high plasma levels of glucose. This process of glycation is irreversible and thus a measurement of the HbA1c correlates with average plasma glucose over time. Since red blood cells have a lifecycle of about 120 days, this correlation is to average plasma glucose levels during these 120 days. However,
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there is evidence which suggests that the relative contribution of the plasma glucose level to HbA1c values is highest in the period 2 to 4 weeks before the end of life of the red blood cell (10). HbA1c has been used for decades as a measurement of glycaemic control in patients with diabetes, but now there is increasing interest in the use of HbA1c as a screening tool for diabetes (11). Currently a cut-off value of 6.5% has been incorporated into the diagnostic criteria of diabetes. However, there is still ongoing debate about the usefulness of HbA1c for screening of IFG/IGT (4).

**Impaired glucose tolerance and type 2 diabetes**

The American Diabetes Association has come forward with concise reference values that define normal glucose tolerance, pre-diabetes (IFG/IGT) and diabetes (7;12). However, one should realize that these conditions are not “on-and-off states”, but evolve gradually and progress from healthy normal glucose tolerance to DM2 on a continuous scale. In addition, DM2 patients may not present with the classical symptoms of diabetes (12). These two arguments explain why IGT can remain undiagnosed for years, while this surreptitious condition puts the patient at increased risk of developing macrovascular and microvascular complications even in the absence of progression to DM2 (1). Therefore, IGT should be regarded as a warning sign and managed appropriately.

In lean healthy subjects the 2hr-PG after an OGTT is often significantly lower compared to the baseline plasma glucose level, emphasizing the pathological significance of an increased 2hr-PG (13). Also OGTT allows to distinguish the patients at risk from the up to 30% of obese people whom are metabolically healthy obese subjects with normal insulin sensitivity (2;14).

The detection of IGT by means of HbA1c is generally considered to be inferior to that of the OGTT (1). This is partly due to the fact that the effect of a glucose challenge is not captured by the HbA1c test. A frequently heard argument against the uniform adoption of HbA1c as a diagnostic tool in diabetes is indeed that, with currently proposed guidelines and cut-off values, a great deal of patients with IGT will be missed (1). It has been shown however that HbA1c is affected by postprandial rises in blood glucose. Notably, the respective contributions of FPG and postprandial glucose (PPG) to HbA1c progressively shift depending on the level of glycaemic
control: the relative contribution of postprandial glucose to excess hyperglycaemia decreases as glycaemic control deteriorates, being dominant with HbA1c ≤ 7.3% (15). As a result, HbA1c levels could be above normal in patients with IGT, due to the shifting relationship between HbA1c levels and postprandial hyperglycaemia. However, the potential of the use of HbA1c measurements as a diagnostic tool for IGT remains suboptimal (1). As with measures of glucose, a continuum of risk for the development of diabetes based on A1C levels has been demonstrated (16-18). This makes it difficult to propose cut-off values with coincide with the more traditional definitions of IFG and IGT which are dichotomous.

A study by Selvin et al. supports the existence of a continuum of risk of developing diabetes and has shown that glycated hemoglobin values of higher than 5.5% are already associated with an increased risk of developing diabetes when taking an HbA1c level of between 5.0 and 5.5% as a reference. They also reported that the mean HbA1c in the healthy population (BMI 26.7 ± 4.6) is 5.2±0.1% (19). With the advent of HbA1c as the primary screening tool for diabetes, there is even some call for phasing out IGT and IFG as clear entities which define pre-diabetes (4). However we believe this call to be premature.

**Epidemiological evidence**

The evidence that intensive glucose lowering therapy reduces complications was provided by the U.K. Prospective Diabetes Study (UKPDS) (20), in which patients with an FPG of 6.1-15.0 mmol/l were included, with a treatment target of FPG 6.0 mmol/L in the intensively treated group. Thus, the UKPDS justified screening for abnormal FPG values. As no OGTT was used in the UKPDS, its value was not established and the UKPDS-selection criteria might have underestimated the patients eligible for treatment.

However, when FPG is used alone in screening, 31% of subjects with an increased 2hr-PG as determined by OGTT will not be diagnosed (21). Furthermore, the OGTT has a stronger correlation to prevalent retinopathy when compared to FPG (22). The combined presence of impaired FPG and impaired 2hr-PG in a large Dutch sample of the general population was associated with an Odds Ratio (OR) of 39.5 (95% CI, 17.0-92.1) for the development of T2DM within 6 years, as compared to an OR of 10.0
The added value of OGTT

(95% CI 6.1-16.5) for impaired FPG alone, suggesting improved case finding when adding the OGTT to the FPG (23). Thus, by using the OGTT, the number of patients which are erroneously not treated for (pre)diabetes will be reduced when compared to using FPG only.

Whereas epidemiologic evidence for HbA1c in the detection of diabetes is based primarily on its relationship with the onset of diabetic retinopathy (24-26), a less consistent relationship with FPG levels has been shown (27). The expert committee report on HbA1c suggested that all values between 6.0 and 6.5% be interpreted as a form of pre-diabetes which requires effective prevention strategies (4). However, in a recent study by Zhou et al. it was shown that HbA1c underperformed relative to capillary fasting glucose measurement in the detection of pre-diabetes. In fact the study showed that based on HbA1c measurements alone, people with pre-diabetes could not be distinguished from healthy controls (28).

**Practicality of OGTT**

It is mostly because of practical difficulties that the OGTT is not the current diagnostic tool of choice for most physicians. This may be amplified by access to alternatives such as HbA1c, which do not require patients to fast and provide a lower burden on healthcare personnel. Additionally, various clinical models have been developed to predict the conversion to DM2 from readily available clinical parameters. Wilson et al. predicted the 8-year risk of T2DM in The Framingham Offspring Study by using FPG in combination with BMI, HDL, parental history of DM, triglyceride level and blood pressure (29). In a prospective cohort study, Stern and colleagues showed that a similar clinical model, which included age, sex, ethnicity, FPG, systolic blood pressure, HDL, BMI and parental or sibling history of diabetes, was a better predictor of 7.5 year DM incidence, as compared to OGTT alone (30). It is difficult to justify medical intervention for a high a-priori chance of developing diabetes according to such a model, when FPG is normal and 2hr-PG level is not known.
**Accuracy of testing**

Physiological circumstances like dietary regimens or duration of fasting influence glucose regulation. This in turn explains the variations in plasma glucose levels (31). The 2hr-PG value of the OGTT has been criticized for its variability, and thus limited reproducibility. It is indeed true that the accuracy of the FPG is somewhat better than the 2hr-PG value. In a cohort of 524 subjects, the coefficient of variation of two consecutive measurements within 2-6 weeks was 4.8-7.1% for FPG and 12.7-16.4% for the 2hr-PG value (32). However, with respect to the reference values of pre-diabetes, the lower reproducibility of the 2hr-PG compared to the FPG is accompanied by a larger reference interval of the former (7.8-11.0 mmol/L) compared with the latter (5.6-6.9 mmol/L) (7). A confounder of the FPG may be the duration of fasting. The ADA position statement on this matter suggests that patients should have been fasting for at least 8 hours before FPG is determined. Since the duration of fasting influences the EGP, and thus the plasma glucose concentration, the duration of the overnight fast should be precisely defined (33).

However in both FPG and OGTT the need for fasting is a serious limitation and the lack of this necessity with the measurement of glycated hemoglobin is one of the main advantages in its use in detecting diabetes. Although the measurement of glycated hemoglobin is associated with a decreased burden on the patient, the measurement also had to cope with significant inter-laboratory differences. However, several initiatives on this issue have been completed that have largely eliminated these problematic differences (34). With the introduction of the IFCC values, HbA1c has made a great step forward in terms of uniformity and reproducibility of measures internationally (35). Regarding fluctuations in plasma glucose, HbA1c is much less prone to inconsistent outcomes than the OGTT because it measures average plasma glucose levels over time. However there are still concerns of interference in HbA1c essay methods by various hemoglobinopathies, uremia and ethnic variations. Recent technologies have greatly reduced the number of assays susceptible to errors caused by hemoglobinopathies, anemia or uremia (11). Even though these causes of errors are infrequent, physicians should still be aware of them, especially within patient populations where hemoglobinopathies are highly prevalent. There is also ongoing debate whether HbA1c cut-off values should be race-specific. It has been shown
that with the adoption of HbA1c as a diagnostic test for diabetes, the incidence of diabetes will vary among the different racial groups (36). This is an issue which will require further investigation.

**Implications in clinical practice**

The recent UKPDS follow up study has made it clear that early intensive treatment of DM reduces mortality (37). In addition, the prevention of the development of DM has become a major area of interest. The STOP-NIDDM trial provided evidence that prevention or delaying of DM is possible, highlighting the importance of early detection (38;39). Both FPG and the 2-hr PG values were used to include patients in this trial.

In support of this, the Diabetes Prevention Program Research Group, who randomly assigned 3,234 patients with FPG of 5.3-6.9 mmol/l and 2hr-PG of 7.8-11.0 to placebo, metformin or a lifestyle program, found that lifestyle improvement reduced the incidence of DM by 58% and metformin by 31%, as compared to placebo (40). In practice, lasting compliance with lifestyle changes is poor at best. In such cases the OGTT and FPG can provide an additional rationale for medical treatment. According to the 2008 ADA medical standards “in addition to lifestyle counseling, metformin may be considered in those who are at very high risk (combined IFG and IGT plus other risk factors) and who are obese and under 60 years of age (7).”

Data from the National Health And Nutrition Examination Survey from 2005-2006 also shows that patients with pre-diabetes have substantially higher cardiovascular risk, having a mean Framingham 10-year risk for cardiovascular events of 8.5% (CI, 6.0-10.6%), which was almost twice that of normoglycaemic subjects (5.2% [CI, 3.9-6.4%], p<0.001). Of the 1,547 subjects without diabetes, 34.6% (CI 30.3-38.9%) had pre-diabetes (41). Furthermore, treating pre-diabetes and screening for pre-diabetes seems to be cost-effective (42).

One should consider however that a normal FPG or HbA1c does not exclude the presence of IFG or IGT. We propagate to be aware of the pitfalls of simple measurements as the FPG and HbA1c, to exclude a multifactorial complex metabolic disorder such as IGT and DM2.
HbA1c-measurement, FPG and OGTT are different diagnostic entities, each with its own set of advantages and disadvantages (see table 1). When it comes to testing patients at risk however, we believe that the current evidence supports an important role for additional testing with the OGTT until reliable HbA1c reference values for pre-diabetes are established. This has the advantage of testing the important postprandial glucometabolic response and subsequently treating IGT and IFG, something which is lacking in the current switch to HbA1c as the preferred screening tool.

**Table 1: Advantages and disadvantages of OGTT and HbA1c testing.**

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<thead>
<tr>
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<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>OGTT</td>
<td>Tests postprandial glucometabolic response directly</td>
<td>Test is laborious</td>
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<tr>
<td></td>
<td><strong>Suitable for detection of IGT/IFT</strong></td>
<td>Test requires fasting</td>
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<td></td>
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<td>Unsuitable for use in large-scale screening programmes</td>
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<td></td>
<td></td>
<td>Test is relatively expensive</td>
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<tr>
<td>HbA1c</td>
<td>Test is time efficient</td>
<td>Test only informs about average glucose over time</td>
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<tr>
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<td>Test does not require fasting</td>
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<tr>
<td></td>
<td><strong>Suitable for use in large scale screening programmes</strong></td>
<td>Assay interference is possible (e.g. hemoglobinopathies)</td>
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<td>Test is relatively cheap</td>
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<tr>
<td>FPG</td>
<td>Test is time efficient</td>
<td>Test only informs about fasting glucose levels</td>
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<tr>
<td></td>
<td><strong>Test is relatively cheap</strong></td>
<td>Test requires fasting</td>
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