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MINIREVIEWS

Oral glucose tolerance test in diabetes, the old method revisited

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Abstract

The oral glucose tolerance test (OGTT) has been widely used both in clinics and in basic research for a long time. It is applied to diagnose impaired glucose tolerance and/or type 2 diabetes mellitus in individuals. Additionally, it has been employed in research to investigate glucose utilization and insulin sensitivity in animals. The main aim of each was quite different, and the details are also somewhat varied. However, the time or duration of the OGTT was the same, using the 2-h post-glucose load glycemia in both, following the suggestions of the American Diabetes Association. Recently, the use of 30-min or 1-h post-glucose load glycemia in clinical practice has been recommended by several studies. In this review article, we describe this new view and suggest perspectives for the OGTT. Additionally, quantification of the glucose curve in basic research is also discussed. Unlike in clinical practice, the incremental area under the curve is not suitable for use in the studies involving animals receiving repeated treatments or chronic treatment. We discuss the potential mechanisms in detail. Moreover, variations between bench and bedside in the application of the OGTT are introduced. Finally, the newly identified method for the OGTT must achieve a recommendation from the American Diabetes Association or another official unit soon. In conclusion, we summarize the recent reports regarding the OGTT and add some of our own perspectives, including machine learning and others.

Key Words: Oral glucose tolerance test; Impaired glucose tolerance; Glucose Utilization;

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Type 2 diabetes; Area under the curve

Core Tip: Oral glucose tolerance test (OGTT) is a useful tool that has been applied from the last century to now. It is used to diagnose impaired glucose tolerance and/or type 2 diabetes mellitus in individuals. Basic research also applied it to investigate the glucose utilization and insulin sensitivity in animals. However, the main aim of each is quite different, and the details are also somewhat varied. In addition to the merits of OGTT in bench and bedside, variations between clinical practice and basic research are also discussed. Notably, recent reports have recommended that the time for OGTT be shorter in individuals. This conclusion needs to be confirmed officially in advance by diabetes associations. This new method is also required to be clarified in animal research. Additionally, perspectives of OGTT application are also conducted in this review including machine learning. Therefore, this report suggests a new way for OGTT practice in the future.

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INTRODUCTION

The oral glucose tolerance test (OGTT) has widely been used in clinics to diagnose impaired glucose tolerance (IGT) and/or type 2 diabetes mellitus (T2DM)[1]. The risk of transient postprandial hypoglycemia in patients with non-alcoholic fatty liver disease has also been identified using the OGTT[2]. Moreover, non-alcoholic steatohepatitis (NASH) linked with T2DM has been a focus, because NASH often occurs within 5 years in patients with T2DM (about 56.49%)[3]. Therefore, the application of OGTT for the diagnosis of non-alcoholic fatty liver disease or NASH is also popular in clinical practice.

The prevalence of T2DM is increasing at an alarming rate and is projected to increase from 171 million individuals in 2000 to 366 million by the year 2030[4]. In the United States, the number of adults living with T2DM is estimated to increase from 463.0 million to 700.2 million between 2019 and 2045. The total annual costs of managing this disease are expected to increase accordingly from 760.3 billion USD to 845.0 billion USD in this period. Therefore, the identification of IGT is important for T2DM prevention strategies in those who are at high risk. To achieve this, the OGTT has been suggested[5]. The use of glycated hemoglobin (HbA1c) levels has been proposed as an alternative to the OGTT. However, using only HbA1c to diagnose diabetes misses more than half of the diabetes cases established by the OGTT[6]. Therefore, the OGTT was introduced as the most suitable method[7].

The OGTT is also used in basic research, mainly focusing on glucose homeostasis of animals. Insulin resistance (IR) and insulin sensitivity have been identified using the results of the glucose- insulin index obtained from the OGTT in animals[8]. The diagnosis of T2DM was not included in this basic research. IGT in animals was also the main target in basic studies. Although research in animals may be useful to studying the basis of human disease, there are clear differences between species regarding metabolic regulation[9]. Therefore, the OGTT has limitations in basic research[10].

The OGTT has been applied over the last century by using the plasma glucose concentrations, measured after either an overnight fast or glucose loading, as a useful tool for diagnosing IGT. Indications for performing the OGTT are numerous, as described in a recent review article[11]. In this report, we explore the concerns regarding the OGTT, revisited for both bedside and bench.

OGTT IN CLINICAL PRACTICE

The OGTT was standardized by establishing an oral glucose load of 75 g and 2-h post-glucose load glycemia (2hPG), according to the Expert Committee of the American Diabetes Association (ADA)[12]. Overnight fasting glucose (FPG) and impaired fasting glycemia (IFG) were also recommended by the ADA. However, the FPG cut-off values for diabetes and/or IFG are far from being equivalent to the corresponding 2hPG values according to epidemiological data[13]. Additionally, it has been documented that impairment in insulin secretion is more relevant in IFG, while faltering insulin sensitivity is peculiar to IGT[14]. Otherwise, the concerns regarding the OGTT are that it is time consuming, poorly reproducible, and not well accepted by patients. Therefore, the ADA expected to include more subjects whose OGTT results were conclusive for diabetes or IGT, as described previously[15].

Although FPG cannot be equated to 2hPG, it has been demonstrated that the 2hPG predicts the risk of heart disease more effectively than FPG[16]. Basically, the plasma glucose levels obtained during the OGTT are related to both insulin sensitivity and secretion. As β-cell function is already substantially impaired in prediabetes, shortening the OGTT to use the 30-min or 1-h post-glucose load glycemia (1hPG) has recently been suggested[11]. Therefore, identifying high-risk individuals using the 1hPG seems an important and novel strategy to prevent the development of T2DM and cardiovascular disease. The addition of 30-min PG values to traditional glucose biomarker such as FPG and 2hPG values may assist the identification[11]. However, the faster the post-load glucose drops towards FPG, or the lower the rise in post-load glucose, the more efficient the β-cell function[15]. Another review article summarized the clinical reports to suggest that a 1hPG level of ≥ 8.6 mmol/L (or 155 mg/dL) to identify individuals with reduced β-cell function should be considered for adoption in clinical practice[17]. One-hour time points during a standard OGTT and the morphological characteristics of the glucose curve during the OGTT are associated with heightened risk of incident diabetes. The 30-min PG indicates first-phase insulin response. Diminution of the 30-min PG suggests β-cell dysfunction as an early lesion in the development of T2DM.

OGTT THROUGH QUANTITATIVE ANALYSIS

The shape of the glucose curve follows the pattern of a rise and fall in blood glucose after a fixed glucose loading, most commonly after a 2-h 75 g OGTT. The curve shape can be grouped into three categories by the blood glucose levels collected at fixed time points (such as 0, 15, 30, 60, 90, and 120 min) - monophasic (a gradual increase in glucose with a single peak and then a fall), biphasic (a gradual rise to a peak, a fall in glucose to a nadir and a subsequent rise), and unclassified (a continuous rise without a peak). The rationale for using these definitions is mainly due to the association of the curve shapes with pathological features of T2DM and the ease of categorization. The monophasic and unclassified curves, compared to the biphasic curve, are associated with lower insulin sensitivity and decreased β-cell function[18]. Additionally, the monophasic and unclassified curves are better predictors of prediabetes in individuals at high risk of diabetes[19]. However, the application of simple shape changes to diagnosing prediabetes and/or diabetes is challenging, as described recently[11]. A monophasic curve was identified during a 2-h test, but it became a biphasic curve after a 3-h test for no discernible reason[20].

Latent class trajectory analysis is another statistical tool that supplies probabilities for grouping pairs into different morphological classes while considering measurement error and intra-individual variability[21]. Four patterns have been described (Classes 1–4) that correspond to increasing glucose levels and declining insulin sensitivity and secretion with time[22]. However, concerns related to increased cost and patient burden associated with collecting blood at one to three additional time points and the expertise required to assess heterogeneity in curve shapes have limited its clinical use[23].

The area under the curve (AUC) is derived from the OGTT data to calculate the total rise in blood glucose during the OGTT using the trapezoidal rule[24]. It has been applied in scientific reports to show the variations in increased blood glucose during the OGTT. However, a marked difference in fasting blood glucose between individuals interrupted the data of the AUC. Therefore, the incremental AUC (iAUC) was developed to minimize this difference[25]. However, the iAUC obtained by subtracting the baseline value of fasting plasma glucose has been challenged as being

problematic[24]. Then, the positive incremental AUC (pAUC) was further suggested, and only the values above the baseline value were considered; those below the baseline were ignored in studies[25]. The total AUC (tAUC), iAUC, and positive incremental area under the curve (pAUC) have been applied in clinical practice. It has been indicated that the tAUC expresses the best correlation with the 2-h glucose level from the OGTT, and the total glucose response was better represented by the tAUC than by the iAUC or pAUC in a clinical report[26]. Mathematically, iAUC is suitably indicated by ΔAUC. However, ΔAUC has widely been applied in pharmacokinetics in another method. Therefore, iAUC is more popular than ΔAUC for applications in metabolic research. In epidemiological analysis, the superiority of the AUC for identifying individuals at high risk for progression to T2DM has been demonstrated [27]. However, application of the AUC in clinical practice is not popular[11].

Sophisticated mathematical and statistical methods such as machine learning algorithms have been developed to extract the features from OGTT glucose curves to predict diabetes[28]. Using a simplified, integrated model that is freely available online will increase the accessibility for OGTT analysis, as described previously[11].

OGTT IN BASIC RESEARCH

In basic research, the use of the OGTT in animals has mainly focused on glucose homeostasis. Unlike in clinical practice, the OGTT has not been used for diagnosis in basic research. IR and insulin sensitivity were identified using the results of the glucose- insulin index obtained from the OGTT in animals. Generally, IGT is widely reflected in a larger iAUC of the plasma glucose disappearance curve during the OGTT. The OGTT showed a marked increase in $AUC_{0\text{-}120min}$ from the experimental animals, indicating success in the induction of a diabetic model[8,29]. Diabetic animals were then used to screen the activity of an investigated substance, either a herbal extract or a nutrient. When the slope of the glucose disposal phase is markedly changed and the AUC is lower than that of the vehicle-treated control, it means that the investigated substance has the ability to alleviate IGT, probably due to enhanced glucose utilization[9]. Based on this merit, the AUC of OGTT data has been widely applied in animal research. The shape of the glucose curve during the OGTT is used as a reference only.

Generally, the animal subjects of these studies were maintained in a room under constant temperature and humidity, receiving standard chow. The FPG levels were stable without critical variations between animals, which is quite different from those of individuals in clinical practice. However, the FPG level can be affected by the use of agents in animals receiving a repeated daily treatment for several days; this has pharmacologically been termed as a “chronic effect”. Unlike in clinical practice, the changed FPG cannot be ignored, as described previously[10]. An agent, either a chemical compound or a natural product, may interrupt glucose homeostasis during chronic treatment[30]. Fortunately, no report has applied the iAUC in animals receiving such chronic treatment[8]. This means that researchers understand the situation regarding changes in glucose homeostasis induced by an agent during chronic treatment. Therefore, the AUC is generally used in all reports including samples that show a critical reduction in FPG after chronic treatment in diabetic animals.

Moreover, the plasma insulin level during the OGTT has also been a focus of basic research. Hyperglycemia may stimulate higher secretion of insulin to result in an increase in the plasma insulin level. Therefore, the shape of the insulin curve in parallel to that of the glucose curve may assist as a reference for the condition of insulin secretion and/or insulin sensitivity. However, it is difficult to assess changes in insulin potency in clinical practice, and there is a gap in the current scientific literature on insulin stability.

Overall, the OGTT in clinical practice is not the same as that used in basic research, as shown in Table 1. However, the merits of the OGTT for diagnostic use in clinics and for screening activity in basic research have been applied for many years[11]. The glucose curve supplies a brief indication of insulin sensitivity and secretion on the blood glucose level after a fixed glucose load. A 2-h 75 g OGTT is widely applied in clinical practice, and the same has also been applied in basic research, except the loaded glucose amount was modified. When the OGTT is revised to 30-min or 1hPG in clinical practice, the protocol of the OGTT in basic research should also be improved.

Table 1 Differences in the oral glucose tolerance test used in clinics and in basic research

Subjects	Clinical Practice	Basic Research
Main aims	Diagnosis	Assay of responses
Applications	75 g for 2hPG	2 g for 2hPG
New method	75 g for 30 min or1hPG	Unknown
Identification	Shape of curve	Calculated AUC
Fasting PG	Important	Included
Plasma insulin	Reference	Important
Conscious	Clear	Anesthesia
Cost-effective	No	Yes
Interpretation	Diet and exercise	Pain sensation
Circadian factor	Yes	Can be regulated
Bias	Allergy to glucose	Artificial errors
Fasting concerns	Yes	No
Reproducibility	Not so good	Reliable
Drug interaction	Yes	No
Indications	Anemia or borderline PG	Less
Others	Age or renal glycosuria	Genetics

1hPG: 1-h post-glucose load glycemia; 2hPG: 2-h post-glucose load glycemia; AUC: Area under the curve; PG: Post-glucose load glycemia.

OGTT IN PERSPECTIVE

The FPG, 2hPG, and HbA1c have been indicated to have performance limitations that seem to make them unsuitable for the diagnosis of high-risk individuals[11]. An alternative method is consequently required. Therefore, a 30-min or 1hPG OGTT has been suggested, using a level of ≥ 8.6 mmol/L (or 155 mg/dL) as the criterion in clinical practice[17]. Recently, diabetes prediction models using the OGTT with or without other metabolic risk factors have been reported. A historical cohort study compared the future risk for diabetes among groups using the insulinogenic index [31]. The time to glucose peak could be a valuable epidemiological tool to indicate β-cell function in populations with a high risk of diabetes[32].

New biomarkers in circulation after glucose loading are also helpful in the diagnosis of T2DM. Fasting is important to the assay but is not favored by the individuals who received the OGTT. Therefore, circulating biomarkers less influenced by food and/or feeding are more useful. These biomarkers remain to be found and developed in the future. It has been demonstrated that the output of incretins, including glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, is negatively associated with higher IR biomarkers, such as: HOMA-IR, fasting insulin, and fasting free fatty acid levels[33]. However, endogenous incretins are regulated by glycemia, particularly intestinal glucose[34]. Therefore, incretins seem unsuitable for use as biomarkers in clinical practice. Otherwise, delay in the glucose peak time in individuals shows a gradual aggravation in glucose metabolism and a decrease in insulin sensitivity and/or secretion[35]. However, the peak and decline in plasma glucose levels during the OGTT reflect the interplay between multiple factors. Thus, application of the OGTT seems limited in the study of the pathogenesis of T2DM without other indicators as described above.

Reactive hypoglycemia (RH) has been mentioned in clinical practice, probably due to gastrointestinal dysfunction or insufficiency that leads to relative insulin secretion or increased insulin sensitivity[36]. Obese individuals have higher rates of RH after a prolonged OGTT in clinics. Hypoglycemia may be due to a variety of reasons, such as increased endogenous insulin, low secretion of anti-insulin hormones, or organic lesions such as insulinoma, proliferation of islet β cells, or drug-induced hypoglycemia caused by overtreatment in patients with diabetes[37]. Biomarkers involved in RH remain obscure and could be a good target to develop.

Osteocalcin levels are negatively associated with glucose[38]. People with diabetes have lower levels of osteocalcin, higher levels of glucose, and lower levels of insulin when fasting. During the OGTT, both bone resorption markers and bone formation markers decrease within 20 min[39], although insulin does not increase osteoblastic production of osteocalcin in healthy humans. Therefore, endogenous substances regulated with glucose homeostasis may be suitable for development as biomarkers.

Machine learning has been reported to be capable of predicting glucose tolerance [40]. A support vector machine along with a rule-based explanation was documented for extracting features from OGTT data for the prediction of diabetes[28]. The features deduced from the plasma glucose concentrations provide the optimal feature subset and have the strongest predictive power for the future development of T2DM. This may provide a complementary and cost-effective tool for clinicians to screen outcomes. Moreover, the prediction of IGT *via* machine learning could also be employed to fill in IGT status when the OGTT is technically not possible or to estimate retroactively IGT status from stored fasting samples[40]. Due to this minimization of the limitations, machine learning is helpful in clinical practice.

CONCLUSION

There is no doubt that the OGTT is a useful tool; it has been applied since 1885, when it was proposed. It will continue to be used in the future with mild improvements, made by step by step. It has been widely suggested in recent years that the duration of the OGTT should be shortened to use the 30-min or 1hPG. The glucose level obtained from a single OGTT could be a valuable tool of high clinical significance and could enhance prediabetes risk stratification. The derived problem, including the calculation of the AUC, shall be a concern in the future. Basic research has also applied this tool with different aims. It is still uncertain whether or not a shorter version of the OGTT is suitable for animals. Altogether, the OGTT will be able to be applied continuously from bench to bedside without hesitation once each problem has been addressed.

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