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DIABETIC Medicine

REVIEW

Are all glucose solutions used for oGTT equal?

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Abstract

Aims: Oral glucose tolerance tests (oGTT) are widely used for the diagnosis of diabetes. It is well known that the reproducibility of oGTT is poor and that a number of factors have an impact on the outcome of this diagnostic test. It appears as if one aspect, the oral glucose solution (OGS) used has not achieved much attention. Very little is published about this, despite the fact that apparently most often not a pure and freshly prepared glucose solution is used but a ready-to-use solution prepared by a (pharmaceutical) company.

Methods: A literature search was performed to find respective publications.

Results: It appears as if no or only a small number of not adequately designed clinical-experimental studies have been performed comparing different OGS head-to-head.

Conclusions: The composition of such OGS, including the excipients added to improve taste and smell, can have an impact on blood glucose increase after drinking the given OGS. Such factors can also have an impact on endogenous insulin secretion. If significant differences in the blood glucose excursions exist depending on which OGS is used, this calls for the use of a standardized OGS in oGTT to have a comparable outcome everywhere.

KEYWORDS

diabetes diagnosis, diagnostics, oral glucose tolerance test

1 | INTRODUCTION

Diagnostic tests for the diagnosis of diabetes are done millions of times per year worldwide. Usually, a certain amount of glucose solution is given to the test subject to challenge their metabolic system: The oral glucose tolerance test (oGTT). This is relatively easy to perform test to diagnose diabetes; however, to have a reproducible outcome (= having the same diagnosis when the test is repeated in the same subject), test performance requires fulfilment of quality criteria to avoid false results.[1] In view of the constant rise in the number of diagnosed patients and the many patients without a diagnosis, a reliable diabetes test is of high relevance. This also holds true for pregnant women that might develop gestational diabetes mellitus.

The (relative) increase in blood glucose (BG) subsequent to drinking an oral glucose solution (OGS) is measured, when the BG increases above certain cut-off values in the hours after starting this diagnostic test, this is indicative of diabetes.[2] It is well-known that many factors have a profound impact on the "quality" and outcome of the oGTT, e.g. adequate preparation for the OGTT (diet recommendation, no smoking, limited physical activity, no infections, etc.). Also the quality with which BG is measured, how often this is measured and the blood samples are handled (adequate test tubes should be used to avoid glycolysis/pre-analytical handling) has an impact on the outcome.[3-6] In addition, a number of physiological factors (like gastric emptying) are also the reason for the well-known high intra-individual variability of the oGTT;

however, factors that have an additional influence on this variability should be avoided as good as possible.[7]

There are numerous guidelines, chapters in textbooks, publications, etc., about the oGTT and how to perform this test; however, it appears as if one aspect has received limited attention and this is the OGS itself. Nothing specific about how this solution should be prepared is presented in the literature, also not in the otherwise quite detailed WHO standard consisting of 50 pages or in other literature.[8-10] A PubMed literature search provided a limited number of hits with a focus on the OGS (search items: "diabetes oral glucose test diagnostic test"). Many of the published studies are >40 years old or had questionable study designs with small sample sizes, etc.[11] It appears as if no recent systematic evaluations of the BG excursions induced by (various) OGS products has been performed.

This apparent lack of interest in OGS might be driven by the—speculative thought—that everybody assumes that dissolving some spoons of "sugar" in a given amount of drinking water is a no-brainer. Clearly, sugar is a readily dissolvable disaccharide of glucose and fructose; however, in contrast, pure glucose does not readily dissolve in water. In practice, not only freshly prepared OGS (with a number of issues, see below) are used. There are a variety of commercially available ready-to-use OGS products that are used in many countries regularly. Nevertheless, no information about which type of OGS is used in which country, type of practice, research project, etc., could be found. Thus, like with many other aspects of the way oGTT's are performed in daily practice, not much is known about OGS and in which way this substance might influence the outcome of an oGTT.[12] One large clinical trial which provides the basis for most recommendations and guidelines for the treatment of women with gestational diabetes, the so-called HAPO study, provides much relevant pieces of information (e.g. about the relevance of adequate preanalytical handling of blood samples); however, a ready-to-use OGS (Trutol) was used in this study and the OGS preparation as a topic on its own was not discussed.[13]

The aim of this manuscript is to discuss different aspects of OGS that might be clinically relevant and to stimulate some interest in this topic.

What is already known?

Oral glucose solutions are mandatory for oGTT; however, no details about how rapid the glucose is absorbed when it is freshly prepared or a ready-to-use solution is used can be found in the literature. Also, no information about the impact of excipients added, etc., on glucose absorption could be found.

What this study has found?

It appears if little attention was paid that far on the impact of the oral glucose solution and if this is freshly prepared or ready-to-use on the outcome of this important diagnostic measure.

What are the implications of the study?

It should be studied in adequately designed studies, i.e. with a head-to-head comparison, what the glucose profiles with different glucose solutions are. Attention should also be paid to other factors that might have an impact on the insulin/glucose response induced.

2 | WHICH TYPE OF OGS IS USED IN WHICH COUNTRY?

To receive some information about which type of OGS is used in other countries, I contacted some selected colleagues in other European countries (besides Germany) and the US in the year 2019 about which OGS they are using in their practice/hospital for oGTTs. This induced most often the same initial reaction(s): 'I have no clue... We always use XYZ... I have never thought about this...'. It appears as if the OGS receives no attention at all, this is regarded as a 'commodity'. The more detailed responses were:

- In the Netherlands, a ready-to-use solution from the local pharmaceutical manufacturer Added Pharma is apparently used (https://www.addedpharma.com/nl/pharma-producten/farmaceutische-middelen).
- In Denmark, glucose is weighed out in hospitals and mixed with water immediately before use. In practice, a ready-to-use solution is used, but it is not clear which one.
- In Austria, the ready-to-use solutions Trutol (https://www.thermofisher.com/order/catalog/product/401009P#/401009P) or Glucoral (https://www.germania.at/produkt/glucoral-75-citron) are used. Glucose is probably also weighed out and dissolved.
- In Portugal, the ready-to-use solution, TopStar is offered, which is available both as a 75 g solution (75 g/300 ml) and as a 50 g solution (50 g / 200 ml). Either orange or lemon flavour is added to it. This solution is also sold in Norway, but there at a price of about 5 Euros.
- In the US, the ready-to-use GlucoCrush Glucose Tolerance Beverage by ThermoScientific (https://www.cardinalhealth.com/content/dam/corp/web/documents/brochure/CardinalHealth-GlucoCrushSellSheet.pdf) is used at least at one specialized centre

TABLE 1 Properties of different OGS products.

Content	Reconstitution (freshly-prepared)	Accu-Check Dextro O.G.-T	Trutol 75 (HAPO)	Topstar Glucose High Concentrated Solution 'Lemon' or 'Orange'
Glucose	75 g pure glucose (or 82.5 g glucose monohydrate)	Mixture of mono- a. oligo saccharides	Glucose	Dextrose monohydrate (50 g/75 g or 100 g ready-to-use in 200 or 300 ml)
Additives	None	Currant juice	Citric acid, tropical fruit bowl, natural and artificial	Fruit Punch, Orange, Lemon and Cola
Water	Tap water	Purified	Purified	+
Conservation	None	K-Sorbat (E202)	Na-Benzoat (E211)	Sulphated ash >0.1% Chlorides (p.p.m)
Waste	Small plastic bags	Glass bottle, no recycling	Glass bottle	Cristal-PET

in Chicago.

It appears as if in many countries ready-to-use OGS are used; however, this is clearly not a systematic evaluation. One also wonders which type of OGS are used depending on their economic situation, i.e. are ready-to-use OGS more often used in developed countries or not?

3 | FRESHLY-PREPARED ORAL GLUCOSE SOLUTION

If water-free glucose is used for the preparation of freshly prepared OGS, which is not very well soluble, i.e. it requires constant stirring when the powder is slowly given into the water (never the other way round!). If glucose monohydrate is used, which is better soluble, the weight of the water has to be taken into account, i.e. 82.5 g has to be used to have 75 g glucose (Table 1). The type of water used to dissolve the glucose is probably most often tap water, i.e. not filtered or carbonated water.

Preparation of fresh OGS has some disadvantages:

- The possibilities for inaccuracies in the preparation of this solution are numerous (this requires the precise measurement of the added liquid) and require a suitable, draft-free workplace so that no glucose powder is blown away.
- It is not easy to completely empty the sachets containing the weighed amount of glucose monohydrate and to pour any powder adhering to the plastic surfaces into the drinking cup.
- In many cases, sediment of glucose will remain in the cup if the glucose solution is not stirred carefully and until the glass is completely empty. It is a challenge for practice teams to ensure this happens, especially when accompanying multiple patients to perform the oGTT.
- Mixing the glucose solution in the laboratory of a busy practice can present a hygiene problem. Suitable premises are de facto not available in smaller practices and clinics.
- This is a time-consuming procedure that requires personnel with certain skills.

An advantage of freshly prepared OGS is the lower costs for the health insurance; however, the time consumed by the pharmacist and the practices is not reimbursed.

3.1 | Quality checks on OGS practices

Due to the fact that no respective publications could be found, it appears as if no systematic evaluations of the glucose content in freshly prepared OGS were performed.

Such measurements would not only provide information about how much glucose is truly in freshly prepared OGS, but also about the variance between OGS prepared in the same practice on one day and from days-to-day. This would require that from each and every OGS that is prepared and used for oGTT in a given practice over a period of time (weeks or months), a small sample is collected in adequately sealed test tubes and sent to a central lab (this represents a kind of quality check or proficiency test ('Ringversuche'/ ring trials)). To be able to measure the high glucose concentration in the OGS adequately (usual laboratory glucose measurement methods are optimized to measure relatively low glucose levels), a respective measurement procedure has to be set-up that allows measurement of such glucose levels with sufficient quality.

4 | READY-TO-USE ORAL GLUCOSE SOLUTION

Most probably worldwide, a number of different ready-to-use OGS exist. Some are listed in Table 1; however, many others (like Lucozade, Glucolemon, Glucorange, Rapilose, Hycal, Dextropak) are not listed.[6] Excipients (like benzo hydrate or citric acid) are also added to improve the stability of OGS.

A major reason for using ready-to-use OGS is that it does not require a member of the team to handle the procedure, which should be outlined in a SOP, in an appropriate manner. To handle the preparation of one freshly prepared OGS in a given period of time might be doable; however, most often a number of oGTT are performed in parallel in the morning hours because the test subjects should be fasting. The use of ready-to-use OGS reduces the burden on the nurse or whoever performs the oGTT and also the risk of handling mistakes. There are also reports stating that pregnant women prefer ready-to-use OGS due to a lower incidence of associated nausea and that the variability of the incremental areas under paired tolerance curves was lower with this in comparison to a freshly prepared OGS.[14]

It is of interest to note that one ready-to-use OGS that was widely used in Germany until recently (Accu-Chek® Dextrose O.G-T., Roche Diabetes Care, which is not commercially available anymore) is not a pure glucose solution, but a mixture of mono- and oligosaccharides that after enzymatic cleavage represents 75 g of water-free glucose.[11,15] The advantage of using such a solution, which also contains black currant juice, is the better taste and smell. This OGS also contains 3.5–4.3 mmol (136–169 mg) potassium and a small amount of alcohol (0.01–0.06 Vol.-%). The disadvantage is the higher viscosity of such a preparation ("syrup"), making it somewhat more difficult to drink.

When this ready-to-use OGS was developed, the pharmacodynamic properties of this were compared to that of a pure glucose solution in some publications.[11,15,16] These studies report no significant differences between the two OGS; however, this similarity in responses can be due to an insufficient study design. In some studies, differences were seen when different ready-to-use OGS were compared, additionally, there is also a recent study, in which differences between the effect of ready-to-use OGS and pure glucose solutions were found.[14,17-20] The absorption of maltose (a two-glucose disaccharide) or starch hydrolysates in the gut appears to be slower than that of glucose itself (but more reproducible); however, the side effects (see below) are massively reduced, especially in pregnant women.[14,17-19,21]

In Germany, recently a proposal for a standardized and quality-controlled ready-to-use OGS was published.[22] If such a OGS would be used statewide and paid for by the health insurance companies, then this would be an important step forward.

5 | 'SIDE EFFECTS' OF OGS AND COMPLIANCE

In practice, other aspects of OGS are also of high relevance:

5.1 | Impact of psychological aspects/ stress

Participation in the oGTT is a kind of stress for the subjects, i.e. they will have an increase in cortisol levels, growth hormone and epinephrine. This (and other factors) might influence gastric emptying, i.e. the speed with which the OGS is transferred into the gut and the glucose is absorbed. No current references could be found that evaluated such aspects.

5.2 | Nausea/vomiting/syncope

After drinking the OGS (especially when drinking freshly prepared pure OGS) at least a subset of the subjects shows side effects like nausea, or even vomiting or loss of consciousness due to a vasovagal syncope; however, no data are available about how frequent such "side effects" show up in daily practice. Especially for pregnant women, the oGTT represent a challenge because they should be fasting for at least 8 h and are not allowed to drink something during the oGTT.[23] The nausea is associated with delayed gastric emptying caused by the high osmolality of the glucose solution. The rapid

absorption of a relatively large amount of glucose whilst being in a fasting state induces physiological reactions. Such events require termination of the oGTT and repetition on another day. If such 'side-effects' show up, they disrupt the usual procedures in the practice and might induce a negative feelings of other subjects being also in the practice for an oGTT.

5.3 | Taste/smell

In this context, the taste and smell of the OGS are important factors, they can influence the speed with which the OGS is drunk (should take place within 3–5 min) and if all of it is drunk. Certain flavours (aromas) are added to ready-to-use OGS (also to freshly prepared OGS?) to improve taste and provide a good smell; however, it is not known if such excipients have an impact on endogenous insulin secretion (no study investigating this topic could be found). As this secretion is also triggered by smell and anticipation of eating, this might be the case, which in turn has an impact on BG levels measured.

5.4 | Prevalence of such side effects

It appears as if no data exist about the prevalence of such 'side effects', i.e. no published data could be found in a literature search. Probably they are more prevalent with freshly prepared OGS in comparison to ready-made OGS.

6 | COSTS

Glucose is an affordable product; however, at least in some countries when it is handled by pharmacies or a pharmaceutical company (to manufacture ready-to-use OGS), it is regarded as a 'drug' (and not as a food product). In this case, glucose must be manufactured, transported and stored according to the regulatory quality requirements combined with such a status. If the preparation of the OGS is done by a pharmacist, the costs for OGS might be higher than that of commercially manufactured OGS.

It would be of interest to evaluate the costs of freshly prepared vs. ready-to-use OGS; there might be considerable differences between countries but also inside countries depending on a number of factors. One would assume that the costs can be reduced if one or two manufacturers per country manufacture a given ready-to-use OGS in large quantities, employ a kind of industrial manufacturing.

The vast majority of people with diabetes live in developing countries. Measurement of HbA1c is too expensive for diagnosis in such countries; however, the performance of a relatively cheap 1 h OGTT is possible. Nevertheless, this requires that a reliable method for blood glucose measurement is at hand; systems used by patients to check their glucose levels are not adequate. The major question (cost-effectiveness) is whether the OGTT identifies a population as having diabetes that has a higher risk of micro- and macrovascular complications than the HbA1c (or vice versa).

One aspect in favour of ready-to use OGS is that the risk of (human) errors in preparation is massively reduced, which is an important safety aspect. If each practice is using its own SOP, this can be the source of variability in the OGS manufacturing that one would like to avoid.

7 | EVIDENCE

As mentioned before, a literature search did not provide hits for an up-to-date comparative study evaluating different OGS products. It appears as if no results from an investigation under controlled clinical-experimental conditions have been performed to clarify the following questions:

- Are there differences in the BG-increasing effect and the increase in circulating insulin concentrations between different ready-to-use solutions?
- Is there a difference in the frequency of side effects?
- In parallel, the effect of a freshly prepared OGS containing 82.5 g of glucose monohydrate and one containing 75 g of anhydrous glucose should be studied.

In such a study, the same subjects should be tested repeatedly under identical conditions; however, it has to be acknowledged that to fulfil this requirement is more difficult than it might appear. The behaviour of the subjects on the days before the testing (e.g. with respect to physical exercise) is highly relevant to establish comparable starting conditions on the different test days. For example, the diet the study subjects eat (e.g. consuming a sufficient amount of carbohydrates) before the oGTT should be similar for several days because the pre-test diet can affect the outcome of this test. Ideally, such a study would be performed with healthy subjects and subjects with a range of prediabetic glucose disorders. Another option is to carry out a randomized controlled trial. Ideally, both approaches would be carried out to obtain information on the inter- and intra-individual variation.

On the different test days, different ready-to-use OGS would be administered in random order plus freshly-prepared OGS (with and without flavours). It would also be

of interest to study how intra-individually reproducible the glucose excursions are, i.e. the same OGS should be given on, e.g. three study days to the same subjects (probably only a sub-set of these). An issue is that day-to-day physiological differences in gastric emptying and insulin secretion (glucose handling) might have a larger impact of glucose excursions after drinking the OGS than differences in composition of the OGS, which in turn might be a reason for the well-known high variability in the reproducibility of oGTT. Administration of the same OGS on three consecutive study days will help to understand how much variability is due to physiological changes. Conditional on the non-optimal reproducibility of the oGTT, even when the general conditions are closely followed, such a study will require a relatively large sample to be able to distinguish differences between the various glucose solutions. To avoid that such a study is (severely) underpowered and without knowing if there is a "true" difference between OGS—whilst having a clear physiological day to day variations—providing a good estimate of the effects of various OGS is difficult. However, if no (significant) differences in glucose excursions in a well-designed and executed clinical study can be seen with 30 or 40 subjects, the magnitude of the effect can be assumed to have no clinical relevance. The study should include a measurement of the 1 h glucose value. Current research suggests this to be a valid predictor of diabetes risk. In future, a shorter 1-h OGTT may be the standard. Also, HbA1c should be measured and compared with the 1 and 2 h glucose values.

Such a study would be of tremendous help to understand if the "glucose" in the different OGS is absorbed in a comparable manner in the gut and induce the "same" glucose excursions.

If there are differences in glucose responses after administration of ready-to-use OGS, this may be due to the flavours added to them. It is possible that these have an effect on insulin secretion. It is not investigated whether it makes a difference in the BG increasing effect if the glucose is dissolved with 100, 200 or 300 ml of water during self-preparation. Clearly, the less water, the more difficult it will be to dissolve. The speed of dissolution will also depend on the temperature of the water used, i.e. it will go easier with warm water.

A key question is, who is willing to sponsor such a study?

8 | CONCLUSION (= CALL FOR ACTION)

- It appears as if the OGS for the oGTT was not regarded as a relevant pre-analytical variable that far and the main reason for this might be that the use of different OGS products is not an issue at all; however, as long as nobody has looked into this with appropriate measures, we don't know if this is an issue or not.
- A diabetes diagnosis has far-reaching consequences for the patients, their social environment and the health care system. To avoid the risk of a wrong diagnosis as good as possible, it should be better understood what the impact of the OGS is. In case the type of OGS used is of relevance, a standardized OGS should be used.
- In case of a "wrong" diabetes diagnosis (e.g. in a woman with GDM), one can foresee that lawyers ask for the impact of the OGS on the diagnostic test result. Without good data from appropriate studies, the discussion might become difficult.
- A clinical-experimental comparative study should be performed that validates the different OGS.
- Clearly, the poor reproducibility of the oGTT is driven by a number of factors, may they be patient-driven or by the test situation (= OGS), potential sources of error should be minimized.
- In case different ready-made OGS have an impact on the glucose profiles induced, it is at least a consideration that the numbers given for diabetes prevalence for different centres/countries might differ from each other as a result of this factor. If this is the case, then the same OGS should be used worldwide to avoid this issue. This would be an issue the WHO would be interested in. An outcome might be that an evaluation of OGS is initiated in different countries to have a better understanding of what is going on.
- Maybe different countries can continue to use what they like as long as their OGS is traceable to a higher order reference OGS solution. Or a higher order substance(s) that is/are dissolved and a higher order liquid that it is dissolved in.
- The view on the relevance of the OGS might differ between medical specialities, i.e. for a GP dealing mainly with a diabetes diagnosis in patients with type 2 diabetes, the approach might differ from that of a gynaecologist who is mainly concerned with GDM diagnosis in women or a specialist diabetologist/endocrinologist focusing on patients with type 1 diabetes.

9 | RECOMMENDATIONS

- WHO and other organisations such as national diabetes associations and International Diabetes Federation might be roped in to standardize this aspect of the oGTT.
- A standardized OGS should be used to reduce the variability of at least one of the many factors that have an impact on the outcome of the oGTT.

- In case a standardized OGS is used, large-scale manufacturing of this, e.g. a pharmaceutical company should be of help to cut down the costs for such a solution drastically.
- A SOP for the performance of oGTT should exist in every practice that performs such diagnostic tests, also addressing the OGS.
- In light of advances in personalized medicine, novel testing alternatives should be considered. Epigenetic biomarkers might give an indication prior to the development of clinical dysglycaemia.

10 | OUTLOOK

In view of the limitations of the oGTT the question is about alternative procedures for the diagnosis of diabetes.

For a number of years, HbA1c measurements are employed for diabetes diagnosis. However, it is not clear to which extent measurement of this parameter is truly used for diabetes diagnosis. This parameter avoids many issues of the oGTT (single blood draw only, subjects must not be fasting); however, estimation of the HbA1c has its own issues.[24,25] Several studies have shown that the overlap between HbA1c and glucose-based diabetes diagnoses is low (e.g. 30% defined by both criteria).

It might also be, that in the future, systems for continuous glucose monitoring (CGM) will be worn by the test subjects for a couple of days. Analysis of the glucose profiles might provide a good/different insight into their glycaemic status.

A very different novel approach is a non-invasive bloodless test for diagnosing diabetes. It is still being investigated, but it is a potential breakthrough because it uses an app instead of a blood draw.[26,27]

CONFLICTING OF INTERESTS

LH hold shares in the Profil Institute for Metabolic Research, Neuss, Germany. LH is a consultant for a range of companies that develop new diagnostic and therapeutic options for the treatment of patients with diabetes.

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