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CLINICAL APPLICATIONS

An Analysis of How to Measure Glucose during Glucose Clamps: Are Glucose Meters Ready for Research?

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Abstract

This article provides a perspective on the challenges of appropriate glucose measurement in the context of glucose clamp experiments. In a first step, the core outcome parameters of a clamp experiment, the blood glucose target level, and the glucose infusion rate will be identified. The relation of these core parameters to glucose measurement are discussed. From there, the core quality parameters of glucose measurement within a clinical research setting are identified and assessed in light of their practical implications, with a specific consideration of the work presented by Cohen *et al*. in this issue of the *Journal of Diabetes Science and Technology*.

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Since their introduction into the arsenal of metabolic research tools by DeFronzo *et al*. in the late seventies,[1] glucose clamps have increasingly gained importance. Based on this technical principle, including its variants, e.g., hyperglycemic, euglycemic, and hypoglycemic glucose clamps, a great variety of different scientific topics can be tackled. For example, by means of the glucose clamp technique, both whole-body and organ-specific insulin sensitivity can be measured, predefined blood glucose concentrations for various purposes can be generated, and most importantly, blood glucose properties of almost any antidiabetic drug can be characterized with respect to their time-action profile. The latter can be done with a high level of precision and accuracy so that authorities like the European Medicines Agency regard glucose clamps as the gold standard for the investigation of new blood glucose-lowering drugs.[2]

Beyond a specific experience in how to manage a glucose clamp, which is sometimes referred to as an "art," the key factor for the success of each and every glucose clamp is the frequent, fast, and reliable measurement of the subject's actual blood glucose. This is of huge importance as the deviation of actual blood glucose from blood glucose target level provides the signal on which the computation of the amount of glucose to be infused intravenously, aiming to adjust actual blood glucose to the predefined blood glucose target, is based. Meaning, the actual data from blood glucose measurements represent the input variable for some form of algorithm, either software or investigator based (the latter is also called experience, which will then determine the amount of glucose to be administered until the next blood glucose measurement is due).

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Abbreviations: (FSM) Freestyle Mini™, (QC) quality control

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The principal objective of this approach is to maintain blood glucose during glucose clamps both stable and close to the blood glucose target, i.e., to minimize deviations of the actual blood glucose from the target value. Based on inaccurate blood glucose measurements, however, it becomes quite easy to under- or overestimate true glucose requirements of subjects, leading to potential study endpoint bias. Most obviously, flawed study results could turn into misleading conclusions about the properties of a drug or a device in development.

This issue's article from Cohen *et al*. addresses a relevant issue in that their study looks into the question if the FreeStyle Mini™ (FSM) blood glucose analyzer, a device designed as a meter for the measurement of a patient's capillary blood, is suitable for clinical research purposes in glucose clamp protocols. The FSM is not a marketed device in the United States but can be compared with the FreeStyle Lite™ from the same manufacturer.

First of all, Cohen and colleagues, as we do, rightly identify the need for accurate, rapid, and economically feasible measurement devices for research purposes, in particular, for glucose clamps. Based on their study findings, they do conclude that the FSM is such a device and is suitable for use in glucose clamp protocols. In response, we would like to apply some challenges to that conclusion: first, by asking questions that we believe should be answered before joining Cohen and colleagues in their conclusions and second, by providing some thoughts based on our experience in the field.

Like Cohen *et al*., we do acknowledge that performance criteria for a medical device intended for clinical home use may not necessarily be appropriate for its employment in clinical experimental studies. Devices utilized in a clinical research setting should be comparable with the gold standard in all aspects of their performance. Hence, for a device to be introduced into clinical research for the first time, a validation process should be performed, reflecting a clinical point of view (error grid analysis), a statistical approach (e.g., accuracy and precision), and its adherence to the recommendations of scientific societies, in this case, the American Diabetes Association.

The results of the error grid analysis with 99% of readings for the FSM in Zone A unequivocally indicate an excellent performance of the FSM—albeit from a clinical perspective only. Looking at the data from a more challenging scientific perspective, however, leads to a somewhat different appraisal. A mean absolute difference between a handheld device and a reference method of 13.0 mg/dl corresponding to a percentage difference of 5.8% may very well be regarded as not sufficiently reliable to justify its use in a clinical experimental setting. For example, in the context of a glucose clamp study, a mean deviation of approximately 6% between the blood glucose readings on the basis of a meter and the measurements performed by a reference method would result in a substantial under- or overestimation of the subjects' glucose requirements. This false estimation, in turn, would result in an even more substantial under- or overdosing of the amount of glucose to be infused intravenously in the aim to maintain the blood glucose at the target level. It should be emphasized that a 6% *mean* deviation between the meter and reference method-based measurements represents a systematic bias, which for the case of glucose clamp studies, would primarily hamper the comparison of results between studies in terms of the absolute amount of glucose infused. The comparison of different treatments within a study, in contrast, would not be affected.

In addition to the concerns related to the mean difference between FSM and the reference method it is worth it to consider these differences separately in a low glycemic, near-normoglycemic, and high glycemic range—simply because many glucose meters are known to have larger differences relative to the gold standard the further away the actual blood glucose is from the normal range. Hence, clustering the performance evaluation of a meter into distinct ranges should be the approach to address and assess these range-specific glucose meter performance differences. Regrettably, no data are provided in that respect in the article of Cohen and coworkers. A corresponding subanalysis would be desirable.

In addition to the validation procedure of a medical device intended to match a reference method, two other aspects deserve mentioning when comparing the new method with the reference method. The first relates to costs, and the second relates to specimen management. In the setting of our institute, the cost per glucose measurement by means of a standard laboratory glucose analyzer is approximately 10 cents per sample (probably a little bit less than that), including all consumables. The cost per test strip for most glucose meters, including the FreeStyle brand, is usually above 50 cents. Specimen management, in contrast, is very easy with the FSM, which does not require any preanalytical specimen processing before the measurement, which certainly represents a "convenience plus" for the FSM.

Finally, we would like to discuss an issue that is rarely, if at all, addressed in the context of medical device comparisons: quality control (QC) procedures and

resources. Obviously, laboratory results can only be regarded as reliable if appropriate QC procedures are performed in regular intervals. In the case of blood glucose measurement, these procedures include, but are not limited to, device calibrations (preferably performed as a two-point calibration), periodic accuracy tests in order to exclude systematic errors, precision controls, and last but not least, determinations of intra-assay device variance. Unfortunately, Cohen and colleagues did not allude to any QC aspects in their comparison of FSM and YSI—which we would recommend when discussing the pros and cons of various devices.

In summary, we are not convinced by the results of Cohen and co-workers to an extent that would make us want to give up on utilizing gold standard laboratory methods for glucose clamps, knowing that we may have to compromise on the issue of convenience to be very sure that we are applying the most precise, accurate, and reproducible method at an unbeatable price.

References:

1. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol. 1979; 237(3):E214–23.
2. European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products. Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus. CPMP/EWP/1080/00. 30 May 2002.