clinically apparent that when blood glucose is <3.9 mmol/l point accuracy should be given more emphasis than rate accuracy. A strength of CG-EGA is its ability to vary the input of either rate or point accuracy to overall clinical accuracy depending on blood glucose range. Third, the results of CG-EGA vary with time intervals. This is also an intuitive strength of CG-EGA, which is designed to account for increased noise associated with frequent sampling. We advocated (2) adopting a uniform sampling protocol with reference and/or sensor pairs taken every 10–15 min to standardize comparisons of rate accuracy, which is a sampling scheme based on physiological considerations of possible glucose change rates. Fourth, Wentholt et al. (1) questioned the appropriateness of the formulae to shift point EGA based on interstitial time lag. However, the authors reported an average time lag of ~7 min in one of their sensors, which is identical to that assumed for CG-EGA, thus confirming that ~7 min is a reasonable average for blood-to-interstitial diffusion delays. CG-EGA software allows setting this parameter to any value <7 min.

We are pleased that both the discussion regarding CG-EGA and the analysis of time series data have begun, and we look forward to continuing this important dialogue. However, we also recommend careful consideration of basic statistical assumptions when analyzing sensor-generated glucose data; their inherent temporal structure should be taken into account.

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DOI: 10.2337/dc06-1901

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A Critical Appraisal of the Continuous Glucose–Error Grid Analysis

Response to Clarke et al.

We thank Clarke et al. (1) for their thought-provoking response to our article (2). With their comments (1), they not only took on the important issue of how to optimally assess the accuracy of continuous glucose monitors (CGMs); they moved the discussion one step further.

In our study (2), we did indeed take the statistical liberty of deriving degrees of freedom from all pooled data points—in contrast to the proposal by Clarke et al. (1) who compared the accuracy of two sensors using one average mean absolute deviation (MAD) value per patient. The latter approach may be too rigid because not all readings are interdependent. For example, postprandial glucose sensor readings at lunch and at night depend little on each other, if at all. It is common practice to derive degrees of freedom from pooled data in the sensor field. In a previous study, Clarke et al. (3) compared the accuracy of two CGMs in 16 type 1 diabetic patients by using the continuous glucose–error grid analysis (CG-EGA). The difference in pooled readings in the hypoglycemic area that ended up in zones A and B was reported to be highly significant between both sensors (88 vs. 62.8%, respectively) ($P < 0.0005$). This level of significance implies that degrees of freedom were derived from all data pairs in the hypoglycemic range (250 mg/dl) rather than from the actual amount of participants ($n = 16$). Even with a strict statistical policy, the better MAD for the microdialysis sensor in the hypoglycemic area in our study (2) (12.0% for the 7-min corrected microdialysis sensor vs. 25.2% for the needle-type sensor, calculated per patient [df = 12], $P = 0.036$ by Wilcoxon's signed-rank test) and the larger sensitivity for hypoglycemia associated with this sensor (75.0 [75 data pairs] vs. 55.9% [56 data pairs], $P = 0.018$ by Pearson's χ^2, with 16 of 16 and 12 of 15 hypoglycemic episodes detected by the microdialysis and needle-type sensor, respectively, $P = 0.06$ by Pearson's χ^2) contrasted with the CG-EGA that noted no difference (51.5 vs. 60.0% accurate readings and benign errors in the hypoglycemic range [df = 42], $P = 0.841$ by Pearson's χ^2 for the microdialysis and the needle-type sensor, respectively). Therefore, even with a mild statistical approach (i.e., deriving degrees of freedom from 43 data pairs rather than 13), CG-EGA could not confirm the different accuracy of the sensors in the hypoglycemic range.

As to the order of CGS data points, the sensor's ability to follow the rate and direction of glucose changes is nicely reflected by the MAD: A sequence of glucose values that has been incorrectly reported by a given sensor (e.g., 90 → 82 → 72 mg/dl instead of 72 → 82 → 90 mg/dl) will result in a worsened MAD.

In reaction to the comment by Clark et al. (1) in regards to time consumption, we were happy to learn that the software for CG-EGA has become available. Nevertheless, the laborious collection of frequent blood samples on fixed intervals (in addition to the construction of a rate, a point accuracy plot, and, finally, a combining matrix) will remain inevitable drawbacks of CG-EGA.

With the attempt to standardize the length of the time intervals, Clark et al. clearly tried to improve the CG-EGA methodology. Nevertheless, a time interval that can vary by 5 min (10–15 min) still leaves the door open for interobserver variability.

As to our finding in a previous study (4) of a 7-min delay that was inherent to the microdialysis instrument itself and not seen in the needle-type sensor, Clarke et al. (1) alluded to a (much-disputed) constant 7-min physiological delay resulting from the relationship between interstitial and blood glucose. This physiological delay has been reported to be anywhere between 0 and 30 min, so the 7-min assumption made for the CG-EGA is questionable. Fortunately, Clarke et al. have now implemented into the software the possibility of setting the delay <7 min.

Currently, the optimal way to assess a CGM seems to be the combination of MAD calculated per glucose range, com-

bined curve fitting with assessment of horizontal and vertical shift, sensitivity, and positive predictive value for detecting hypoglycemia.

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DOI: 10.2337/db06-2157

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Breast-Feeding and Risk for Childhood Obesity

Response to Mayer-Davis et al.

The study by Mayer-Davis et al. (1) reflects the fact that maternal nutrition plays an important role in the pathogenesis of childhood obesity. Breast milk contains linoleic acid (of the n-6 polyunsatured fatty acids [PUFA] series) and α linolenic acid (of the n-3 PUFA series) as well as longer chain derivatives, such as arachidonic acid (of the n-6 PUFA series) and docosahexanoic acid (of the n-3 PUFA series). Maternal intake determines content of breast milk, which ultimately affects the infant's future health. Childhood obesity is probably an immune inflammatory response to a faulty diet of the mother (before and during gestation and lactation) consisting of high n-6 PUFAs, low n-3 PUFAs, and deranged n-6–to–n-3 ratio (2). In those who are breast-fed, breast milk provides longer-chain n-3 PUFAs, which prevent ectopic accumulation of fatty acids in muscle and liver (3,4). Formula feeding does not provide this benefit. Cow's milk content depends on whether it is pasture fed (more n-3 PUFAs) or given commercial feeds (more n-6 PUFAs). Breast-fed infants have a muscle membrane fatty acid composition similar to insulin-sensitive adults, and formula-fed infants have a muscle membrane fatty acid composition similar to insulin-resistant adults (5). Correcting n-6 and n-3 PUFAs in the diet is currently needed for changing global health for one and all.

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DOI: 10.2337/dc06-2243

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Breast-Feeding and Risk for Childhood Obesity

Response to Mayer-Davis et al.

We read with great interest the recent study by Mayer-Davis et al. (1) on the impact of breast-feeding on childhood obesity risk in the presence of maternal diabetes or obesity. The authors drew conclusions that seem to directly oppose previous observations from our group (2,3). However, we would like to deliver three arguments suggesting that the presented data can also be interpreted in a completely different manner and in no way exclude, but rather support, a potentially negative dose-depending effect of early neonatal breast-feeding on overweight risk in offspring of diabetic/overweight mothers, as observed by us.

First, the majority of fully adjusted estimates for the effect of maternal diabetes have 95% CIs that include decreased as well as increased odds ratios over a wide range (e.g., odds ratio 0.79 [0.29–2.16] for breast milk only vs. formula only). By statistical definition, one therefore cannot exclude the possibility that the true effect of breast-feeding on overweight risk in the presence of maternal diabetes/obesity is not beneficial but deleterious, at least in a considerable number of cases.

Second, breast-feeding during the 1st month by diabetic mothers increased overweight risk compared with formula feeding. This, in fact, confirms rather than rejects our observations. Moreover, this is unlikely to be accounted for by reverse causation, since no dose response–like relation between duration of breast-feeding and risk of overweight was observed in offspring of diabetic mothers. These data may even support our hypothesis of a crucial and probably even deleterious impact of breast-feeding by diabetic mothers during the early neonatal period.

Finally, the authors stated that our observations might reflect "appropriate" growth rather than untoward effects. This, however, does not correspond with increased prevalence of overweight in the highest tertile of early neonatal intake of diabetic breast milk, using the symmetry index (2) additionally validated against BMI (4). Most importantly, this interpretation completely ignores deleterious ef-