Invited Commentary

Continuous Glucose Monitoring; coming of age?

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Abstract

In a recent issue of the Journal of Clinical Endocrinology and Metabolism, an Endocrine Society Clinical Practice Guideline on Continuous Glucose Monitoring is published, co-sponsored by the European Society of Endocrinology (1). Such a guideline is a necessary step in the maturation of any new technology. This commentary tries to delineate where we stand some ten years after the first retrospective continuous glucose monitoring device entered the market from a European perspective.

Introduction

The Task Force evaluated three potential uses of Continuous Glucose Monitoring (CGM): 1) real-time CGM in adult hospital settings; 2) real-time CGM in children and adolescent outpatients and 3) real-time CGM in adult outpatients. Overall, it gives an excellent overview of the current status, and makes worthwhile reading.

Hospital setting

The Task Force recommends against the use of real-time continuous glucose monitoring (RT-CGM) alone for glucose management in the Intensive Care Unit (ICU) or operating room until further studies provide sufficient evidence for its accuracy and safety in these settings. The main concern here is the limited number and size of studies on sensor accuracy, with very few data in the hypoglycaemic range. Hypoglycaemia has been noted as a risk factor for mortality in the ICU setting (2). Furthermore, there is conflicting evidence on possible disturbing factors like hypotension, vasopressor medication etc. The Task Force extensively
discusses the recent controversy arisen around the use of point of care glucose measurements in the ICU. It also rightfully notes the need for reestablishing the efficacy of intensive insulin therapy in achieving tight glycaemic control, following the unexpected increased mortality noted in NICE-SUGAR(3). Of note, the first study reporting on glycaemic outcomes in the ICU, showing a lower incidence of hypoglycaemia with the use of CGM, is not discussed (4).

Outpatient use

As to CGM in the outpatient setting, the task force recommends its use in patients from all age groups above 8 years old, either to lower HbA1c or to maintain a low HbA1c while lowering the incidence of non-severe hypoglycaemia. The guideline makes a distinction between children and adolescents on the one hand and adults on the other. This distinction also follows from the results of a landmark trial in this area, the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring trial(5). In fact this trial consists of three identical parallel trials, one in children, one in adolescents and one in adults. At first glance, only adults seemed to benefit from CGM, with a significant 0.5% HbA1c decrease, as compared to the control group using self monitoring of blood glucose (SMBG) only. At closer examination, this unexpected and perhaps even disappointing outcome could readily be explained by the large proportion of participants discontinuing CGM use. In a per protocol analysis, those using the device benefited to a similar extent, irrespective of their age. Thus the following truism emerged: a device that is not used will not work. However, the fact that many users, i.e. motivated trial participants, discontinued the use of CGM illustrates this is not a magic bullet. Few relevant predictors of use could be identified. It is obvious that user friendliness, including the high rate of false-positive alarms, needs improvement. Also it
seems obvious that many people choose to ignore their disease as much as possible and live
their life as if the disease was not there, probably for right personal reasons (6).
This brings us to the question how appropriate the intention-to-treat analysis is in this field.
Intention-to-treat analysis reached a sacrosanct status due to its validity in drug trials,
especially pertaining to trials evaluating drugs prescribed to reduce a given risk. In conditions
like hypertension and osteoporosis, roughly half of those who are prescribed a drug stop it in
the first year, as determined from pharmacy databases. On top of this, there are people who
pick up their prescription, but do not take all tablets, or any tablet for that matter. Rightfully,
third party payers argue that all pills, also those not swallowed, have to be paid and that
therefore the drug should have such a powerful effect that this remains evident, also when
patients who were prescribed the drug but do not take it for no matter what reason are still
included in the efficacy analysis. Thus the intention-to-treat analysis was born. However, now
returning to the CGM field, it seems valid to take the per protocol analysis as the primary
analysis. If CGM devices are not used they don’t need to be paid for, and the number of
sensors used is readily determined by the treatment team by taking a look at the sensor results
uploaded to a website maintained by the manufacturer. However, the third party payers will
rightfully ask for cost-efficacy analyses. Only one is known to me, which is not mentioned by
the guideline (7). This analysis reports on cost-efficacy in the JDRF CGM trial, using the
intention to treat results. They estimated a price of USD 100,000 for one QALY gained,
above the cut-off level usually considered justified for new drugs or technology.
CGM was brought to the market in 1999. If one would have polled diabetes health care
providers on their expectations at that time, a reduction in the occurrence of severe
hypoglycaemia would have been mentioned by most, if not all. Disappointingly, such a
reduction was not seen, one trial even noting an increase in the occurrence of severe
hypoglycaemia (8). Reasons for this include the fact that the sound and vibration alarms are
insufficiently able to alert the user during hypoglycaemia, when cognitive dysfunction has
already set in (9). Second, devices are likely to be taken off during activities which carry a
high risk to induce hypoglycaemia, such as full contact sports. Third, despite ongoing
improvement, accuracy of current glucose sensors is still suboptimal, with a relatively high
number of both false positive and false negative alarms(10). To improve the positive
predictive value of the hypoglycaemia alarm, many patients choose to set their individual
threshold for the hypoglycaemia alarm at lower values, thereby by definition also increasing
the false negative rate. The Task Force notes a reduction in the occurrence of severe
hypoglycaemia during observational follow-up studies of the JDRF CGM trial. Possibly the
learning curve to prevent severe hypoglycaemia by using these devices takes longer than
expected. These uncontrolled observations raise hopes, but will not be convincing for third
party payers. Controlled trials in people at high risk for severe hypoglycemia, notably those
with hypoglycaemia unawareness, are urgently needed.

The task force does not mention whether the method of insulin administration (i.e., insulin
pumps versus multiple daily injections [MDI]) should influence whether RT-CGM is
supported. In adults, however, it should be noted that in all published studies (5;8;11-15) less
than 30 patients were randomized to CGM use in combination with multiple daily injection
therapy. Also, the task force abstains from commenting on the two trials showing HbA1c
improvements of 0.6 to 1.2% when using a combined insulin pump-CGM device with
mealbolus advisor as compared to MDI with SMBG (16,17). Indeed, probably this combined
device should be seen as a single integrated device, rather than as a combination of two
devices with a bolus advisor.
The task force suggests that treatment guidelines be provided to patients to allow them to safely and effectively take advantage of the information provided to them by RT-CGM. Will guidelines for how to optimally use these devices be useful? Intuitively one would expect this, but it should be noted that the most successful trials in this field just handed out the device without any education, if only because the health care providers were at the beginning of their personal learning curve (5;12).

The task force suggests that short-term retrospective CGM may be of benefit in adult patients with diabetes to detect nocturnal hypoglycemia, the dawn phenomenon, and postprandial hyperglycemia, and to assist in the management of hypoglycemic unawareness and when significant changes are made to their diabetes regimen. The task force notes some small trials who showed benefit, but ignores the largest trial on retrospective CGM (18), perhaps because results of this trial were not reported separately for people with type 1 and type 2 diabetes.

**Pregnancy**

Task Force chose not to comment on one of the most frequently mentioned indications for CGM, that is pregnancy. Based on one small but high quality trial, the use of intermittent retrospective CGM during pregnancy can be supported (19). The lack of trials in pregnancy reminds us of a similar ill foundation for the widely claimed benefits of insulin pump therapy during pregnancy. Similarly instructive is the fact that the first randomized trial of rapid-acting insulin analogs in pregnant women with type 1 diabetes was only published more than ten years after the introduction of this drug class (20).

**CGM Reimbursement in Europe**
How applicable is this guideline for Europe? It seems likely it will give further fuel to the many ongoing debates with third party payers throughout Europe. Current status of reimbursement in Europe is as follows. In Israel, children with type 1 diabetes who have experienced more than two severe hypoglycaemic episodes within one year are entitled to CGM compensation. In the Netherlands and part of Italy, retrospective CGM is currently reimbursed. The Czech Republic covers up to four sensors per year for retrospective CGM and in Sweden, real-time CGM is reimbursed for patients using CSII and experiencing two or more severe hypoglycaemic episodes per year, children who require at least ten plasma glucose tests per 24 h and patients with HbA1c >10% while receiving optimized insulin therapy. In the Netherlands, reimbursement was recently given for adults with an HbA1c persistently above 8% despite intensive treatment, children and pregnant women, all with type 1 diabetes. In addition, real-time CGM is now covered by the majority of health plans in the USA, including the federal Medicare program. Reimbursement is generally available for type 1 patients with severe hypoglycaemia or those who are not meeting American Diabetes Association HbA1c targets (21).

Conclusion

Continuous Glucose Monitoring is coming of age. If reimbursement follows the published evidence, increasing reimbursement is expected for pump patients who do not succeed in maintaining a satisfactory HbA1c, but who show that they can sustain CGM use for a certain period of time. Clinical trials in patients with hypoglycemia unawareness are urgently needed.

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