A REVIEW OF TIGHT GLYCEMIC CONTROL

There's still work to be done toward the best definition of TGC; the lab and POCT teams will continue to play a significant role.

By David Plaut

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Diabetes mellitus is associated with significant morbidity and mortality and escalating costs; its prevalence is increasing to epidemic proportions.[1] Studies have consistently documented the importance of glycemic control in delaying the onset and decreasing the incidence of both the short- and long-term complications of diabetes.[2] Unfortunately, glycemic control is difficult to achieve and challenging to maintain.

Tight glycemic control (TGC) has often been defined as a blood glucose level in the range of 80–110 mg/dL, although this is not universally used in practice. Considerable research has been conducted on the benefits and pitfalls of TGC in both in-patients and out-patients.[3]

There are two ways to mimic the release of insulin from the normal pancreas: 1) multiple daily injection therapy and 2) an insulin pump. Both are good methods. In multiple daily injection therapy, the patient takes three or more insulin shots per day. Usually, either short-acting or regular is injected before each meal and a shot of intermediate- or long-acting insulin at bedtime.

With an insulin pump, there is a constant small dose of regular insulin provided. The patient will have the pump release extra insulin when needed, such as before a meal. With either method, blood glucose levels must be measured several times a day.

Here, we review some of the clinical work to give an overview of what we know and what we need to know about monitoring the vast number of diabetics, pre-diabetics and in-patients.

ICU Impact

First consider patients in ICU. They are susceptible to sepsis, excessive inflammation, critical illness polyneuropathy and multiple organ failure, the latter often being the cause of death.[4] Most ICU patients, even those who did not previously suffer from diabetes, are hyperglycemic, which is presumed to reflect an adaptive development of insulin resistance.

Marik and Preiser[5] reviewed seven randomly controlled studies, including over 11,000 ICU patients, and found that TGC did not reduce the 28-day mortality (odds ratio 0.95) or the incidence of blood stream infections (OR 1.04). They also noted that the incidence of hypoglycemia was higher in the TGC group (OR 7.7). It appears that the relation between mortality and the proportion of calories provided parenterally is significant ($p = 0.005$).

The Leuven Study

Also consider the Leuven Intensive Insulin Therapy Trials, a study from 2003 where 1,548 ventilated, surgical ICU patients were treated with insulin infusion.[6] The randomly assigned intensive insulin therapy group received insulin infusion tailored to control blood glucose levels in the range 80–110 mg/dL, whereas the conventional treatment ▶▶

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group received insulin only when glucose levels exceeded 200 mg/dL, and in that event were maintained in a target range of 180-200 mg/dL. (Unfortunately, not all publications describe the glucose method used.) In this study, intensive insulin therapy induced a 43% reduction of intensive care mortality risk and a 34% reduction of hospital mortality (p=0.005). The treatment reduced the risk of severe infections by 46% and was associated with a 35% reduction in prolonged (>10 d) requirement for antibiotic therapy (p< 0.001). In addition, excessive inflammation was prevented. Statistical analysis indicated that control of blood glucose (BG) levels, rather than insulin administration itself, explains the observed clinical benefits.

TGC Protocols

In a study covering four years and more than 10,000 patients in a Level I trauma center, Treggiari et al.[7] used three TGC protocols:

- no protocol (no glucose limits),
- target glucose of 80–130 mg/dL and
- target glucose of 80-110 mg/dL.

The main outcomes were mortality either in the ICU or the hospital. Study authors found that insulin use increased from 9% in protocol 1 through 25% in 2 and 42% in 3. The patients in protocol 3, tighter control, had a higher mortality (OR 1.15) which occurred more frequently in those patients with an ICU stay of three or fewer days. There was a fourfold increase in the incidence of hypoglycemia from protocol 1 to 3.

On the other hand, Eriksson et al.[8] studied 2,000 adult trauma patients using a pre-TGC (80-200 mg/dL) and a post-TGC protocol (80-110 mg/dL). The mortality was significantly higher in the pre-TGC period (21.5%) compared to the post-TGC (14.7%). The glucose levels were significantly lower in the post-TGC period—131 versus 145 mg/dL, p<0.001.

Diabetes and Coronary Artery Bypass Grafting

In a study[9] from 1995 to 2008, a total of 4,658 patients with known diabetes or perioperative hyperglycemia (preoperative glycosylated hemoglobin ≥8 or post-operative serum glucose >126 mg/dL) underwent coronary artery bypass grafting. The patients were grouped into three post-operative glycemic groups: tight (≤126 mg/dL), moderate (127-179 mg/dL) and liberal (≥180 mg/dL). They found that moderate glycemic control was superior to tight glycemic control, with decreased mortality and major complications. This is remarkable, as their TGC was at least as high as some moderate glycemic controls.

These data are consistent with a study funded by the NIH in the period from 2005 to 2008,[10] at which time the study was stopped when it appeared that TGC had a 25% higher mortality for the TGC group. In the study mentioned above[8] the difference between

TGC and moderate control was a 45% greater mortality with TGC.

Unanswered Questions

Klonoff[11] proposes we need to answer several questions:

- How safe is intense insulin treatment (IIT), with various glycemic targets, from the risk of hypoglycemia?
- How tightly must BG be controlled for this approach to be effective?
- What role does the accuracy of BG measurements play in affecting the safety of this method?

For each state of impaired glucose regulation seen in the hospital, such as hyperglycemia, hypoglycemia or glucose variability, the benefits, risks and goals of treatment, including IIT, might differ. With improved accuracy of BG monitors, IIT might be rendered even more intensive than at present because patients will be less likely to receive inadvertent overdosages of insulin. Greater doses of insulin, but with dosing based on more accurate glucose levels, might result in less hypoglycemia, less hyperglycemia, and less glycemic variability.[11]

Turning from the questions of how tight glycemic control should be, we look at the role the lab plays. In the case of blood glucose three measurement methods are used: hand-held devices (POCT), paper or plastic sticks to test a drop of blood, blood gas analyzers and analyzers in core labs.

Each method is subject to specific challenges and limitations that can affect the overall system performance. Weber and Neeser[11] point out several salient facts concerning the identification and documentation of the type of the sample. They argue that fasting glucose values in venous blood are 5–10% lower than in arterial samples, while capillary samples show 5–15% higher values compared to venous blood samples. Similarly, venous or capillary plasma samples are showing 10–15% higher values compared to whole blood hemolysate. Hand-held instruments for measuring glucose have not always been found without significant error and variation. ■

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