CONTINUOUS BLOOD GLUCOSE MONITORING: A REVIEW AND PREVIEW

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Abstract

Physicians inappropriately think of blood glucose as a stable value because technology reduces a continuously varying parameter into a point-in-time measurement. Continuous blood glucose monitoring (CBGM) will force us to change this bad habit. Data management principles are suggested which will be necessary for conceptualizing the new data. The physiology of normal blood glucose fluctuations will be studied for the first time and the diagnosis of diabetes will be duly defined. Most importantly, closed loop insulin delivery systems will be capable of correcting abnormal glucose metabolism in diabetes. Thus, the development of CBGM will change our concepts of physiology, disease and therapy.

Introduction

In clinical medicine and most clinical investigation today, many continuously varying parameters are monitored by one-point-in-time measurements. This approach is adequate if the function measured varies slowly, as does body weight, height or bone density, or varies cyclically, as does basal body temperature or plasma cortisol concentration. But when a parameter changes rapidly and irregularly, single measurements are inherently inadequate. Blood glucose concentration is a case in point.

The concentration of blood glucose varies physiologically by 50% to 100% several times daily. These variations are tightly regulated by hormonal mechanisms which are necessary for the survival of the species. When the glucose regulatory mechanisms go awry, life is threatened by either hypoglycemia or hyperglycemia, the latter being diabetes. Largely because of the glucose monitoring tools available to us, we have come to think of blood glucose in static terms, as though single measurements were representative.

This paper will review the current status of blood glucose monitoring in clinical and investigative medicine, and will review progress toward a practical continuous blood glucose monitoring (CBGM) device. On the assumption that such technology will be available in the relatively near future, the paper will focus on how CBGM may change our concepts of normal physiology and disease.

Blood Glucose Monitoring

The history of blood glucose monitoring

Reliable measurements of blood glucose (actually total reducing substances) were first established early in this century. Prior to that time, diabetes was diagnosed either with complex and unreliable assays or, more simply, by tasting the urine. The ability to measure blood glucose lead to the definition of diabetes as a disease of hyperglycemia, although many other metabolic abnormalities exist which could conceivably have been used to define the disease had their assay been available before that of blood glucose. The availability of a blood glucose assay also facilitated the discovery of insulin since it allowed easy demonstration of the pancreatic hypoglycemic factor.

Over the past two decades, glucose assay by total reducing substance has been replaced by a specific glucose oxidase enzymatic technique. Glucose oxidase may now be bound to urine dip sticks, sticks used to measure whole blood, or membranes used for automated glucose analysis. The result is a simple, specific and relatively inexpensive measurement of blood or urine glucose. But the measurement must be made extracorporeally.

Diabetics traditionally have monitored their urine glucose concentration each morning or several times a day. This approach provides limited insight into changes in blood glucose—the parameter of interest—because a) a time lag exists before urine is tested, b) the renal threshold over which glucose spills into the urine is variable from patient to patient, and c) the urine glucose concentration will vary widely depending on dilution of urine by free water. For these reasons, monitoring of blood glucose by the patient has been a major advance in clinical diabetic care.
blood glucose self monitoring is accomplished by applying a drop of blood to a glucose oxidase impregnated stick and measuring color development. Motivated patients may do this three to seven times daily, but even seven points spaced throughout the day provide only a gross reflection of the continuous fluctuations in blood glucose. For research purposes, bedside CGM devices have been available in recent years.

Current CGM machines are large (measured in cubic feet), and expensive (about $300,000). They require a venous blood withdrawal line which must maintain a precise rate of flow, and they require a sensitive, calibrated glucose oxidase membrane. The Biostator (Life Sciences Division of Miles Laboratory, Inc.) requires a fulltime operating technician. Nevertheless, CGM has been a valuable research tool. The wide fluctuation of blood glucose in insulin dependent diabetics was a surprise to clinicians used to seeing fairly stable urinary glucose spillage. It was found that most diabetics on conventional insulin management have their peak blood glucose concentration after breakfast, and that blood glucose often reaches a nadir early in the morning, rising spontaneously at 8-9 a.m. (the "dawn phenomenon"). But the Biostator and similar devices are not practical for blood glucose monitoring on an ambulatory, outpatient basis.

Hemoglobin A1c determination is another recent addition to clinical blood glucose monitoring. Normal hemoglobin A is progressively glycosylated as it circulates in peripheral red blood cells by a non-enzymatic and essentially irreversible modification of the N terminal of hemoglobin's alpha chain. This conversion of hemoglobin A to hemoglobin A1c occurs at a rate directly proportional to the blood glucose in which the erythrocyte circulates. Given the slow turnover of erythrocytes and the irreversibility of the glycosylation reaction, the mean hemoglobin A1c represents an integrated value for blood glucose over the previous six to eight weeks. It is not possible, however, to derive a specific number for mean blood glucose from the hemoglobin A1c, and little is known, in fact, about whether the hemoglobin A1c is affected by peak, mean or variations in blood glucose.

The widespread availability of external insulin infusion devices, and the coming implantable insulin infusion devices, have lead many investigators to attempt development of a small, implantable glucose sensor. The ideal sensor would be small, specific (not cross reacting with any other blood constituents), efficient in its energy requirement (allowing implantability without an external power source), and of long life (at least months, preferably years). Its output could be either an electrical power signal or a radio frequency signal.

Several approaches to glucose sensing are under development, reviewed in reference 9. Glucose oxidase fixed to membranes--the system used in external devices--has been used, but its need for frequent replenishment of the enzyme may be a limiting factor. A platinum electrode measuring oxidation reactions linked to a potentiostat is another approach. Current changes up to 70 microamperes per mg/dl change in glucose are reported, but the challenge will be to derive patterns specific for glucose, as the platinum electrode also reacts to blood urea and amino acids. A similar device has been reduced in size and interference reduced by a potential step method. Another approach utilizes laser absorption spectroscopy with an attenuated total reflection (ATR) prism. The theory is that optical rotation is imparted by glucose in direct proportion to its concentration. Interference from other blood constituents remains the major problem. Other systems are being tried, but none has yet attained or approached the ideal requirements listed above.

The remainder of this discussion assumes that a workable implantable glucose sensor will be developed. It is impossible to predict exactly when this will occur, but a reasonable guess with adequate margin for error would be two to ten years. There is a need, therefore, for specialists in both clinical medicine and information management systems to prepare for the time when CGM becomes readily available.

Potential Influence of Continuous Blood Glucose Monitoring

Data Management

Conceptually, the simplest data management application of CGM is for the closed loop "mechanical pancreas." The output data from the glucose sensor would be used to regulate insulin delivery, holding blood glucose concentration in the normal range. Many algorithms have already been proposed for this application, based on Biostator-type devices. Given a sensor with adequate signal output, such algorithms could be programmed into a computer with little difficulty. But the problem would be deciding exactly what is desirable and feasible in a closed loop sensor. It may be desirable but relatively difficult, for example, to provide the counter-regulatory capability, raising blood glucose if insulin has caused hypoglycemia. Infusing glucose automatically would require a very large reservoir: infusing a hyperglycemic hormone such as glucagon is probably unnecessary. My choice would be to let the normal liver counter-regulate excessive insulin infusion.
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orins insulin responses to rising glycemia in the intrusion rate consistent with maintaining self-correcting, seeking the lowest insulin function of both absolute and delta blood insulin, intrusion would increase promptly, a

expected to represent means for an interval. To be sure, pattern recognition approaches have been applied which exceed physician performance in some areas of medicine such as the diagnosis of cardiac arrhythmias. But most laboratory values are interpreted with little recognition of their variation over time. If a fasting blood glucose was 110 mg/dl at a September office visit and 120 mg/dl in December, this is a "improvement", although it may have ranged from 90 to 190 mg/dl in the interim, with no consistent downward trend. The physician should really know now the blood glucose has fluctuated throughout the interval, but presenting weeks or months of CGM data will cause instant data overload. My proposal would be to present the data both numerically and graphically. Numerical presentation should include, for each hour of the day, over the period covered (e.g., 2 weeks to 5 months), the mean blood glucose, a measure of variance, and the number of instances in which glucose was outside of fixed limits.

The mean amplitude of glycemic excursions (MAGE) might also be provided. Graphically, the data would be presented as overlapping plots of 24 hr. time vs. blood glucose. To indicate trends, a color spectrum would be used, e.g., yellow for the earliest data, snaking incrementally to red for the most recent day. This approach would require sophisticated graphics. But ultimately, the best presentation of CGM data will be determined by which expression of blood glucose is most important medically.

There are no data available on which to decide what measurement of blood glucose correlates best with the development of acute or chronic complications of diabetes, whether the peak, the mean, the variance, etc. This will be a crucial area of research. The approach to treating diabetes would be significantly different, for example, if it were found that a mean blood glucose of 110 mg/dl is no worse than a mean blood glucose of 190 mg/dl (normal), but that any peaks over 150 mg/dl pose a serious risk.

We are not even certain whether patients with impaired glucose tolerance ("borderline" or "chemical" diabetes) are at risk for developing the complications of diabetes. But even before studying these questions of risk, CGM would be used to establish the definition of blood glucose variation in normal, non-diabetic people during normal life activities. A good deal could be learned about physiologic control of glycemia.

Physiology

To date, CGM has been used only on hospitalized subjects on standard diets and artificial interventions such as hormone infusions, pharmacologic manipulations of endogenous hormone secretion or dietary modifications. Such studies have produced extensive literature, but very little on glucose fluxes in normal life. The effects of real-life stress (overt or internalized), of normal activity, varying meals, sleep, pregnancy, menstrual cycles, etc., should be documented. And a study should be made of whether certain levels of blood glucose now called "normal" are in fact risk factors. Tandem degrees of hyperglycemia, less than we now call diabetes, could well be dangerous.

Symptomatic reactive hyperglycemia may be one of the most common causes of distress but is virtually undiagnosable by current techniques. Patients present with symptoms which are easily written off as anxiety or hypoglycemia. We administer a standard glucose load by mouth and follow hourly blood glucose. If this artificial test is equivocal or "normal", we reject the diagnosis of hyperglycemia. But it is likely that many people have symptomatic hyperglycemia perhaps from idiosyncratic responses to particular meal or activity pattern. The diagnosis could be verified only by CGM.

The merity of continuously changing physiologic variables is a fertile area for study, while overt diabetes is to some extent genetic, nothing is known about whether normal regulation of blood glucose is genetically transmitted or whether, in fact, some forms of diabetes are simply extreme examples of normal familial patterns of glycemic regulation. A theory being considered by some geneticists would hold that genetically linked variations in regulatory response time may trigger changes which ultimately result in type II diabetes. Such theories could be readily
Diagnosis

The diagnosis of diabetes is now established either by continuous, severe hyperglycemia or by an abnormal response to the oral glucose tolerance test. Arterial diagnostic criteria identify those people who are likely to develop the clinical complications of diabetes; if there were no complications, high blood glucose would not be called a disease at all. And, as mentioned, we do not know what level of hyperglycemia is necessary for the development of complications (or what aspect of hyperglycemia), for this ignorance is that our definition of diabetes finds only severely abnormal glycemic regulation.

With the definition of normal glycemic excursions firmly established, the distribution of these excursions in the population could be analyzed. Is there a normal, asymmetric, bimodal, or other pattern in large groups of people? From these data a far more meaningful definition of diabetes could be established than is possible with our current use of glucose tolerance testing. The early diagnosis of diabetes may become a useful effort.

Population screening for early diabetes has fallen into disrepute largely because of the complexity of oral glucose tolerance testing, and the insensitivity of random blood glucose testing. But with a simple CGM device, it would be possible to screen accurately at least high risk individuals (pregnant women, obese people, those with strong family history, etc.). Screening would be of use only after normal limits are established, but could allow early treatment which might be expected to reduce the long term sequelae of diabetes.

Treatment

With the sort of algorithms mentioned earlier, CGM data could be readily incorporated into a closed loop insulin infusion device. Indeed, unsuccessful attempts at such implantable pumps have been made, with the external diastat as a bedside prototype. For those diabetics who do not require insulin, CGM would nevertheless permit a new level of understanding of the efficacy of treatment by diet or oral hypoglycemic agents. The treating professional "closes the loop" with therapeutic interventions.

The cumbersome testing of blood or urine glucose is a mainstay of current diabetic therapy which would be made obsolete by CGM. Results of CGM could be stored and transmitted over telephone lines to the physician’s office, allowing rational intervention at appropriate times, rather than doctor’s office visits being scheduled quite arbitrarily every month or two or three. And with early warning systems in place, admissions for diabetic control (particularly for the endstage complications of poor control, diabetic ketoacidosis and hyperosmolar nonketotic coma), could be reduced drastically. Since about 1/3 of all acute care hospital days are now attributable to diabetes, technologies used to reduce acute admissions could have a significant impact on health care costs.

Clinical Investigation

A number of investigative areas would be opened up by CGM, some already mentioned. The National Institutes of Health is now starting a 10 year study of the effect of blood glucose control on longterm diabetic complications. The study will require considerable sacrifice on the part of patients, and tens of millions of dollars to accomplish. Most of the expense is caused by the elaborate treatment and monitoring regimen required to maintain different levels of glycemia. With CGM, particularly in a closed loop insulin delivery system, such a study would be no more difficult than changing algorithms in a RDM and monitoring the incidence of complications. Furthermore, since normal glucose-insulin dynamics could be established, there may be no point in testing the effect of abnormal blood glucose.

An almost infinite series of other studies can be imagined testing the effects on blood glucose of a variety of drugs, diets, etc. The ability to monitor out patients would both increase the validity of studies (by circumventing the need for artificial hospital settings) and make them far easier (by eliminating the need for frequent static blood glucose measurements).

Conclusion

It seems likely if not inevitable that practical CGM will be developed in the relatively near future. This paper has reviewed the history of glucose monitoring, and referred to some of the promising technical approaches being developed for CGM, but simply having available a CGM device will by no means assure its optimal use.

CGM would not just refine our ability to diagnose a disease state. Such technologic advances as CAT scanning or digital subtraction angiography, important as they are, simply sharpen our ability to visualize structures and document abnormalities, diagnosing diseases we know to
be defined by structural abnormalities. CDBM, on the other hand, will force us to change our thinking about what is normal and what is disease.

We have been so attached to static blood glucose measurements that we think of diabetes in terms of individual blood glucose concentrations. To be ready for CDBM, students of the biological sciences will have to learn new ways to evaluate continuously varying parameters. Information management systems will have to be developed which promote the appropriate utilization of continuous data. The goal is for our therapeutic interventions to be rightly thought of as affecting a continuous pattern of blood glucose concentration rather than just certain moments of blood glucose concentration. This new dimension in data management and clinical medicine is necessary to prepare for CDBM in the not distant future.

References