Outpatient Technologies for the Treatment and Prevention of Diabetes

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Abstract

Diabetes care has undergone dramatic changes throughout time that can be attributed to breakthroughs in either pharmacotherapy or technology. These breakthroughs were aimed at either improving outcomes in terms of reduction or prevention of complications or enhancing our capacity to diagnose the disease because of the human and economic impact of failing to diagnose and intervene appropriately.

Recent advances in outpatient technology for glucose measurement have brought to the field of diabetes the capacity to better achieve both of these necessary goals: detection and effective intervention. These new technologies are extending the capabilities of both physicians and patients to diagnose diabetes and effectively control blood glucose. They are also increasing awareness and diagnosis of states of elevated glucose that may be associated with an increased risk of diabetes. This allows patients with elevated glucose to be targeted for prevention strategies before the development of diabetes.

The advancement of technology has affected the treatment of diabetes mellitus throughout the history of the disease. Most of the technological advances in the field have affected patient care rather than the diagnostic aspects of the disease.

Clearly, the biggest technological advance in outpatient care until now was the introduction of devices for self-monitoring of blood glucose (SMBG) in the 1970s. This advance was immediately useful in the clinical management of people with diabetes, and it served as the foundation upon which the Diabetes Control and Complications Trial was designed and successfully carried out.[1]

In the past 2 years, a newer technology, namely, continuous glucose monitoring, has received approval from the Food and Drug Administration and become available. This technology, like those of the past, has applications in both diabetes treatment and patient education. However, it may also enable earlier diagnosis of diabetes or diagnosis of glucose elevations lower than those that are diagnostic of diabetes but still high enough to play a significant role in the occurrence of conditions that are caused by glucose toxicity. This new technology may thus have as great an impact as did SMBG in transforming both the role of diabetes clinics to treat and prevent diabetes and the ability of patients to manage self-therapy.

The concept of self-therapy is based on the original definition of intensified diabetes treatment, which was "a systematic therapeutic plan consisting of intensified insulin substitution (multiple daily insulin injections including twice daily NPH insulin, or continuous subcutaneous insulin infusion) dose-adapted by the patients based on blood glucose self-monitoring several times a day and liberalization of dietary regulations (avoidance of meal planning) and other lifestyle restrictions based on a comprehensive structured … treatment and teaching program with the aim to encourage the patients to conduct self-therapy."[2]

Contributing to patients' success in the appropriate anticipatory use of insulin is the addition of carbohydrate-counting skills. These easily mastered skills allow for the appropriate determination of insulin required for food ingestion even as meal quantity and composition is varied. This can be viewed as low technology, but it cannot be denigrated in terms of its impact on successful outcomes.

The gauge by which we measure the success of intensive therapy for diabetes is its ability to achieve endpoints that are commonly accepted to

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be of great benefit to patients. These guideposts of success include avoidance of severe hypoglycemia; maintenance of hemoglobin A_{1c} (A1C) levels <7.0%; prevention or correction, if necessary, of hypoglycemia unawareness; and last, but probably most important, accomplishment of the previous three objective targets with success subjectively measured by patients' ability to live a normal lifestyle.[3] The latter goal must be present to ensure that the three former ones are adopted by the most important member of the health care team—the patient.

The ultimate goal in treating and caring for people with diabetes is still finding a cure for the disease. This means the complete and absolute achievement of normal blood glucose levels at all times and under all circumstances for people diagnosed with all types of diabetes. As all health care providers know, the complete normalization of blood glucose at all times in the outpatient setting remains elusive. Because of the impossibility of achieving this holy grail of total glucose normalization, it is fortunate that its achievement is not required to improve both health and quality of life for people with diabetes.

Treatment of Established Disease

Successfully combining knowledge of blood glucose levels and delivery of insulin is the mainstay of treatment of type 1 diabetes and insulin-requiring type 2 diabetes. Despite advances in pharmacotherapy for people with type 2 diabetes (who represent 90% of all diabetic patients in the United States), 40% of these patients require insulin to achieve desirable blood glucose levels. This is not because of clinicians' or patients' failure to adequately treat the disease or to implement dietary and lifestyle changes. Rather, it is the result of the progressive nature of type 2 diabetes, as measured in terms of declining β-cell function over time.[4]

Achieving blood glucose levels in the target range has been shown to reduce the occurrence, progression, and severity of complications. Unfortunately, SMBG in patients with type 2 diabetes by current capillary blood glucose technologies does not improve their average glycemic load, as measured by A1C levels.[5]

In theory, improved knowledge of blood glucose levels should confer on type 2 diabetic patients more power to better self-manage their disease. Indeed, the benefits of such knowledge to type 1 diabetic patients, in terms of improved A1C levels and resultant outcomes, are known. But in practice, type 2 diabetic patients who do not use insulin actually have poorer glycemic control associated with greater frequency of SMBG.

People with poorer control of their disease are motivated to do better and so test more frequently to obtain the information they believe will empower them to do better. However, they often find the information obtained inadequate to ensure their success in improving or ameliorating the complications of diabetes. This may be because many of the complications of type 2 diabetes, such as neuropathy and cardiovascular disease, have already been firmly established by the time their diabetes is diagnosed.[6–8]

An alternative position, however, is that it may be patients' exposure to elevated *postprandial* glucose loads specifically that needs to be corrected to avoid complications. In this view, knowledge obtained through SMBG is seen as extremely limited and not adequate to describe the dynamic and continuous fluctuations of glucose that occur in the course of 24 hours. Although no interventional studies aimed at normalizing postprandial glucose specifically are available, many epidemiological studies have linked postprandial glucose to increased macro- and microvascular complications.[9]

The importance of postprandial blood glucose is in both its contribution to A1C and its linkage with complications. Control of postprandial glucose is hampered because capillary blood glucose detection, even when performed a minimum of four times daily, is limited. The newer outpatient glucose monitoring technologies provide a more complete picture of patients' wide excursions in blood glucose both above and below the normal range. They also detect both postprandial and asymptomatic/unrecognized hypoglycemia occurring at any time of the day or night.[10,11]

The Cygnus Glucowatch supplies blood glucose readings every 20 min, and the Continuous Glucose Monitoring System (CGMS) makes available 288 blood glucose readings in a 24-h period. Widespread use of these devices in evaluation and therapeutic intervention will supply a wealth of information about patients' glucose levels during monitoring periods.

The information these devices provide is not limited to the blood glucose level at the time measured, but also includes C-max (amount of time and level of glucose above the normal range postmeal) and T-max (amount of time until maximum glucose level) data. This information varies with type of meal, but interestingly and importantly, it also differs from breakfast to lunch to dinner.

When combined with knowledge about meals, medication, physical activity, and biopsychosocial variables, the information obtained with these outpatient technologies will give patients and providers the ability to make very specific changes in therapy or adjustments in factors resulting in improved blood glucose control. This ability can lead to a reduction in elevated blood glucose levels and correspondingly lower A1C test results, while also reducing the number of hypoglycemic events.[12]

Identification of Glucose Elevations

As mentioned above, our current failure in preventing the complications of diabetes is linked to the fact that, for many patients, complications are already present at the time of diabetes diagnosis. The delay in diagnosis and the lack of patient and provider recognition of the progressive pathological process of ever-increasing glucose levels and glucose toxicity result in a failure to be able to intervene early enough to make a difference. This is true not only in relation to the progression of complications, but also as regards the progression from impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) to full-blown type 2 diabetes.

Early identification of glucose elevations can delay or prevent the development of diabetes in patients who are at high risk for the disease.[13] Until recently, detecting IFG and IGT was not a goal because of a lack of evidence that diabetes could be delayed

or prevented by lifestyle or pharmacological interventions. With the recent release of the Diabetes Prevention Program results, however, diagnosing IFG and IGT has become a priority.[14] This diagnosis most often will take place in outpatient settings and will rely on various technologies, both old and new.

Certain individuals by virtue of heredity and genetics carry an increased risk of developing diabetes. Foremost among these are first-degree relatives of people who have type 2 diabetes or metabolic syndrome disorders. Thorough family and personal health histories can identify many of these at-risk individuals. Among the recognizable risk factors are both high and low birth weight; irregular menstrual cycles; polycystic ovarian syndrome; family history of diabetes; obesity; cardiovascular disease; personal history of gestational diabetes; lipid and uric acid abnormalities; neuropathies; and noninfectious and nonautoimmune liver disease.[15,16]

For a high-risk individual thus identified, the next necessary step is to determine whether that person has normal glucose tolerance, insulin resistance, IFG, IGT, or frank diabetes. Until recently, this was accomplished by sending patients to a clinical laboratory for either a fasting or glucose-loading test. However, both the fasting plasma glucose measurement and the oral glucose tolerance test have limitations in specificity, sensitivity, and reproducibility. By contrast, patient-performed continuous glucose monitoring is extremely reliable[17] and provides information on glucose excursions that occur in real-life settings. This new technology allows health care providers to obtain the diagnostic information they need in a timely and more useful manner.

Conclusion

Many disease states have been identified as being caused by or causally related to elevated glucose levels that are not high enough to be diagnostic of diabetes. Non-alcoholic steatohepatitis, autonomic and peripheral neuropathy, and cardiac arrhythmias are three examples. Older technologies did not allow for early diagnosis of glucose elevations either temporally or quantitatively. Both of the new technologies discussed here offer information not only to detect pre-diabetic elevated glucose levels, but also to help tailor interventions to normalize these excursions. It is expected that this improved ability to diagnose and target glucose elevations will minimize or ameliorate the medical conditions and complications associated with them.

As use of these new outpatient technologies becomes more widespread, at-risk and symptomatic patients will no longer be left waiting for the appropriate diagnostic laboratory tests to be ordered, but instead will arrive for their clinic visits with the necessary information already in hand to recognize glucose excursions and speed treatment by the most appropriate means available. Improved outpatient technologies will thus result in the true democratization of diabetes and the full inclusion of patients in the diabetes care team by making them an integral part of the most difficult obstacle to success, namely, diagnosis.

References

[1]The DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993

[2]Muller UA, Femerling M, Reinauer KM, Risse A, Voss M, Jorgens V, Berger M, Mulhauser I, for the ASD: Intensified treatment and education of type 1 diabetes as clinical routine. *Diabetes Care* 22 (Suppl. 2):B29–B34, 1999

[3]Bolli GB: How to ameliorate the problem of hypoglycemia in intensive as well as nonintensive treatment of type 1 diabetes. *Diabetes Care* 22 (Suppl. 2):B43–B52, 1999

[4]Turner RC, Cull CA, Frighi V, Holman RR, for the U.K. Prospective Diabetes Study Group: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirements for multiple therapies (UKPDS 49). *JAMA* 281:2005–2012, 1999

[5]Harris MI: Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes. *Diabetes Care* 24:979–982, 2001

[6]Lotufo PA, Gaziano JM, Chae CU, Ajani UA, Moreno-John G, Buring JE, Manson JE: Diabetes and all-cause and coronary heart disease mortality among U.S. male physicians. *Arch Intern Med* 161:242–247, 2001

[7]Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE, Hennekens CH: A prospective study of maturity-onset diabetes mellitus and the risk of coronary heart disease and stroke in women. *Arch Intern Med* 151:1141–1147, 1991

[8]Thomas PK, Ward JD: Diabetic neuropathy. In *Complications of Diabetes.* Keene H, Jarrett J, Arnold E, Eds. London, Edward Arnold, 1975, p. 151–178

[9]The DECODE Study Group: Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 354:617–621, 1999

[10]Boland EA, Delucia M, Brandt CA, Grey MJ, Tamborlane WV: Limitations of conventional methods of self blood glucose monitoring: lessons learned from three days of continuous glucose monitoring (CGMS) in pediatric patients with type 1 diabetes (Abstract). *Diabetes* 49 (Suppl. 1):A98, 2000

[11]Gibson LC, Halvorson MJ, Carpenter S, Kaufman FR: Short-term use of the MiniMed continuous monitoring system to determine patterns of glycemia in pediatric patients with type 2 DM (Abstract). *Diabetes* 49 (Suppl. 1):A108, 2000

[12]Bode BW, Gross TM, Thornton KR, Mastrototaro JJ: Continuous glucose monitoring used to adjust diabetes therapy improves glycosylated hemoglobin: a pilot study. *Diabetes Res Clin Pract* 46:183–190, 1999

[13]Tuomilhehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001

[14]The DPP Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002

[15]American Diabetes Association: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (Committee Report). *Diabetes Care* 25 (Suppl. 1):S5–S20, 2002

[16]American Diabetes Association: Screening for diabetes (Position Statement). *Diabetes Care* 25 (Suppl. 1):S21–24, 2002

[17]Gross TM, Mastrototaro JJ: Efficacy and reliability of the Continuous Glucose Monitoring System. *Diabetes Technol Ther* 2:S19–S26, 2000

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